Pharmacotherapy of Depression

Edited by

Domenic A. Ciraulo, MD

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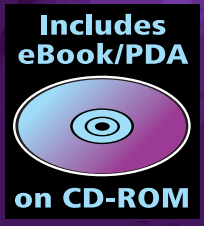

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PREFACE

For many years, we have taught clinical psychopharmacology to residents in psychiatry, neurology, and medicine, as well as to medical students, nurses, psychologists, counselors, and social workers. We have also maintained active clinical practices and research programs. It is our hope that these experiences have produced a book that will serve as a resource in antidepressant therapy for clinicians from many different disciplines.

The purpose of *Pharmacotherapy of Depression* is to provide a comprehensive overview of antidepressant therapy for clinicians. The contents have evolved from our years of seminars, lectures, and case discussions with our trainees and from our continuing medical education programs. We have tried to provide sufficient depth in reviews of the research literature to support clinical recommendations without burdening the reader with information that has little relevance to the clinical use of antidepressants.

We are indebted to the outstanding clinician scientists who have contributed to this volume and to our students who have guided us in its development. We hope that the reader will find that the final product represents a solid foundation for clinicians who are, or will be, prescribing antidepressants. It comes very close to replicating the formal didactics that our trainees experience. Although in practice we supplement this with intensive supervision of patient management, we hope that *Pharmacotherapy of Depression* will stand alone as a guide to the use of medications for the treatment of depressive illness.

Domenic A. Ciraulo, *MD*
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1 Biological Theories of Depression and Implications for Current and New Treatments

David J Goldstein, MD, PhD
and William Z. Potter, MD, PhD

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1. INTRODUCTION

Unipolar major depressive disorder is a common condition that has both emotional (mood and anxiety) and physical aspects *(1)*. The physical manifestations are common features of depression present in up to 80% of depressed patients *(2)*. These physical symptoms occur in nearly all body systems and are often the presenting features in the nonpsychiatric setting. The most common physical symptoms are sleep disruption, fatigue, pain and discomfort, and appetite disturbance.

Thus, because depression impacts all body systems *(3,4)*, it is not surprising that investigations attempting to determine the effects of depression on hormones, neurotransmission, brain imaging, sleep architecture, immune function, and so on, have tended to identify differences between depressed patients and normal subjects. However, many of these investigations have not been replicated, or show significant overlap between depressed and nondepressed groups leading to

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subsequent investigations of subgroups. Such investigations are further complicated by the temporal adaptation that occurs in many biological systems. For example, the hormonal effects of acute stress are different from those of chronic stress. Few studies have attempted to account for such temporal influences.

Genetic studies of depression have shown high heritability for depression, although much stronger for the bipolar than the unipolar form. Given that the concordance of depression even in identical twins is considerably less than 100%, it is likely that environmental events such as psychosocial and physiological stress play a substantial role. With unipolar depression, which is our focus here, a positive family history of depression predisposes individuals to earlier onset, longer time to recovery, greater severity, and more chronicity *(5,6)*. Thus, there are significant genetic factors, probably including both susceptibility and resistance genes, that modify the risk of developing depression. Moreover, patients with high genetic risk for affective disorders are more vulnerable for developing depression following stressful events than patients who have a low genetic risk *(7)*. For example, early childhood maltreatment is associated with elevated rates of depression, anxiety, and other psychiatric disturbance *(8)*. Although early stress can alter the hypothalamic–pituitary axis, cortisol-releasing hormone, monoamines, γ-aminobutyric acid (GABA), and glutamate systems, the subsequent caretaking environment or pharmacological interventions, such as selective serotonin reuptake inhibitors (SSRIs), benzodiazepine agonists, adrenal steroid inhibitors, tricyclic antidepressants (TCAs), and electroconvulsant therapy (ECT) can moderate, prevent, or reverse these effects *(9–11)*.

Until the 1990s, most attempts to evaluate the neurobiology of major depression were based directly or indirectly on research into the mechanisms of known antidepressant medications. The inherent circularity of exploring a mechanism already shown to be related to antidepressant activity has limited the discovery of novel treatments that have activity at sites other than the one of the previously known mechanism. In the last decade, there have been more attempts to understand manifestations of depression that are not based on known antidepressant mechanisms and to present rationales for novel therapeutic agents. A major theme emerging from recent studies is that structural and functional changes in the hippocampus and/or prefrontal cortex produced by stress in genetically susceptible individuals are part of the pathophysiology of depression *(10,12–16)*. Prior to the era of high-resolution structural magnetic resonance imaging (MRI) and functional positron emission tomography (PET) investigations, the approach to studying the relationship of stress to depression was through evaluating stress-responsive neuroendocrine systems, with those that control the release of glucocorticoids receiving the most attention.

Because so many recent reports have focused on aspects of stress, we review this body of work in the greatest depth to provide a relatively elaborated example

of an integrative approach to understanding unipolar depression. This is followed by a critique of the limitations of such a model for developing new treatments and examples of other abnormalities that may still prove fruitful sources of identifying targets of interest.

2. NEUROENDOCRINE SYSTEMS

Numerous perturbations of the neuroendocrine system have been described in depressed patients. Most of these findings appear to be related to changes that occur subsequent to, or as part of, a stress response.

2.1. Hypothalamic–Pituitary–Adrenal (HPA) Axis in Depression

The HPA axis is the primary neuroendocrine system mediating the stress response and includes the hormones and structures mediating the production of glucocorticoids. Corticotrophin-releasing hormone (CRH), also known as corticotrophin-releasing factor (CRF), is produced in the paraventricular nucleus (PVN) of the hypothalamus. It is a major regulator of basal and stress-induced release of proopiomelanocortin (POMC) and POMC-derived peptides, such as adrenocorticotrophic hormone (ACTH) and β-endorphin, from the anterior pituitary. ACTH acts on the adrenal cortex to promote synthesis and release of cortisol and other glucocorticoids. Glucocorticoids inhibit subsequent release of CRH and ACTH. GABA inputs from the hippocampus inhibits the stress response by decreasing CRH synthesis in the central nucleus of the amygdala *(17)*. Serotonin, norepinephrine (NE), and acetylcholine inputs from the amygdala and hippocampus stimulate secretion of ACTH. Serotonin neurons terminate on inhibitory GABA neurons to block GABA inhibition of CRH synthesis *(18)*. Dampened GABAergic tone in rats exposed to maternal separation enhances CRH expression in the amygdala and activation of the neuroendocrine system *(19)*. Thus, it appears that GABA might play a tonic regulatory role on the HPA axis.

The mechanisms underlying disturbance in the HPA axis include increased secretion of any or all of the hormones in the cascade or decreased sensitivity to negative feedback at any or all levels of the axis *(20)*. CRH antagonists reduce stress-induced increases in plasma catecholamines, tyrosine hydroxylase mRNA in the locus coeruleus (LC), and CRH mRNA and Type 1 CRH receptor mRNA in the PVN *(21)*, giving evidence of a tonic regulatory role of CRH in specific brain regions.

Cortisol is elevated over 24-h periods in severely depressed patients *(22)*, consistent with increased stress as part of the syndrome. Dexamethasone, a synthetic glucocorticoid, suppresses ACTH release in most healthy individuals at a standard dose *(23,24)*. Depressed patients have a significantly higher rate of nonsuppression than controls although rates of nonsuppression are still not that

high *(25)*. This is one example of considerable overlap between patients with and without depression in a measure that distinguishes some, but not most, patients meeting the broad criteria for the diagnosis of depression.

CRH, which is increased in cerebral spinal fluid (CSF) and plasma in some depressed patients, activates the sympathetic nervous system, inhibits gastric emptying, and gastric acid secretion. CRH also inhibits the secretion of growth hormone (GH) *(17)*. After injection of CRH, the amount of ACTH released is less in depressed patients than in normal subjects *(26,27)*. This blunted ACTH secretion suggests that there is increased central CRH release *(28,29)* because, in animals, stress and adrenalectomy lead to hypersecretion of CRH and down-regulation of receptors in the anterior pituitary *(30)*.

2.1.1. HPA Axis, Anxiety, and Stress

Acute stress leads to release of CRH, ACTH, and cortisol (HPA axis activation). With continued stress, adaptive changes occur. Most studies to date have focused on various animal models of stress. These reveal feedback inhibition by glucocorticoid receptors in the hippocampus and pituitary, down-regulation of postsynaptic norepinephrine receptors as well as up-regulation of inhibitory autoreceptors and heteroreceptors on presynaptic NE neurons.

In some types of anxiety, adaptive changes during chronic stress lead to lower levels of corticosterone and ACTH than seen acutely *(31)*. In other types of anxiety, there are enhanced increases in corticosterone *(32)* and prior stress experience can lead to augmentation of subsequent stress response. The multiple forms of stress and anxiety that can be associated with depression and multiple interrelated possible physiological responses render any simple generalizations inappropriate. For instance, some relatively time-limited stressors lead to long-term HPA axis effects. Severe prenatal stress or early maternal deprivation stress leads rats to have higher corticosteroid concentrations with exaggerated glucocorticoid responses to stress persisting to adulthood *(33,34)*. A review of how this may account for the great impact of early neglect and abuse as well as its potential role in the etiology of depression is available elsewhere *(10)*.

2.1.2. Limbic–Cortical–Striatal–Pallidal–Thalamic (LCSPT) Tract, Stress, and Depression

The LCSPT tract consists of several extensively interconnected brain structures: hippocampus, amygdala, caudate nucleus, putamen, and frontal cortex. These regions have glucocorticoid receptors *(35,36)*; and thus may be affected by variations in glucocorticoid concentrations. Most imaging studies (e.g., three-dimensional MRI) show measurable, but relatively small, changes in volumes of LCSPT tract structures between depressed and control subjects; and postmortem brain studies have also noted volume loss. The hippocampus, the most studied

of these structures, most consistently shows volume loss. Because these LCSPT brain structures are interconnected, they mutually influence each other; and effects, such as volume loss, in one structure might be expected to be reflected in structural or functional changes in the other structures.

Nevertheless, evaluation of volume reduction in the other LCSPT structures has lacked consistency with volume loss observed in some, but not all, studies. The lack of consistent findings in such studies has led to hypotheses related to subsets of patients who have reduction in structure volume rather than the alternative hypothesis that there is a significant overlap of LCSPT tract size between depressed and normal subjects. It should also be noted that compensatory changes, such as the presence of increased neurons in the PVN of the hypothalamus *(37,38)*, may possibly obscure detection of volume loss. It has been noted that there is an apparent association of greater hippocampal atrophy with depression subtypes that are more likely to have hypercortisolemia *(39)*. Another possibility that might have led to the lack of consistency in findings across studies is that the volume loss is small and may not be detectable using the techniques and technologies utilized by all evaluators. It should also be noted that volume loss does not necessarily imply cell loss which, when observed, may involve glia rather than neurons (*see* later discussion).

The cause of the reported hippocampal volume loss is unknown. Various proposals include the following: (a) depression susceptibility is associated with stress-related volume loss, precedes the onset of depression, and is central to the development of depression *(12,15)*; (b) neuronal loss occurs secondary to exposure to hypercortisolemia *(40)*; (c) glial cell loss results in increased vulnerability to glutamate neurotoxicity because glia are responsible for most glutamate removal from the synapse and the production of brain-derived neurotrophic factor (BDNF). Thus, glial loss results in increases in synaptic glutamate and decreases in BDNF in the LCSPT tract, both potentially resulting in neuronal loss; (d) stress results in reduction in neurotrophic factors *(41)*, such as BDNF and glial-derived neurotrophic factor, which tonically suppress apoptosis, the latent biochemical (suicide pathway) leading to cell death *(42)*; and (e) stress results in reduced neurogenesis *(43,44)*.

Additional evidence supporting a role for the LCSPT tract in depression is that late-onset depression is more common in age-associated medical and neurological disorders that cause damage to the LCSPT tract *(45)*. Prolonged maturation and stabilization of neural elements and synapses in the prefrontal cortex (PFC) continues into adulthood. This neural plasticity may make the PFC more susceptible to reductions in neuronal density *(46)*.

If the state of depression produces or increases reductions in critical brain structures, then the ability of antidepressants to increase neurotrophic factors

such as BDNF may prove as therapeutically important as the relief of symptoms. We are unaware, however, of any data that addresses the possibility that drugs marketed as antidepressants have protective brain effects in humans although there is MRI data consistent with the possibility that lithium has neurotrophic effects in humans *(47)*.

2.1.3. Hippocampus: Possible Pivotal Role Among LCSPT Tract Structures?

During stress, normal feedback mechanisms in the HPA axis fail to operate, leading to damage to hippocampal neuronal cells *(48)*. Stress is associated with damage to the hippocampus in animals *(41)*. Sustained fetal social stress in vervet monkeys causes neuronal degeneration of the CA3 region *(49)*. Chronic restraint stress in rats causes atrophy of apical dendrites of CA3 pyramidal neurons, which could lead to decreased volume without loss of neurons themselves *(50)*. Cold water immersion stress in rats causes structural damage to the CA2 and CA3 fields and decreases CRH in hippocampus *(51,52)*. Chronic exposure to corticosterone also leads to loss of CA3 region neurons *(40,53)* and decreased dendritic branching and length in hippocampus *(54)*. For example, Cushing's syndrome, an endocrinopathy manifest by overproduction of cortisol, leads to reduced hippocampal volume *(55)*.

In man, those studies reporting hippocampal volume loss show it to persist over years and after depression has resolved. The amount of volume loss appears best related to the total lifetime duration of depression, not the age of the patient *(56,57)*. Whether or not hypercortisolemia is related to findings of decreased hippocampal volume remains, however, to be demonstrated. The close relationship that might have been predicted from preclinical studies has not, to date, been established.

Nonetheless, other lines of evidence point to linkages between glucocorticoids and hippocampal volume. For instance, hippocampal lesions lead to increased release of glucocorticoids during stress *(58,59)* and this release may lead to further damage of the hippocampus *(60)*. Hippocampal atrophy may result in impaired cognition, a feature of depression. Patients with hippocampal atrophy may be more treatment resistant *(61)*; however, because the amount of hippocampal atrophy tends to be related to the duration of depression, hippocampal atrophy may be a surrogate marker for earlier onset and more frequent recurrence. This brings us back to the potential of restorative processes that may prove important in the long-term treatment and management of depression.

2.1.4. Neuronal Plasticity and BDNF

BDNF is a downstream target of the cyclic adenosine-monophosphate (cAMP) pathway. It regulates neuronal survival and synaptic plasticity both during development and in adult brain *(62)*. Stress is associated with decreased BDNF *(63)*.

Serum BDNF concentration is inversely proportional to depression severity as assessed by the Montgomery-Asberg Depression Rating Scale score *(64)*. When BDNF is infused into the midbrain, it produces an antidepressant-like effect in two behavioral models of depression, learned helplessness and forced swim tests, suggesting that BDNF is involved in depression *(65)*.

Consistent with this possibility, the cascade of events that follow antidepressant treatment can produce increased BDNF. Chronic antidepressant treatment increases G_s coupling to adenyl cyclase, which results in increased cAMP, which increases Ca^{2+}-dependent protein kinases and leads to increased expression of the transcriptional regulator cAMP response element-binding protein (CREB) *(66,67)*, which increases both BDNF expression in limbic structures, including hippocampus, and the BDNF receptor, TrkB *(68)*. Chronic administration of antidepressants and electroconvulsive seizures increase proliferation and survival of new neurons consistent with the effects shown after activation of the cAMP–CREB cascade or incubation with BDNF, which increases differentiation of new cells into neurons *(69)*. Taken together, these findings suggest that part of the treatment of depression should include interventions that enhance neurotrophic factor activity *(13,14)*.

2.1.5. How Strong Is the Case for a Major Role of Stress and the HPA Axis in Depression?

As reviewed previously, multiple lines of preclinical and clinical evidence argue that depression is associated with functional and/or structural alterations in the brain that are consistent with HPA dysfunction. Furthermore, whatever the primary biochemical effects of antidepressant treatments, pathways exist whereby long-term effects impinge on components of the HPA axis *(70)*. What is not addressed by recent formulations is the failure to translate the finding of hypercortisolemia in depression reported three decades ago *(22)* into a convincing diagnostic tool and/or predictor of treatment response despite diverse and sustained efforts *(23)*. As more sensitive methods have become available to document region-specific changes in structure or in function in the brains of patients with depression or effects of antidepressants on glucocorticoid receptor function in preclinical models there has been a new wave of circumstantial evidence to support statements such as "disturbed regulation of CRH neuronal circuitry plays a causative role in producing cardinal signs and symptoms of depression" *(71)*. The problem for the clinician or neuroscientist focused on providing or developing the best treatments is that no measure or combination of biochemical and physiological measures has allowed for a stable, reasonably replicable, and robust means of distinguishing a depressed from a normal individual, or for predicting an individual patient's response to different classes of antidepressants.

A primary focus on the HPA axis and, more recently, LCSPT tract risks subsuming findings of alterations in other measures as merely secondary. As is

succinctly reviewed in what follows, investigators have reported that other neuroendocrine or neurotransmitter systems are just as consistently dysregulated in depression as the "primary" HPA one. As catalogued in Table 1 and conceptualized in Figs. 1 and 2, these constitute a multitude of complex and potentially interrelated findings relevant to the pathophysiology and treatment of unipolar depression(s). As noted at the outset, trying to fit manic-depressive illness and unipolar depression into a common pathophysiologic model is an even more difficult task, particularly when one considers the differences in spectrum of efficacy between putative mood stabilizers and antidepressants. Therefore, we continue to restrict our focus and only occasionally refer to those studies on bipolar disorder that help to elucidate investigations of unipolar depression.

Given the complexity of findings, even within the broad category of patients with unipolar depression and the spectrum of marketed antidepressants with highly variable efficacy, it is not surprising that researchers look for unifying hypotheses. Unfortunately, those that have been proposed and tested, such as definable NE or serotonergic types of depression, have not been supported and those, such as the primacy of HPA axis dysfunction, have not been testable in the absence of appropriate pharmacologic agents. Reasoning that we should remain open to all lines of evidence, we will highlight reports of many other classes of abnormalities in depression that may or may not ultimately prove to be related to those of the HPA axis. In the absence of a compelling scientific case to narrow one's focus, we may best achieve therapeutic advances by targeting each of the systems implicated in depression and evaluating the potential advantage of selective interventions either alone or in combination (*see* below).

2.2. The Hypothalamus–Pituitary–Thyroid (HPT) Axis, GH, Somatostatin, and Prolactin (PRL) in Depression

It has been noted for many decades that many behavioral symptoms of hypothyroidism—dysphoria, anxiety, fatigue, and irritability—overlap those of depression. This observation, plus the clinical finding that small doses of thyroid may potentiate the effects of antidepressants, *(72)* has sustained an interest in the relevance of this system to depression. Thyrotropin-releasing hormone (TRH) released from hypothalamus stimulates TRH receptors in the pituitary to release thyroid-stimulating hormone (TSH), which stimulates specific receptors in the pituitary to release tri-iodothyroxine (T3) and thyroxine (T4) hormones. A subset of depressed patients show a blunted TSH response to TRH, others symptomless autoimmune thyroiditis *(28)*, and still others an exaggerated TSH response to TRH (reviewed in ref. *71*). Preclinical studies on the modulation of multiple neurotransmitter functions in the brain, coupled with clinical observations on rates of mood switches in bipolar disorder, point to the possibility that to under-

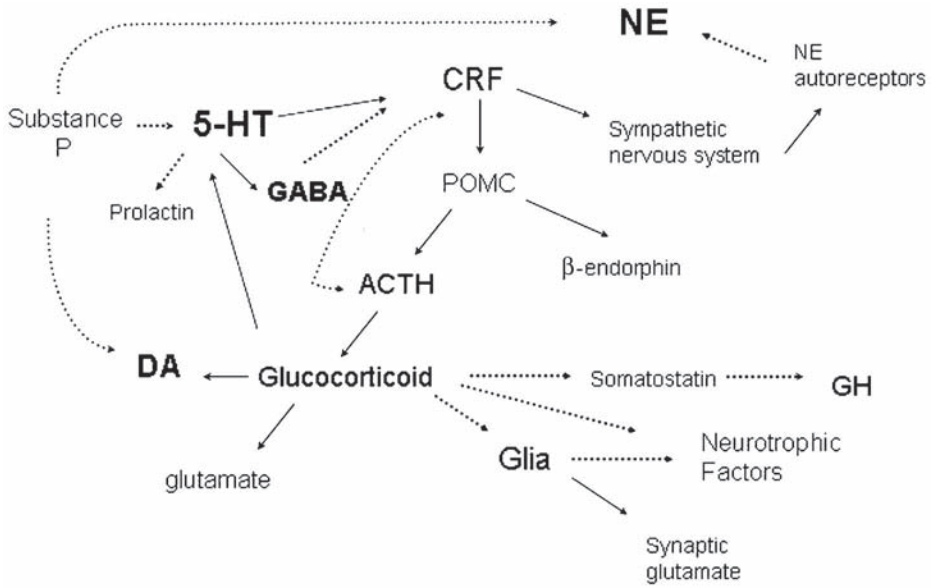

Fig. 1. Interaction of neuroendocrine system involved in the depression cascade. Solid arrows imply stimulatory effect; dashed arrows imply inhibitory effect.

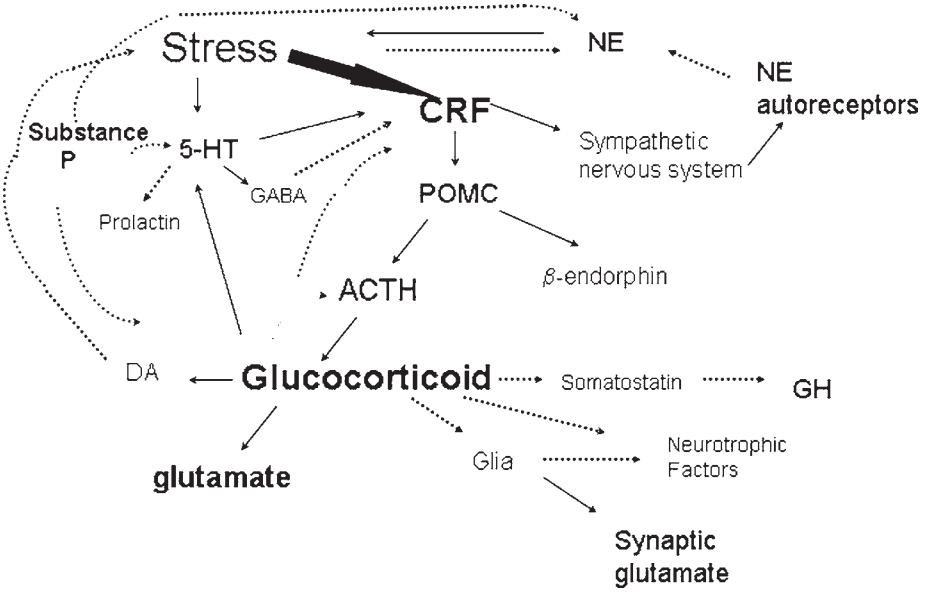

Fig. 2. Depression cascade. Hormones and neurotransmitters that have larger fonts tend to have increased concentration; those with smaller fonts tend to have reduced concentration. Solid arrows imply stimulatory effect. Dashed arrows imply inhibitory effect.

Table 1. Hormones and Neurotransmitters That Demonstrate Alterations in Depression and the Potential Effects on Producing Symptoms[a]

Hormone or Neurotransmitter	*Change*	*Symptom*
CRH (plasma, CSF)	Increased	Reduced hunger
		Diminished sex drive
		Heightened arousal
		Reduced delta sleep
		Increased core body temperature during sleep
Norepinephrine (total turnover)	Decreased	Anergia
		Anhedonia
		Anxiety
		Irrational beliefs
		Diminished libido
		Sleep disturbance
		Decreased REM latency
		Increased REM duration
		Decreased pain suppression
Serotonin (function)	Decreased	Depressed mood
		Aggression
		Reduced impulse control
		Diminished libido
		Sleep disturbance
		Decreased time in REM sleep
		Decreased REM latency
		Decreased slow-wave sleep
		Appetite disturbance
		Decreased pain suppression

(continued on next page)

Dopamine (CSF)	Decreased	Impaired cognition Reduced motivation Anhedonia Decreased motor activity Increased appetite
Cortisol (plasma)	Increased	Insomnia ?Osteoporosis Hippocampal volume loss Treatment resistance Loss of concentration and memory
GABA (plasma, cortical postmortem samples)	Decreased	Reduced grooming Reduced appetite
BDNF (postmortem samples)	Decreased	Hippocampal volume loss
CAMP–(CREB (postmortem samples)	Increased	Hippocampal volume loss
GH (plasma)	Increased Blunted diurnal rhythm Blunted response to $\alpha_2$agonist	
Somatostatin (plasma)	Decreased	
Melatonin (plasma)	Increased	Sleep disturbance

[a] *see* text for references.

CRH, corticotrophin-releasing hormone; CSF, cerebrospinal fluid; GABA, γ-aminobutyric acid; BDNF, brain-derived neurotrophic factor; cAMP, cyclic adenosine-monophosphate; CREB, cAMP, response element-binding protein; GH, groeth hormone; REM, rapid eye movement.

stand certain forms of depression it will be necessary to understand altered function of components of the HPT axis *(73)*.

GH and somatostatin, the hypothalamic GH-suppressing factor, regulation has also been found to be altered in depression. A change in the diurnal rhythm of GH may be reflected by increased plasma concentrations *(74)*, a finding that is opposite in direction to what would be provided if CRH were exerting control (discussed later). It is here worth recalling that cortisol abnormalities are also best described in terms of the diurnal pattern with elevations only observed at certain times of the day *(75)*. GH increases to α_2 agonists (e.g., clonidine) are blunted in depressed patients *(76,77)*. This blunted GH response has been consistently replicated and complemented by findings of blunted responses to uptake inhibitors, such as desmethylimipramine, which increase the intrasynaptic concentrations of the endogenous α_2 agonist NE *(78)*.

Interestingly, somatostatin concentrations are reported to be reduced in the CSF of depressed patients compared with controls, although this finding is not specific to depression and may be related to elevated cortisol concentrations *(26,79,80)*. A reduction of the inhibitory factor is also consistent with the previously described elevation of GH in blood but not the blunted response to α_2 stimulation. The latter is most consistent with several lines of evidence implicating altered α_2 function in depression *(81)*. The complex interrelationships of neuroendocrine and monoamine function are not well enough understood to allow us to test for primary causality of any single abnormality.

Another highly replicated neuroendocrine abnormality in depression is that of blunted PRL responses to serotonergic stimulation. For instance, there is a blunted release of PRL to a fenfluramine challenge in depressed patients *(82,83)*. PRL responses to intravenous tryptophan, a precursor of serotonin *(84)*, or clomipramine, a potent serotonin uptake inhibitor *(85,86)* are also blunted. Because abnormalities of unstimulated PRL have not been reported, these responses would appear to best reflect altered serotonin function.

As already noted, the interrelatedness of catecholamine and serotonin systems in the brain with modulation of neuroendocrine function makes it difficult to address cause vs effect as reflected in the examples just given. An additional issue is that many of the observed abnormalities involve a circadian component, in other words, they may only show differences at certain times of day, which leads to an interest in a pathophysiological role of altered circadian regulation *(87)*, particularly in terms of seasonal affective disorder (SAD) *(88)*. Melatonin secretion varies over the 24-h period in a circadian pattern related to light and darkness. Its secretion is partly under NE control and exogenous melatonin and/or using light to shift the phase of endogenous melatonin may have a role in the treatment of circadian disorders under which SAD can be subsumed *(88)*. It has

also been suggested that blunted circadian variation in natural killer cell activity in depression may reflect some underlying chronobiological rhythm *(89)*. All of these reports of altered neuroendocrine and possible circadian regulation in depression need to be considered in light of the extensive work on the monoamine neurotransmitters in the brain, which have been shown to be involved in the action of established antidepressant treatments. Despite the theoretical attractiveness of other approaches, no intervention derived from neuroendocrine or circadian hypotheses has yet led to a treatment that, by itself (e.g., light therapy), shows sustained efficacy in a substantial proportion of patients diagnosed with depression. Considerable effort has gone into identifying CRH antagonists that will ultimately allow for a test of whether excess CRH tone plays a pathological role in patients with evidence of hypercortisolemia.

2.3. Classic Neurotransmitters and the Monoamine Hypothesis of Depression

Although agents that modify neurotransmitter action have become the primary therapies for depression and although numerous abnormalities in neurotransmitters have been uncovered in depression, the attempt to establish primacy of any single neurotransmitter or of neurotransmitters over hormones, has been unsuccessful. As emerging technologies permit further examination of new systems, additional perturbations have been noted but findings and formulations of hypotheses have necessarily reflected methods available at the time.

For more than four decades, TCAs and monoamine oxidase inhibitors (MAOIs) have been known to be effective treatments and show serotonergic, norepinephrinergic, and/or dopaminergic activities. These observations provide the so-called pharmacological bridge to the monoamine hypothesis of depression *(90)*, which has guided much research to elucidate the role of the monoamine neurotransmitters, serotonin (5-HT), NE, and dopamine (DA), in the pathophysiology of depression. Further development of more specific agents including SSRIs, NE reuptake inhibitors (NERI), and dopaminergic reuptake inhibitors, has reinforced the importance of monoamine systems for the treatment of depression. Thus, the monoamine hypothesis continues to encourage investigation of the biological basis of depression. Such investigations are now focusing on additional components of monoamine action such as postsynaptic receptors, presynaptic autoreceptors and heteroreceptors, second messengers, and gene transcription factors. For example, several antidepressants have been noted to down-regulate 5-HT_{1A} receptor activity, reducing negative feedback of 5-HT_{1A} in the raphe nuclei resulting in greater 5-HT release *(91)*. Such findings support the possibility of adding a 5-HT_{1A} antagonist to an SSRI to potentiate antagonist effects *(92)*. Alternatively, it has been argued that postsynaptic 5-HT_{1A} receptors

may be a target for antidepressant therapy, although existing evidence suggests that full agonists may have too narrow a therapeutic index in humans to test the hypothesis *(93)*.

In addition to their independent effects, the monoamines interact with all of the systems described here and elsewhere in this chapter. For example, the glia have postsynaptic 5-HT and NE receptors on their cell bodies and processes *(94–96)* that could be expected to affect concentrations of glutamate and neurotrophic factors. Additionally, substance P is co-expressed with 5-HT in ascending dorsal raphe neurons *(96)* and substance P modulates mesolimbic DA activity and is involved in stress-induced activation of the ascending NE projection from the LC *(97)*. For the sake of clarity, we briefly consider each monoamine by itself, recognizing that in vivo there are, among them, complex regional and structure-specific interactions.

2.3.1. Serotonin

A role for 5-HT in depression was established with the use of SSRIs in its treatment. That SSRIs really do depend on 5-HT has been elegantly tested by showing that depletion of tryptophan, a precursor of 5-HT synthesis, leads to return of depressive symptoms in patients with recent response to SSRIs *(98,99)*. Women have lower rates of 5-HT synthesis and thus may show even greater relapse rates in response to depletion than men *(100)*.

Evidence of reduced serotonergic function has been found in untreated depressed patients. Investigators have assessed [3H]imipramine and [3H]paroxetine binding in platelets from depressed and healthy subjects as a possible peripheral marker of the brain serotonin transporter (SERT) with some, but not all, studies showing reductions in depressed patients *(101,102)*. Postmortem studies show similarly decreased serotonin binding in hypothalamus *(103)* as have some imaging studies *(104)*. One might expect more consistent findings in postmortem samples from suicides because low serotonin metabolite concentrations in CSF may be associated with reduced impulse control that might predispose depressed subjects to commit suicide *(105)*. On the other hand, there is no obvious causal relationship between a measure of 5-HT turnover in CSF and density of the transporter.

Mechanistically, 5-HT and the HPA axis are linked. Figure 1 shows the normal interaction of 5-HT, NE, and DA with the endocrine system. 5-HT can stimulate CRH release mediated by 5-HT_2, 5-HT_{1A}, and 5-HT_{1C} receptors. Glucocorticoids tend to enhance 5-HT function, possibly as a compensatory effect in chronic stress. The extent to which this input exerts major influences in humans remains to be established. Nonetheless, preclinical studies point to several potentially important relationships. For instance, acute stress increases 5-HT release transiently, but continued stress leads to 5-HT depletion. Chronic stress

may also increase production of 5-HT_{1A} autoreceptors that further reduce 5-HT transmission. 5-HT_{1A} knock-out mice demonstrate increased stress-like behaviors indicative of "increased anxiety" *(106,107)*. These mice show increased mobility in response to stressors, which is used as a model for antidepressant drugs *(108)*. This data provides a basis for the association of anxiety symptoms with depressed mood.

Imaging studies have investigated the relationship of 5-HT and hippocampal atrophy. PET studies of 5-HT_{2A} binding of [(18)F] altanserin has, however, led to disparate findings *(104)*. It is to be anticipated that development of additional and more selective imaging ligands will clarify many of the suggestive, but variable, findings in depression that tend to overlap with both normal populations and those with other conditions (e.g., Alzheimer's disease).

2.3.2. Norepinephrine

The role of NE has also been demonstrated in clinical trials as well as in depletion studies. α-Methyl para-tyrosine (AMPT), which blocks NE synthesis, does not alter the rating on the Hamilton Depression Rating Scale (HAM-D) in normal subjects, but produces a depressive relapse (increases the HAM-D rating) in patients who remitted to a NE antidepressant such as desipramine or mazindol *(109)*. In contrast, there was no return of depression after AMPT in patients who had remitted on a serotonergic antidepressant *(109)*.

NE neurons in the LC project to almost all major brain regions and serve an important role in regulating and focusing additional and other responses to external stimuli *(110,111)*. Not surprisingly, NE systems are involved in responses to stress because there are multiple interactions between the HPA axis and NE. For instance, under experimental conditions, CRH secretion increases LC neuronal firing resulting in enhanced NE release. NE release stimulates CRH secretion in the PVN, which leads to ACTH secretion. Increased ACTH leads to increased cortisol, which provides a negative feedback to decrease CRH and NE in the PVN.

During behavioral stress, LC neuronal firing is increased *(112)* in association with increased release of NE. This LC responsiveness is enhanced with a novel stress after chronic or prior stress. When stress exposures are repeated in situations that prevent the animal from escaping, the animal exhibits learned helplessness, which is associated with the depletion of NE *(113)*. It is thought that this depletion is the result of the animal's inability to synthesize sufficient NE to replace that which is released *(114)*. Whether such depletion occurs in the human brain following the chronic stress of depression is unknown.

Various approaches to evaluating NE function in depression have been pursued over the last three decades, from quantifying its metabolites in urine to

radiolabel isotope dilution techniques to track its "spillover" in plasma *(115)*. Taken together, there is evidence of a shift toward elevated turnover and release in unipolar depression although values overlap with those observed in age- and gender-matched healthy volunteers. One hypothesis to explain these increases emerges from consideration of reports on altered sensitivity of the platelet α_2 receptor in depression. Subsensitivity of α_2 receptors and/or their coupling mechanism to downstream intracellular events could be responsible for the exaggerated release of NE observed in depressed patients subjected to acute physiological or psychological manipulation (reviewed in ref. *116*).

Despite some evidence for an association of elevated HPA and NE function, relevant and consistent relationships have not yet been established among the available peripheral (blood and urine) measures. It is conceivable that availability of appropriate methods to simultaneously quantify CRH and NE in all brain regions would lead to demonstration of tight relationships. It is equally conceivable that elevations of CRH and NE can occur relatively independently as a function of different subtypes of depression. The result that emerges from such studies will have implications for the treatment and understanding of depression pathophysiology.

As noted above, antidepressant treatment, including that with NE and 5-HT uptake inhibitors, has effects on the NE signal transduction pathway and increases BDNF by blocking stress-induced decrease of BDNF in the hippocampus *(117)*. Furthermore, stimulation of 5-HT_{2A} receptors increases BDNF mRNA *(118,119)*. Consequently, various elements along the NE and 5-HT pathways, including α-receptors, G proteins, cAMP, cAMP–CREB, and BDNF are being evaluated as targets for antidepressant medications *(120)*. As an example, focused on the NE cascade, chronic administration of NE antidepressants, such as desipramine and reboxetine, causes desensitization of the β-adrenoceptor-coupled adenylate cyclase system. Nuclear phosphorylated CREB (CREB-P) decreases in rat frontal cortex after chronic administration and in fibroblasts after incubation, suggesting that NE antidepressants exert direct effects beyond β-adrenoceptors. This would be consistent with deamplification of the NE-mediated signal transduction cascade resulting in "normalization" of increased NE activity, an evolving hypothesis *(121)*.

2.3.3. Dopamine

Deficiencies in DA have been tied to depression and DA is tied to the regulation of the endocrine system. Moreover, there is a long-standing case for a role of enhancing DA function in the treatment of depression, particularly that not relating to monotherapy, as reflected in the special role of MAOIs or bupropion as an adjunctive therapy *(122–124)*. CSF levels of homovanillic acid, a major DA metabolite *(125–127)*, and urinary dihydroxyphenylacetic acid, another major

DA metabolite *(126)*, are reduced in a proportion of depressed patients. Consistent with the tendency for depressed patients to have decreased DA metabolites, imaging (single photon emission computed tomography and the high affinity D_2 ligand ^{123}I-iodobenzamide) studies of D_2 receptor binding have demonstrated 10% more basal ganglion activity in depressed patients than in controls. This may be the result of decreased dopaminergic transmission because decreased intrinsic D_2 occupancy would tend to lead to up-regulation of D_2 receptors *(128)*. When antidepressant treatment is instituted, the D_2 activity decreases in the striatum *(129,130)*, consistent with this hypothesis. Most recently, decreased density of the DA transporter and increased density of D2/3 receptors was found in the amygdala in a study of postmortem brain samples from subjects with depression *(131)*. Finally, in some brain regions, such as PFC, DA is transported by the NE transporter into the presynaptic neuron *(132)*. Therefore, centrally in such areas rich in DA nerve terminals, an NE reuptake inhibitor may act like a DA reuptake inhibitor, and avoid the peripheral dopaminergic effects, as well as cocaine-like effects, that might be seen if the DA transporter itself were universally inhibited.

Increased glucocorticoid activity leads to altered or decreased PFC DA metabolism *(133,134)*, and the increased mesolimbic DA activity *(134)*. DA is also known as PRL-release inhibiting factor beacuse it is released by the arcuate nucleus of the hypothalamus where it binds to the D2 receptor inhibiting the activity of the acidophilic cells of the anterior pituitary, thereby blocking PRL and also GH release. Thus, the blunted PRL response to a serotonergic agent, seen in depressed patients, could involve a dopaminergic component, especially in light of well-known 5-HT–DA interactions *(135)*.

2.4. Other Neurotransmitters: Substance P, Glutamate, GABA, and Enkephalines

Because the neurotransmitter and endocrine systems are linked, as noted previously, effects on other neurotransmitters should also be expected. Thus, there is evidence for involvement of substance P, glutamate, GABA, and opiates in depressed mood. Given that these systems are affected, it is to be expected that there would also be therapeutic effects related to these neurotransmitter systems.

Substance P receptors, particularly the neurokinin-1 (NK_1) receptors, are highly expressed in brain regions, including the amygdala, septum, hippocampus, thalamus, and periaqueductal grey, that are critical to regulation of emotion and neurochemical responses to stress *(136–138)*. Prostaglandin agonists and vanilloid receptor agonists, such as *N*-arachidonyl-dopamine, induce substance P release *(139–140)*. NK_1 antagonists may exert a significant part of their effects through the monoamines. Substance P and 5-HT are co-expressed in ascending raphe neurons in human brain *(96)*. Sustained administration of an NK_1 antago-

nist increased spontaneous firing of dorsal raphe 5-HT neurons associated with reduction in 5-HT_{1A} autoreceptor responsiveness *(141)*. This suggests that NK_1 antagonists enhance 5-HT receptor activation. Additionally, glutamate receptor antagonists can block the effect of NK_1 agonists on firing of 5-HT neurons. This effect is blocked by NK_1 antagonists and an α-amino-3-hydroxy-5-methyl-4-isoxazolepropione acid (AMPA)/kainate glutamate receptor antagonist, suggesting that the neurokinins may act by exciting glutamate neurons that input on 5-HT neurons *(142)*.

Similarly, substance P is involved in stress-induced activation of the ascending NE projection from the LC. An NK_1 antagonist increased NE in the dialysate of frontal cortex in moving rats and increased the firing rate of adrenergic perikarya in the LC *(143)*. Substance P antagonists attenuate stress responses, and block anxiety behaviors in animal tests such as the forced swim test *(144)*, maternal separation-elicited vocalization *(145,146)*, immobilization stress *(147)*, and inescapable foot shock *(148)*.

Because substance P activates NK_2 and NK_3, as well as NK_1 receptors, these too need to be considered. Emerging data on NK_2 antagonists suggests they may be potentially relevant to depression. NK_2 antagonists also block anxiety behavior in the elevated plus maze and the marmoset threat test *(149)*. Anxiolytic and antidepressant drugs down-regulate substance P biosynthesis *(146)*. The NK_2 antagonist SR48968 also mediates LC firing and NE release in PFC *(98)*. In support of the potential role of substance P in depression, there has been at least one placebo-controlled study of an antagonist in depression, in this case specific for NK_1, that showed a significant therapeutic effect *(145)*.

Glutamate also is involved in depression. Both stress and glucocorticoids increase glutamate concentrations in the hippocampus. Glutamate may also be involved in hippocampal neuron death associated with stress *(150)*. Normally, glutamate is removed from the synapse through reuptake by the presynaptic neuron and the glia. Glia convert glutamate to glutamine that gets transported to the presynaptic neuron, which converts it back to glutamate *(151)*. Glucocorticoids impair glutamate removal from the synapse because of disruption of the energetic effects by glucocorticoid, which inhibits glucose transport resulting in depletion of hippocampal adenosine 5'-triphosphate (ATP) concentrations, increases free cytosolic calcium by impairing calcium extrusion from postsynaptic cytoplasm, and blunts compensatory increased activity of antioxidant enzymes compromising the ability of neurons to respond to an insult. Of these effects, those on calcium, reduction of calcium conductance and calcium ATPase pump activity, are likely to be the most significant *(152)*. Thus, it appears that glucocorticoids, when increased, impair the ability of neurons to survive coincident insults, such as hypoxia, metabolic poisons, hypoglycemia, oxygen radical generators, and seizure-related neurotoxicity. Suicide victims have been noted to have desensitization of *N*-D-methyl-aspartate (NMDA) receptors in the PFC as

evidence that glutamate transport might be impaired in depression *(153)*. Additionally, NMDA antagonists are active in the forced swim test *(154–157)*.

Stress and depression are associated with increased number of 5-HT_{2A} receptor-binding sites *(158)*, resulting in increased glutamate release. Glutamate release is suppressed by μ-opioid, metabotropic glutamate (mGlu2), and monoamine β_2-adrenergic and 5-$HT_{1B/1D}$ and, possibly, 5-HT_7 receptors *(96)*. Thus, combined use of both an SSRI and a 5-HT_{2A} antagonist, such as mirtazapine or olanzapine, synergistically suppress glutamate release.

Repeated ECT and chronic antidepressant therapy desensitize NMDA-glutamatergic receptors in rat cortex *(154)*. Antidepressant drugs directly or indirectly reduce NMDA glutamate function *(100)*. It has been proposed that polymorphisms or mutations in the glutamate receptor genes, in particular the NMDA receptor complex might alter susceptibility for development of depression *(159)*.

GABA has been reported to be decreased in plasma in many patients with symptomatic depression *(160)* in depression. $GABA_B$ receptors are coupled to Ca^{+2} channels and may enhance cAMP responses to NE and enhance β-adrenergic down-regulation in response to TCAs *(161–166)*. Imaging studies indicate that depression is associated with reductions in cortical GABA concentrations. This effect may be tied to the 5-HT system. Both a $GABA_A$ antagonist and a selective 5-HT_{2A} receptor antagonist reduced the inhibitory postsynaptic currents in the dorsal raphe nucleus (DNR), indicating that 5-HT_{2A} receptors activate GABA inhibitory inputs to 5HT neurons in the DNR *(163)*. Because antidepressant medications raise GABA concentrations, ameliorating GABA deficits associated with depression, GABA agents have been proposed as useful treatments in depression.

Opiates have effects on mood and interact with other neurotransmitters. Opiates are sometimes used to augment the effects of other treatments in refractory depression *(164)*. Activation of μ-opioid receptors suppresses 5-HT_{2A}-induced excitatory postsynaptic currents, suggesting that μ-opioids suppress glutamate release through the 5-HT system *(96)*. Chronic opiate exposure also up-regulates the cAMP-signaling pathway and increases expression of tyrosine hydroxylase, indicating a noradrenergic effect *(165)*. Endogenous opioids may be involved in the effect of placebo on mood and behavior of patients *(166)*. For example, the use of naloxone in analgesia trials can ablate the placebo response *(167)*.

3. ALTERATIONS IN PHYSIOLOGICAL FUNCTION: CIRCADIAN RHYTHMS, SLEEP, PAIN PERCEPTION, AND APPETITE

Given that depression is associated with perturbations of most endocrine and neurotransmitter systems, it is not surprising that depression alters physiological

function. The neurobiology of depression needs to account for these. Additionally, it is apparent that the location of the insults in the particular individual can account for the specific symptoms of that individual and that the specific treatments used for restoring normal mood would influence the impact of those therapies on specific physiological functions.

Diurnal, nocturnal, and seasonal effects are generated by an endogenous circadian pacemaker, entrained by environmental cues, particularly light/dark cycles. These circadian effects of sleep, temperature, and neuroendocrine secretion are mediated by periodic gene expression originating in the hypothalamic suprachiasmatic nuclei *(168)*. Mutations in clock genes accelerate and delay circadian cycles *(169)*. Serotonergic neurons, which project to the suprachiasmatic nucleus in the hypothalamus help regulate circadian sleep–wake cycles, temperature, and the HPA axis.

As part of circadian effects there are normal 24-h fluctuations in neuroendocrine secretion, especially cortisol, GH, TSH, and melatonin, as already noted. These hormonal systems are often disrupted in depression thought to be the result of heightened arousal. With shorter daylight hours, some individuals who experience the aforementioned have recurring autumn and winter depression (SAD) thought to be related to phase delay in the sleep–wake cycle *(168,170)*.

Sleep is often disturbed in depression. Imaging studies using [18(F)] 2-fluoro-2-deoxy-D-glucose PET have noted changes in oxygen utilization consistent with abnormal arousal in depressed patients associated with increased glucose utilization in ventromedial PFC *(171)* and blunted response in anterior paralimbic regions during rapid eye movement (REM) sleep *(172)*. Hyperaroused patients demonstrate loss of delta sleep, loss of sleep continuity, and increased core body temperature during sleep. Changes in quantitative perfusion MRI have been noted in responders *(173)*.

Because sleep is related to endocrine function and depression, it is interesting that deep sleep has an inhibitory influence on the HPA axis. Activation of the HPA axis or administration of glucocorticoids can lead to arousal and sleeplessness. A 24-h increase of ACTH and cortisol secretion can result in insomnia, consistent with a disorder of central nervous system hyperarousal *(174)*. Additionally, elevated CRH in depressed patients can cause a hyperarousal in some brain regions that can be observed by evaluating brain glucose utilization, consistent with the imaging findings. Sleep deprivation can produce temporary remission of depression in many patients with major depression, perhaps through effects on the HPA axis.

Sleep also is influenced by neurotransmitters. 5-HT neurons project from the DRN to the cholinergic cells of the pons to tonically inhibit REM sleep. Deple-

tion of 5-HT duplicates the findings of increased REM sleep time, decreased time to onset of first REM sleep (REM latency), and decreased amount of slow-wave sleep that are seen in nearly 50% of depressed patients and 10% of controls. Depletion of 5-HT and NE shortens REM latency and increases REM sleep. REM rebound is an aspect of antidepressant rebound *(175)*.

Painful physical symptoms are also common complaints in depression *(176)*. This may in part be related to the shared 5-HT and NE pathways in depression and pain *(177)* because 5-HT and NE modulate pain through the descending pain pathways. Serotonergic projections descend through the rostral ventral medulla and the pontine raphe into the spinal cord where they modulate pain. NE neurons also project through the dorsolateral pons, LC, medial and lateral parabrachial nuclei, and associated areas into the spinal cord to modulate pain. The effects of 5-HT and NE are synergistic in this system. Thus, dual reuptake inhibitors are effective in relieving the physical symptoms associated with depression *(178)*. Recent functional imaging studies indicate that the presence of anxiety may accentuate pain perception *(179)*.

Depressed patients also frequently complain about altered appetite. Both the endocrine systems and neurotransmitters are involved in appetite control. The monoamines that are often perturbed during depression also have effects on appetite. DA modulates sensory feedback and appetite *(180,181)*. NE in the hypothalamus increases meal size and stimulates carbohydrate intake through α_2-adrenergic receptors *(181)*. This effect shows rapid tolerance. Corticosterone up regulates α_2-adrenoreceptors. 5-HT acts through the 5-HT_{2C} receptor to affect eating rate and through the 5-HT_{1B} receptor to affect meal size *(179)*. CRH is a potent anorectic when injected in cerebral ventricles or PVN. Thus, when present, elevated CRH associated with depression may contribute to anorexia.

4. CONCLUSION

Although our understanding of the biology of depression is far from complete, there appears to be a convergence of disparate research inquiries such that a more integrated biology of depression explaining the interrelationship of both the emotional and physical components of depression is now emerging. The neuroendocrine effects of stress and the neurotransmitter effects of depression are now recognized to interact in a tightly linked system that offers a homeostatic mechanism for responding to stress. Additionally, the neuronal pathways for the emotional and physical symptoms have common nuclei and pathways.

Many possibilities emerge from combining observations in patients and animals. Although the validity of extrapolating from animals to humans has not been demonstrated, numerous potential treatments can be proposed based on the test-

able hypotheses of the mechanistic basis of depression. One relatively simple construct is that of depression as a cascade of neuroendocrine effects.

Stress in susceptible individuals results in HPA axis stimulation as an early step leading to depletion of the monoamines 5-HT, NE, and DA near the start of the cascade. If these monoamines are reduced in other ways, they can potentially induce the development of depression in the absence of HPA axis stimulation. Additional systems are influenced by the HPA axis and the monoamines. This interaction can be considered a depression cascade. Based on this hypothetical construct, treatments closer to the initiating factors or early steps in the cascade or those that act at multiple branches of the cascade would be more effective than treatments that act only on a single branch. As one moves down the cascade additional systems are enlisted depending on the individual's susceptibilities. Various branches of the cascade are responsible for some of the symptomatology of depression. Interventions that act on a single unique downstream target (e.g., a single postsynaptic 5-HT receptor) and efforts to identify subsets in which such selective interventions might be effective are likely to fail.

An intervention at the beginning of the cascade would be expected to have a greater impact than an intervention that acts further down the cascade or at a single branch of the cascade. Thus, the tricyclics and combined 5-HT and NE reuptake inhibitors operating at two possible branches would be expected to have greater activity than an antidepressant that acts at only one path *(182–184)*. Some speculate that a component of the glutamate system, which was intimately involved in responses to stress and modulation of multiple transmitters, could play a role near the start of the cascade. An insult further down the cascade might have significant consequences, but might also be limited in its production of symptomatology. For treatments, mechanisms of action further down the cascade are more likely to benefit a limited group of symptoms although, as noted earlier, there are significant interactions among the many systems involved in depression. Additionally, an adjunctive therapy that acts at additional branches from the primary therapy would be expected to be more effective than an adjunctive medication acting at the same branch as the primary medication.

The molecular basis of the liability to depression including the number of susceptibility and resistance genes involved in the development of depression is unknown *(185)*, but such studies hold additional promise of furthering our understanding of the biology underlying this common illness by breaking out of the cycle of defining and refining our information of the underlying effects based on knowledge of an antidepressant effect. Defining the roles of antidepressant therapy-induced genes in neural plasticity may prove useful in understanding the biological basis of depression *(186,187)*. It is through such technology that the uncovering of triggers of the cascade above the HPA axis and the monoamines will be accomplished.

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2 Clinical Pharmacology and Therapeutics of Antidepressants

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CONTENTS

1. INTRODUCTION

An understanding of the clinical pharmacology of antidepressant agents is essential for optimal prescribing. This chapter outlines general principles that influence prescribing, then discusses specific subgroups of antidepressants. There is no generally accepted classification scheme for antidepressants; current groupings reflect marketing practices, the history of drug development, and pharmacological effects. We use the following terms in our discussion: selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), cyclic antidepressants, mixed action agents, selective norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), and alternative (nontra-

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ditional) antidepressants. Readers should keep in mind, however, that we have chosen a compromise classification system that is based on terms commonly used in clinical settings.

1.1. General Principles

1.1.1. Pharmacokinetics and Pharmacodynamics

Clinicians must be familiar with many concepts to understand the importance of differences in pharmacological characteristics exhibited by various types of antidepressants. These are broadly divided into pharmacokinetic and pharmacodynamic properties. Pharmacokinetics refers to drug absorption, distribution, and elimination. Pharmacodynamics refers to drug actions at the receptor and the cascade of events that follow.

Important clinical pharmacokinetic characteristics to be considered when prescribing a drug involve the presence of active metabolites and the length of time required for a drug to reach its steady state or to be eliminated. Drugs that are eliminated slowly or that have long-acting metabolites may present less of a problem if a patient misses a dose and are less likely to be associated with a discontinuation syndrome. On the other hand, if a toxic effect or drug–drug interaction occurs with such drugs, symptoms will persist after drug administration has ceased.

The clinical importance of pharmacodynamics is illustrated by receptor activities that influence the therapeutic response and the adverse effects profile. Clinicians should be cautious about using in vitro binding studies to make inferences about clinical effects, although in many cases there is a good correlation between receptor-binding activity and adverse effects. The relative potency of various drugs at their receptor sites that mediates an antidepressant response provides a rationale for choosing a specific medication, especially when faced with a poor response to the initial therapy. Table 1 presents transporter-binding data for some commonly used antidepressants and their metabolites.

1.1.2. Practical Aspects of Treatment

Prior to initiating antidepressant treatment, clinicians should be confident that a medical condition or substance use disorder is not the primary cause of the depressed mood. Some medical conditions, such as hypothyroidism, are so common that patients should be routinely screened. Other conditions—such as diabetes, anemia, and vitamin deficiencies (e.g., folate and B_{12})—are less common but easily detected, and should also be ruled out. Some medical illnesses are common but more difficult to diagnose, e.g., autoimmune disorders, fibromyalgia, and chronic pain syndromes; fortunately, mood symptoms associated with these disorders often respond to antidepressants. Cushing's syndrome and polycystic ovary

Table 1. Relative Drug Potencies at Transporters

	Relative Potencies		
	Serotonin Transporters	*Norepinephrine Transporters*	*Dopamine Transporters*
Nefazodone	++	++	–
Hydroxynefazodone	+	+	–
Triazole-dione	–	–	–
mCPP	++	+	–
Trazodone	++	–	–
Amitriptyline	+++	++	–
Desipramine	++	++++	–
Paroxetine	++++	++	–
Sertraline	++++	+	–/+
Citalopram	++++	–	–
Fluoxetine	+++	+	–
Fluvoxamine	+++	+	–
Venlafaxine	++	+	–/+
O-Desmethylvenlafaxine	++	+	–
Chloroimipramine	ND	++++	–
Nortriptyline	++	+++	–
Imipramine	+++	++	–
Norfluoxetine	+++	+	–
Desmethylsertraline	++	+	–

–, none; +/–, uncertain; +, ++, +++, ++++ = weak; mild; moderate, strong;
ND = not determined.
Metabolites are italicized.
Adapted from ref. *1–5*. Readers are encouraged to review these experimental studies to understand how different profiles emerge from various techniques.

disease are also commonly associated with mood disorders. Neurological conditions associated with depression include parkinsonism, multiple sclerosis, cerebrovascular disease and stroke, dementia, and Huntington's disease. An association between depression and infectious disease has been found in patients with HIV and perhaps other viral illnesses. The association between depression and carcinoma is controversial; however, when depression is the presenting complaint, usually additional symptoms provide clues to its etiology (e.g., weight loss, pallor, and fatigue that is worse in the evening). When depression is associated with medical illness, treatment of the underlying disease is paramount, but antidepressants are often also necessary. Superior efficacy has not been established for any particular antidepressant; thus, a reasonable approach is to use a medication that is unlikely to interact with drugs that have been prescribed for the primary illness.

Once the diagnosis of a primary depression is established, it is important to consider the following subtypes: unipolar, bipolar, psychotic features, melancholia (some prefer the term "endogenous"), retarded, agitated, and atypical depressions. As is described in sections that follow, many (but certainly not all) studies indicate that the subtype predicts the response to a specific type of antidepressant therapy.

If the subtype of depression is not considered, then all antidepressants will have approximately equivalent efficacy. In this case, the selection of an antidepressant is based on avoiding certain adverse effects and taking advantage of others. For example, in depressed patients with insomnia, a sedating antidepressant is helpful, but daytime administration should be avoided. Similarly, a highly anticholinergic agent would be a poor first choice in an elderly patient because of the potential for urinary retention and memory problems. With the exception of citalopram, escitalopram, and sertraline, many SSRIs produce clinically significant inhibition of cytochrome P450 (CYP) enzymes and are usually not the first choice for patients who are taking other medications that are metabolized by this system.

Once an antidepressant is selected, a trial of adequate doses for at least 8 wk is recommended *(5a)*. The goal of treatment is a complete response; however, many patients will have only a partial remission of their symptoms. In such cases, it may be necessary to adjust the dosage, add other agents, or switch to a different class of antidepressant. Once a full response is achieved, the decision to continue therapy is based on the natural course of depression. In general, treatment of the depressive episode is continued for at least 1 yr. In cases of recurrent depression, a severe single episode, onset of the first episode before the age of 20 yr, and a family history of serious depression, antidepressant therapy may be continued indefinitely.

2. SELECTIVE SEROTONIN REUPTAKE INHIBITORS

2.1. History

Fluoxetine, the first SSRI, was introduced to the US market in 1988 *(5b)*. Other SSRIs—sertraline, paroxetine, and fluvoxamine—followed closely. Although widely used in Europe for some time, it was not until the late 1990s that citalopram, another SSRI, became available to US clinicians; later its enantiomer, escitalopram, was introduced. By the early 1990s, the SSRIs became first-line antidepressants in clinical practice and accounted for more than half of all antidepressant prescriptions. They enjoyed unprecedented marketing success *(5c)*, had great exposure in popular literature and news, and at first were thought to be in orders of magnitude superior to already existing antidepressant drugs. Indeed, SSRI compounds have a more favorable side-effect profile, simpler dosing strategies,

better tolerability, and, thus, promote better adherence than older antidepressants. Their relative safety in terms of overdose, minimal cardiovascular effects, and lower anticholinergic activity make them especially appealing.

As clinical experience with SSRIs has grown, it has become apparent that they have their own share of adverse effects. Also, the equivalence of SSRI efficacy with that of TCAs has been challenged and still remains a matter of some controversy. Even with these concerns, SSRIs are widely used and are effective in a wide range of psychiatric disorders other than depression, such as anxiety disorders, obsessive–compulsive disorder (OCD), panic disorder, bulimia nervosa, social phobia, posttraumatic stress disorder (PTSD), premenstrual dysphoric syndrome (PMDS), dysthymia, and seasonal affective disorder. SSRIs are the most widely prescribed antidepressants in America and worldwide *(5d)*.

Six SSRIs are available in the United States: citalopram (Celexa®), escitalopram (Lexapro®), fluoxetine (Prozac®), fluvoxamine (Luvox®), paroxetine (Paxil®), and sertraline (Zoloft®). Their chemical structures are shown in Fig. 1. All except fluvoxamine have been approved by the Food and Drug Administration (FDA) for use in depression; fluvoxamine is FDA approved for use in OCD, but not depression *(5e)*. In Europe, however, fluvoxamine has been used as an antidepressant for many years *(6)*. In addition to depression, fluoxetine is approved for use in OCD and bulimia nervosa; paroxetine for OCD, panic disorder, and social phobia; and sertraline for OCD, panic disorder, and PTSD. It is unlikely that these approved indications represent true differences in efficacy among these agents, but rather reflect corporate decisions to pursue various indications. The pharmacokinetic properties and the cytochrome-inhibiting properties of the SSRIs are shown in Tables 2 and 3. Of clinical importance is the fact that fluoxetine, paroxetine, and fluvoxamine do not exhibit linear kinetics or dose proportionality. Thus, as the dose increases, there is not a proportional increase in plasma drug levels because of the autoinduction of enzymes that metabolize these drugs. Citalopram, escitalopram, and sertraline differ in this regard, showing linear kinetics at the usual therapeutic doses.

2.2. Pharmacokinetics

Stereochemistry influences the pharmacological activity and pharmacokinetics of SSRIs. Fluoxetine and citalopram are racemic mixtures of the parent compound *(2,7)*. Although the *S*- and *R*-enantiomers of fluoxetine are approximately equivalent in their ability to inhibit serotonin (5-HT) reuptake, their metabolites—*S*- and *R*-norfluoxetine, respectively—are not. *R*-norfluoxetine is not active in terms of serotonin inhibition, while *S*-norfluoxetine is a more potent serotonin reuptake inhibitor than the parent drug *(8)*. Furthermore, the plasma level of the *S*-enantiomer of norfluoxetine can be twice that of the *R*-enantiomer. *S*-norfluoxetine, but not *R*-norfluoxetine, is metabolized via CYP2D6; therefore

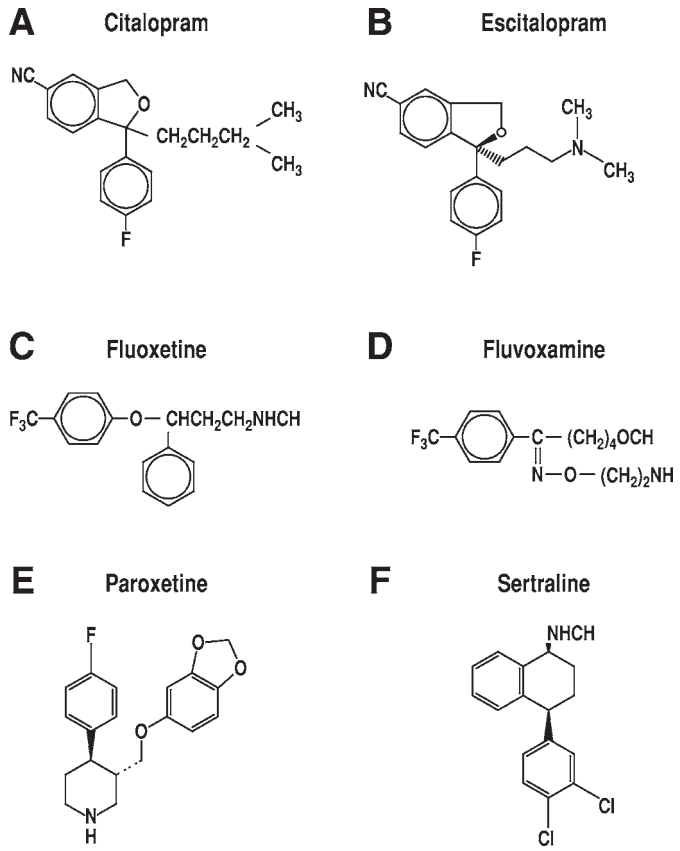

Fig. 1. SSRIs: chemical structures.

individual variations in CYP2D6 or drug interactions have the potential to affect clinical response. Paroxetine and sertraline are marketed as the most serotonergically potent forms of their two isomers. The *S*-enantiomer of citalopram, escitalopram, is its most active form. It is a more potent and a more selective SSRI than citalopram itself *(9)*. These stereochemical differences may be one reason why it has been so difficult to establish therapeutic plasma concentrations for SSRIs and could explain some interindividual differences in antidepressant response and adverse effects.

Another factor influencing the pharmacokinetics of antidepressants is the activity of membrane transport proteins. P-glycoprotein, a member of the adenosine triphosphate-binding cassette family of membrane transport proteins, is an important functional component of the blood–brain barrier (BBB) and intestinal epithelial cells *(10)*. Alterations in P-glycoprotein (P-gp) can thus

Table 2. Pharmacology of SSRIs

	Fluoxetine (Prozac®) (Sarafem®)	*Fluvoxamine (Luvox®)*	*Paroxetine (Paxil®)*	*Sertraline (Zoloft®)*	*Citalopram (Celexa®)*	*Escitalopram (Lexapro®)*
Time to peak plasma level after oral dose	6–8 h	5 h	5 h	4.5–8.4 h	2–4 h	4–5 h
Protein binding	94.5%	77%	93–95%	98%	50%	56%
Elimination half-life	Parent: 1–3 d acute: 4–6 days chronic Metabolite 4–16 days (acute or chronic)	15 h	21 h	26 h (parent) 62–104 hr (metabolite)	33 h	27–50 h (parent) 50–54 (metabolite)
Active metabolite	Norfluoxetine	No	No clinically important metabolites	Desmethyl-sertaline (limited activity	Desmethyl-citalopram	*S*-desmethyl citalopram

Adapted with permission from Ciraulo et al. *(344)*

Table 3. Inhibition of Human Cytochrome P450 by Selected Antidepressants

Cytochrome P450 Enzymes							
	1A2	*2C9*	*2C19*	*2D6*	*2E1*	*3A*	*2B6*
Fluoxetine	+	++	+ to + +	+ + +	——	+	+
Norfluoxetine	+	+ ++	+ to + +	+ + +	——	++	0
Sertraline	+	+	+ to + +	+	——	+	+
Desmethyl-sertraline	+	+	+ to + +	+	——	+	0
Paroxetine	+	+	+	+ + +	——	+	+++
Fluvoxamine	+ + +	+ +	+ + +	+	——	+	+
Citalopram	+	0	0	0	0	0	0
Monodesmethyl-citalopram	0	0	0	+	0	0	0
Escitalopram	0	0	0	+	0	0	0
Nefazodone	0	0	0	0	——	+++	0
Triazole-dione	0	0	0	0	——	+	0
Hydroxy-nefazodone	0	0	0	0	——	+++	0
Venlafaxine	0	0	0	0/+	——	0	0
O-Desmethyl-venlafaxine	0	0	0	0	——	0	0
Mirtazapine	0	0	0	0	0	0	0
Bupropion	0	0	0	++	0	0	+

0, minimal or no inhibition; +, mild inhibition; ++, moderate inhibition; +++, strong inhibition; dash (——), no data available.

Italics indicate a metabolite.

Adapted with permission from Greenblatt et al. *(345)*

affect drug entry into the brain as well as drug bioavailability. Some evidence indicates that paroxetine, fluoxetine, and venlafaxine may be P-gp substrates. Sertraline and paroxetine have the potential to inhibit P-gp activity, but only at concentrations that are 250- to 500-fold higher than those found clinically. In one study, investigators found citalopram brain concentrations to be higher in mice without P-gp activity *(11)*. Nefazodone inhibits P-gp activity in clinically relevant doses *(12)*.

2.3. Dosages (Table 4)

There is no consensus on the optimal dosing of SSRIs. One authority has suggested that adequate trials of SSRIs would consist of at least a 4-wk treatment with either sertraline at least 100 mg/d; fluoxetine, paroxetine, or citalopram at least 20 mg/d; or fluvoxamine at least 100 mg/d *(6)*. We recommend higher doses and an 8-wk trial *(13)*; however, some improvement should be seen after 2 to 3 wk. If the severity of depression remains unchanged after 4 wk, it is unlikely that an additional 2 wk of treatment with the same drug will be successful. Unfortunately, plasma levels do not appear helpful in guiding dosage; therapeutic plasma levels have not been established for any SSRI.

2.4. Mechanism of Action

Prevailing theories on the mechanism of action of antidepressant agents center around their aminergic effects, despite recent data suggesting other mechanisms may be important (*see* Chapter 1). All SSRIs, although structurally different, have the same mechanisms of action: as the name implies, these compounds selectively inhibit the serotonin reuptake transporter (SERT) *(14)*. Although the degree of selectivity varies with the in vitro model used, all of these agents are potent inhibitors of the SERT. Paroxetine may have a relatively greater inhibitory potential at the norepinephrine (NE) transporter and sertraline at the dopamine (DA) transporter, based on in vitro studies; additionally fluoxetine may be a 5-HT_{2C} agonist. The clinical implications of these differences have not been established, however *(15)*. Further complicating matters is the presence of heteroreceptors—5-HT receptors that modulate activity through their location on neurons associated with dopaminergic and noradrenergic actions. Thus, there is great danger in assuming that in vitro binding studies will provide a reliable guide to clinical differences between SSRIs. As with other antidepressants, the onset of full antidepressant activity with SSRIs is usually delayed for weeks.

Acute administration of SSRIs inhibits the SERT on the presynaptic serotonin neuron, resulting in an increased concentration of serotonin around the somatodendritic area of the neuron and to a lesser degree in the synapse itself (*see* Fig. 2) *(16)*. Early effects on serotonin probably account for adverse effects, whereas therapeutic actions depend on subsequent neuronal events. It is only

Table 4. SSRI Doses *(5,6)*

SSRI	*Dose Range (mg/d)*	*Initial Dose (mg)*	*Usual Range (mg)*	*Available Formulations*
Citalopram	10–80	10–20	20–40	Tabs: 20, 40 mg Oral solution: 10 mg/5mL
Escitalopram	10–20	10	10	Tabs: 10, 20 mg
Fluoxetine	10–80	10–20	20–60	Caps: 10, 20, 40 mg*; Tabs: 10 mg; Oral solution 20 mg/5mL
Fluvoxamine	50–300	25–50	150–200	Tabs: 25, 50, 100 mg
Paroxetine	10–50	10–25	20–50	Tabs: 10, 20, 30, 40 mg; Controlled Release 12.5 mg, 25 mg, 37.5 mg Oral suspension 10 mg/5mL
Sertraline	50–200	25–50	100–200	Tabs 25, 50, 100 mg Oral concentrate 20 mg/mL

*Fluoxetine is now available as a "Prozac® Weekly™." The formulation is a delayed release, enteric-coated capsule containing 90 mg; it was calculated to achieve a blood concentration equivalent to a standard daily dose of 10 to 20 mg. The new formulation has been shown to be as effective an antidepressant as daily doses of fluoxetine 20 mg, with similar adverse effects and similar tolerability *(346–348)*. Adherence to the dosing schedule for patients on Prozac Weekly is a bit higher than daily dosing: 87.5% and 79 to 85% patients on daily dosing, respectively; however, the difference appears to be modest *(346,348,349)*. Because fluoxetine and norfluoxetine have long elimination half-lives, occasional nonadherence or skipping a dose is rarely clinically significant with the standard formulation.

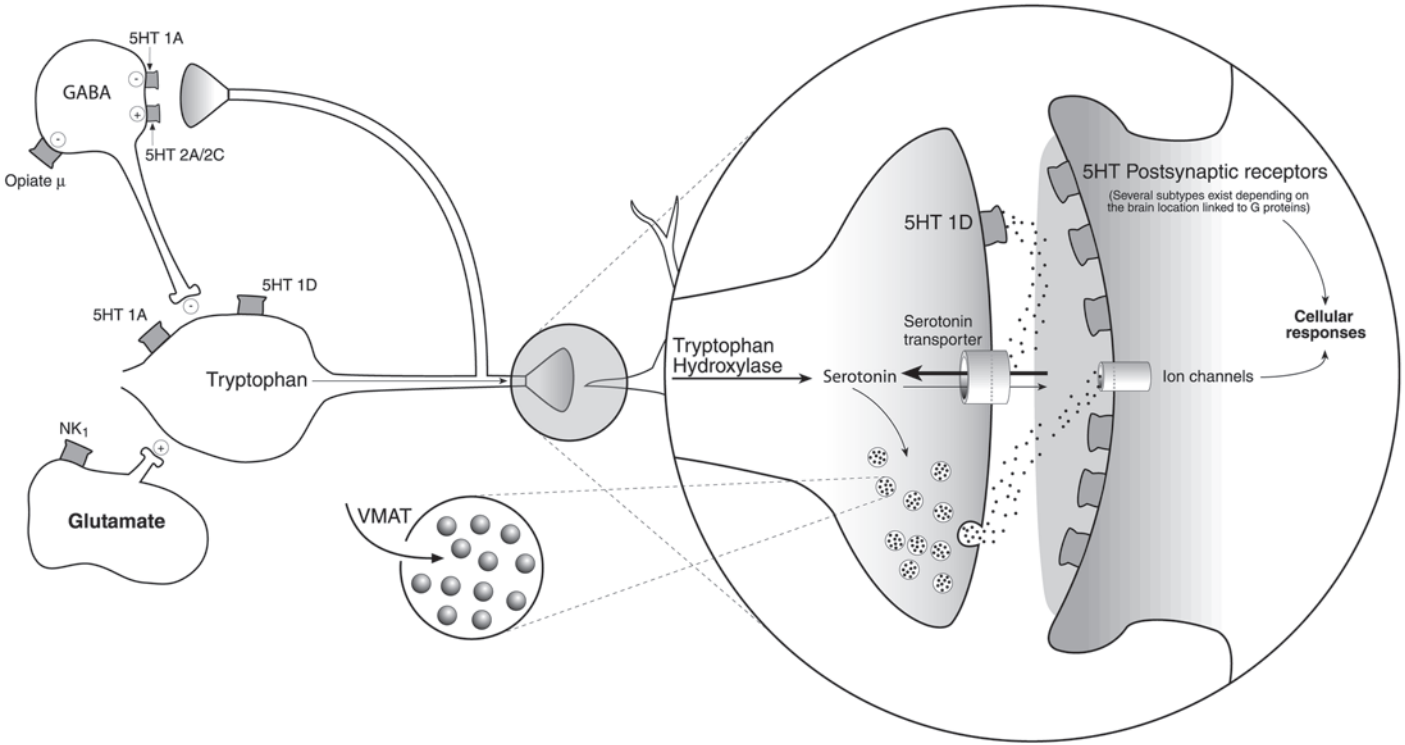

Fig. 2. Artist's rendition of the serotonin neuron emphasizing the potential influences on neuronal activity. The expanded synapse has been adapted with permission from ref. *352*. Abbreviations: 5HT followed by numerals and letters represents different subtypes of serotonin receptors. GABA is γ-aminobutyric acid, an inhibitory neurotransmitter. NK_1 represents neurokinin receptors that activate glutamatergic excitatory neurons. VMAT is the vesicular monoamine transporter that acts to store serotonin in presynaptic storage vesicles. + indicates excitatory input. – indicates inhibition. This figure demonstrates the complex interplay of many neurotransmitter systems with the serotonin neuron.

after some time of continuous SSRI administration (usually ≥2 wk) that the lasting high concentrations of 5-HT in the somatodendritic area of the neuron cause desensitization of a specific subtype of 5-HT autorecptor—the somatodendritic 5-HT_{1A} autoreceptor—which is responsible for inhibiting the release of 5-HT. (It is not clear whether desensitization of the terminal 5-HT_{1A} receptor also occurs.) The result is an increase in the amount of 5-HT within the synapse and desensitization of postsynaptic 5-HT receptors. Additionally, various SSRIs and other types of antidepressants interact differently with 5-HT receptor subtypes. The existence of 5-HT receptor isoforms is also likely, further complicating our understanding of how these drugs exert their antidepressant effect. Downstream activity that affects signal transduction and gene expression is likely to be responsible for the actual therapeutic action and delayed onset of activity, linking the aminergic changes to other mechanisms such as synthesis of brain-derived neurotrophic factor (BDNF).

Some evidence suggests that a loss of SERT binding sites occurs with long-term SSRI administration *(17)*. This occurs only after 10 to 15 d of drug exposure, the time frame of antidepressant response. Recent theories have been proposed to expand the mechanism of antidepressant response to include signal transduction pathways. One such model is based on the belief that antidepressants decrease the activity of protein kinase C (PKC), which catalyzes phosphorylation, thereby directly affecting the SERT or 5-HT receptors or both. Other studies support a role for activation of protein kinase A (PKA) and calcium-calmodulin-dependent protein kinase II (CaMKII). PKA-mediated phosphorylation results in changes in neurotransmission and gene expression. CaMKII, also through the process of phosphorylation, may facilitate neurotransmitter activity. Phosphorylation of cAMP response element binding protein influences gene expression, e.g., the genes responsible for BDNF and its receptor, trkB. Because BDNF is able to promote neurogenesis, it may reverse neuronal atrophy in the brain, believed by some to be the fundamental pathology of depression.

The role of 5-HT_{1A}-receptor desensitization in the SSRI antidepressant response has been examined in studies of pindolol, a β-adrenergic blocker that also antagonizes the 5-HT_{1A} autoreceptor and has been studied extensively as a possible SSRI-augmenting strategy *(18–23)*. It has been hypothesized that pindolol, used concomitantly with an SSRI, can block presynaptic somatodendritic 5-HT_{1A} autoreceptors in the dorsal raphe nucleus more rapidly than an SSRI alone.

Clinical studies are contradictory, complicated by the variability in 5-HT_{1A} blockade observed for the SSRIs, low doses of pindolol, and study design differences. Doses of pindolol that have been used in these studies do not produce complete blockade of the receptor *(24)*. Additionally, genetic polymorphism of the 5-HT_{1A} receptor *(25,26)* and the mixed enantiomer formulations of pindolol complicate the interpretation of existing studies *(27)*. In some studies, pindolol aug-

mented the antidepressant effect of concomitantly administered SSRIs and shortened the time necessary to achieve a full therapeutic response *(18,19,21,28,29)*.

Early open trials were followed by double-blind, placebo-controlled studies. In a French study of pindolol 5 mg three times a day [tid] augmentation of paroxetine, investigators found that the addition of pindolol to paroxetine hastened the antidepressant effect: Hamilton Rating Scale for Depression (HAM-D) scores were significantly lower on days 5 and 10 in the pindolol/paroxetine group compared with the paroxetine/placebo group *(29)*. Also, a statistically significant increase in the proportion of patients who demonstrated improvement (defined by a HAM-D score ≤10 in patients with a pretreatment score ≥18 at the initiation of the study) was found in the pindolol/paroxetine group by day 10 of treatment *(29)*. The rates of response converged by day 15 of treatment, however.

In another study *(21)*, significantly higher response rates were observed in the fluoxetine/pindolol group (75%) compared with the fluoxetine/placebo group (59%). The number of days to reach a sustained response was also lower for the fluoxetine/pindolol group ($n = 19$) compared with the fluoxetine-placebo group ($n = 29$). However, the lag time to onset of therapeutic response was the similar in both groups (15 vs 18 d) *(21)*.

These findings have not been replicated in other studies, however *(20,22,23)*. In a double-blind, placebo-controlled clinical trial of fluoxetine augmented by pindolol (2.5 or 5.0 mg tid), the onset of the antidepressant response, average time to remission, and overall response were not significantly different between treatment groups *(20)*. In another double-blind trial of 34 in-patients with major depressive disorder (MDD), including patients with treatment-resistant MDD, investigators also failed to find any acceleration in therapeutic response to fluoxetine/pindolol (2.5 mg tid), as evidenced by a lack of a significant difference in HAM-D score reduction between groups at week 1 of treatment *(22)*. This study, however, did find a significantly higher response rate in the fluoxetine/pindolol group (60%) compared with fluoxetine group (9%); the outcome measure was 50% reduction in the HAM-D score *(22)*.

Attempts have been made to link SSRI effects to receptor subtype activity along specific 5-HT brain pathways. Although speculative, one model suggests that activation/disinhibition of the serotonergic pathway from the midbrain raphe to the prefrontal cortex may be responsible for the antidepressant effects of SSRIs, along the pathway to the basal ganglia for their effects on OCD, the pathway to the limbic cortex and hippocampus for their effects on panic disorders, and the pathway to the hypothalamus for their effects on eating disorders *(30,31)*.

Somewhat stronger data suggest that certain receptor subtypes contribute to the adverse effects of SSRIs, e.g., 5-HT_3 receptors for gastrointestinal (GI) discomfort; the role of other subtypes remains uncertain, however. Generally, in vitro studies indicate that SSRIs have very low affinity for other neuroreceptors,

including the α, histaminic, and muscarinic receptors; this is consistent with their adverse-effect profile *(5b,14)*.

Paroxetine is the only SSRI antidepressant shown to inhibit NE uptake. In a study comparing NE and 5-HT transporter functions in human transporter transfected cells in serum obtained from patients assigned to either desipramine or paroxetine, *(15)* investigators found that both drugs acted as mixed 5-HT/NE uptake inhibitors, especially at paroxetine doses of 40 mg or more. Sertraline is the only SSRI to show DA reuptake inhibition in in vitro models. These data suggest that the SSRIs are not homogeneous in their mechanisms of action and may explain the well-known clinical observation that switching nonresponsive patients to a different SSRI may yield positive results.

2.5. Drug Interactions/P450 Metabolism

SSRIs are metabolized predominantly by the hepatic CYP450 system and may inhibit their own metabolism or that of other drugs (Table 3). The SSRIs sertraline and citalopram interact minimally with the CYP system; this quality makes them the antidepressants of choice for medically ill patients who require coadministration of an SSRI with other medications.

The inhibitory action of SSRIs may give rise to multiple drug–drug interactions when they are coadministered with other medications; these interactions may have no effect or may lead to intoxication or even improve the therapeutic response to another drug by causing its plasma concentration to rise. Generally, SSRIs that inhibit the CYP450 system impair the metabolism of other medications (P450 enzyme substrates), thereby prolonging their elimination half-life and increasing their blood level. For example, the SSRI inhibition of cytochrome P450 activity may lead to elevated levels of concurrently administered TCAs, which are metabolized by CYP2D6 and CYP3A4 isoenzymes *(32)*. This may result in side effects, but may also permit clinicians to use a low-dose TCA to augment or potentiate the SSRI. Citalopram does not alter TCA levels *(32)*. On the other hand, fluvoxamine inhibits the CYP1A2 isoenzyme and can result in toxic levels of medications that are usually metabolized by this isoenzyme, namely tacrine, warfarin, theophylline, propranolol, and many others.

Because SSRIs are also substrates for the hepatic cytochrome system, medications such as carbamazepine, rifampin, dexamethasone—which induce CYP450 isoenzyme activity—accelerate SSRI metabolism when coadministered with this class of drugs. Medications such as quinidine, cimetidine, and diltiazem inhibit the CYP450 system; thus, coadministration will delay SSRI clearance and may result in toxic levels of SSRI in the blood *(6,33,34)*. Comprehensive lists of drug interactions involving SSRI antidepressants can be accessed through

http://www.drugfactsandcomparisons.com, *The Medical Letter: Adverse Drug Interactions Program,* and other computer databases *(7,33–37)*.

2.6. Adverse Effects

2.6.1. Overview

Although generally well tolerated, SSRIs may produce anxiety, sleep disturbances, and GI discomfort, especially at the initiation of therapy. These symptoms can usually be managed by lowering the dose, slowing the rate of dose escalation, or temporarily treating the target symptom (e.g., ondansetron for nausea or lorazepam for insomnia). More troublesome and persistent are sexual adverse effects, including anorgasmia, decreased libido, ejaculation disturbances, and erectile dysfunction. Transient adverse effects are likely to be the result of acute stimulation of postsynaptic 5-HT receptors, although efforts to link these symptoms to specific receptor subtypes have been speculative. Table 5 lists common adverse effects associated with SSRIs and suggested methods of clinical management.

2.6.2. GI Adverse Effects

The most common GI adverse effect experienced by patients who take SSRIs is nausea, which occurs in 15 to 35% of these patients *(38,39)*. Some of these patients may also experience vomiting, diarrhea, or both *(5e)*. These symptoms tend to decrease over time, in most cases after a few weeks of treatment. For some patients, they may be quite troublesome and interfere with adherence. If lowering the dose is unsuccessful in resolving these symptoms, we recommend symptom-specific therapy. Ondansetron and other 5-HT_3 blockers (e.g., mirtazapine) are very effective for nausea, ranitidine may be helpful for dyspepsia; and loperamide may be used to reduce diarrhea. Occasionally, a medication change is required. For example, if diarrhea is problematic, changing the medication to paroxetine may be helpful.

Very rare cases of hepatotoxicity, in the form of either cholestatic or hepatocellular injury, have been reported with fluoxetine, sertraline, and paroxetine *(40–42)*. The incidence of such cases is quite low; sertraline, for example, has been associated with hepatotoxicity at a rate of 1.28 cases per 100,000 patient-years *(42)*.

2.6.3. Central Nervous System (CNS)

Both tension headaches and migraines have been reported to worsen when patients start taking SSRIs *(5e)*, although improvement has also been noted.

In some cases, headaches tend to increase in frequency over time *(39)*. Both sedation and insomnia are known to occur, especially at the initiation of treatment, although this varies somewhat with the SSRI. Some patients report an increase in dreaming, vivid dreams, and nightmares. Some authorities believe

Table 5. Common Adverse Effects Associated With SSRIs

Symptom	*Approximate Incidence in Clinical Practice*	*Management*
Headache	Common initially, especially with fluoxetine	Dose reduction, slow/stop dose increases, NSAIDS, or change to another antidepressant
Nervousness	Common initially, highest with fluoxetine, sertraline, but can occur with others	Dose reduction, slow/stop dose increases, lorazepam, or change to another antidepressant
Insomnia	Less common with paroxetine	Dose reduction, slow/stop dose increases, add lorazepam or sedative antidepressant, or change to another antidepressant
Drowsiness	More common with paroxetine	Dose reduction, slow/stop dose increases; some clinicians recommend adding temporary stimulant (methylphenidate)
Nausea	Common for all agents generally at initiation of therapy	Antiemetic agents (5-HT_3 blockers such as ondansetron are preferred by some clinicians) or mirtazapine
Sexual dysfunction	30–60%; paroxetine slightly higher than others, but difference probably not clinically significant	Dose reduction, slow/stop dose increases, sildenafil (Viagra), or change to another antidepressant, bupropion, nefazodone
Anorexia	Only early in treatment	Time limited
Dizzy/lightheaded	5–10%, fluoxetine at low end	Dose reduction, slow/stop dose increases, or change to another antidepressant
Tremor	Common early in treatment for all agents	Dose reduction, slow/stop dose increases, or change to another antidepressant
Diarrhea	More common with sertraline and less common with paroxetine	Dosage reduction, slow/stop dose increases, loperamide, add low dose of an anticholinergic antidepressant, or change to another antidepressant
Constipation	Most common with paroxetine	Dosage reduction, slow/stop dose increases, temporary laxatives/stool softener, or change antidepressant

that fluoxetine causes the highest incidence of insomnia, nervousness, restlessness, and anxiety *(38)*.

Tremors, increased anxiety, anger attacks, and akathisia have been observed with SSRI treatment in a small proportion of patients *(43,44)*. In general, the incidence of extrapyramidal symptoms (EPS)—such as parkinsonism, dystonia, and akathisia—is quite low, but does occur *(43,45)*.

SSRIs may induce a switch to mania, with rates estimated as high as 10 to 20% by some experts *(6)*, but under 5% by most others *(46)*. In one report, bipolar patients switched to a manic state at a rate of 4% while taking placebo; it has been estimated to occur at a rate of 11% in patients taking TCAs *(46)*. Evidence for the induction of mania or hypomania in patients with unipolar depression has been mostly anecdotal; the rate of manic switch in these patients is estimated at less than 1% *(46)*. Some believe that antidepressant-induced manic episodes are generally milder and of shorter duration than the spontaneous manic episodes experienced by bipolar patients *(47)*.

Behavioral toxicity may also occur with SSRIs. The "apathy syndrome" may occur in patients who have been treated successfully for depression but develop a loss of motivation, passivity, and lethargy, a condition often described by patients as "flatness." This condition can be distinguished from the depressive state by a lack of prevailing sadness and tearfulness, decreased concentration, a sense of hopelessness and/or helplessness, and suicidality. The recommendation for these patients is a decrease in the SSRI dose, addition of a stimulant, or both.

2.6.4. Suicidality

Reports of treatment-emergent suicidal ideation in patients being treated with fluoxetine began to appear during the early 1990s *(48)*. Subsequent studies, however, did not confirm a greater risk of *de novo* suicidal ideation in patients being treated with an SSRI. A study of more than 1000 outpatients in Boston centers failed to find a relationship between increased suicidality and fluoxetine treatment *(49)*. A meta-analysis of 17 double-blind studies comparing fluoxetine, TCAs, and placebo in 3065 patients with major depression failed to detect an increased risk for the emergence of suicidal ideation with fluoxetine compared with either placebo TCAs; moreover, suicidal ideation was found significantly less often in patients taking fluoxetine than in patients taking a placebo *(50)*. A recent study concluded that although a small percentage of patients experienced increased anxiety, anger attacks, and akathisia during SSRI therapy, there was no evidence of a direct link between SSRI use and violent or suicidal behavior *(44)*. Recent reports and litigation have claimed an association between suicidal ideation and paroxetine, however, especially in children. At the present time, the FDA is reviewing website advises against the use of paroxetine and children with MDD and its association with suicidal ideation. Fluoxetine is currently the only drug approved by the FDA for use in Pediatric MDD.

Some clinicians remain convinced of such an association, even if it is extremely uncommon. According to some practitioners, the rare case of suicidal ideation can be explained by the adverse somatic effects of the SSRI. One possible mechanism that has been proposed is the excitatory properties of SSRIs, which may energize some patients to act on preexisting suicidal plans *(51)*. It has also been suggested by some that SSRIs induce akathisia and severe insomnia, which are associated with self-destructive or aggressive impulses *(51)*. The emergence of akathisia-like effects may trigger suicidal thoughts or impulses, especially in susceptible patients *(52)*.

It has been noted that the association between SSRIs and suicidality, even if it truly exists, may be lost in larger epidemiological studies *(51)*. Furthermore, most clinical trials exclude suicidal patients from participation, thus undermining the possibility of generalizing from pooled data analyses *(51)*. In any event, the findings do not alter the usual clinical practice of monitoring all depressed patients closely for the emergence of suicidal ideation, especially early in treatment.

2.6.5. Serotonin Syndrome

Serotonin syndrome is a potentially fatal condition resulting from excessive serotonergic activity, usually as a result of the coadministration of medications with similar mechanisms of action. It can occur when an SSRI is combined with an MAOI *(53)* or with another type of drug that increases central serotonergic activity, such as another SSRI, another antidepressant—especially clomipramine, but also nefazodone, venlafaxine, trazodone, amitriptyline, and imipramine—and other drugs, such as tramadol, meperidine, amphetamine, cocaine, and tryptophan *(54)*. Unfortunately, this syndrome is often not recognized in a timely manner owing to its varied and nonspecific symptoms *(54)*. Diagnostic criteria for serotonin syndrome were proposed by Sternbach *(53)*. In general, patients with serotonin syndrome will present with cognitive changes (e.g., confusion and disorientation) behavioral changes (e.g., agitation or restlessness), neuromuscular problems (e.g., ataxia, hyperreflexia, and myoclonus), and/or autonomic dysfunction (e.g., fever, shivering, diaphoresis, or diarrhea) *(53)*.

Some have suggested more stringent criteria that require a triad of pyrexia, neuromuscular symptoms, and mental status changes *(54)*. Fatalities have been associated with this syndrome *(5,53,54)*. Therapy for serotonin syndrome consists of discontinuation of the offending agent and supportive patient care. Dantrolene and bromocriptine have been used, with mixed results.

It should be noted that even reversible MAOIs such as moclobemide can produce serotonin syndrome when administered with an SSRI (e.g., citalopram) *(55)*. This syndrome may also occur as a result of pharmacokinetic drug–drug interactions. Five suspected cases of serotonin syndrome were reported in HIV-

infected patients taking fluoxetine concomitantly with antiretroviral therapy (protease inhibitors and non-nucleoside reverse transcriptase inhibitors) *(56)*. The symptoms were attributed to the inhibition of the P450 enzymes by the antiretroviral drugs and the resultant elevation of SSRI blood levels, which, in turn, resulted in an enhanced serotonergic tone. The patients recovered completely after SSRIs were stopped or their doses adjusted.

2.6.6. Endocrine System

The endocrine effects of SSRIs are still not fully elucidated. This picture is complicated by neuroendocrine disturbances in depression. It has been postulated that activity in the hypothalamus–pituitary–adrenal (HPA) axis is enhanced in depressed patients, possibly in an attempt to normalize neuroendocrine function *(57)*. Plasma levels of adrenocorticotropic hormone (ACTH) were reduced in these patients, but cortisol and vasopressin remained at the same levels during treatment with fluoxetine *(58)*. A possible explanation for these findings in depressed patients is that SSRIs can restore the negative feedback effect of glucocorticoid on ACTH levels and return the HPA axis to its normal state *(58)*.

Rarely, SSRIs can cause the syndrome of inappropriate antidiuretic hormone secretion (SIADH) *(6)*. Citalopram, for example, has been implicated in seven cases of SIADH. One such case was recently reported in an 87-yr-old man with PTSD; it occurred a week after his citalopram dose was increased from 10 to 20 mg per day *(59)*. The risk of developing the syndrome seems to be related to increasing age, female sex, concomitant use of hyponatremia-inducing medications, and increasing SSRI doses *(59)*. SSRIs have also been reported to produce galactorrhea and increased prolactin levels *(5e)*.

Weight loss may occur in patients initiating fluoxetine therapy *(60,61)*; but these effects are transient (with a possible exception in some elderly patients). Fluoxetine, as well as paroxetine and citalopram, has actually been known to cause weight gain in patients during long-term therapy *(61,62)*. The rate of significant weight gain (defined as a 7% increase in weight from baseline) during long-term therapy has been estimated at 6.8% for fluoxetine and 4.2% for sertraline. Paroxetine may be associated with the greatest weight gain, estimated at 25.5% *(62)*. Topiramate is sometimes added to therapy with these drugs to reduce weight; however, clinicians should be aware that topiramate may cause hyperchloremic, non-anion gap metabolic acidosis (decreased serum bicarbonate).

2.6.7. Hematologic Effects

There have been some reports of serotonergically mediated platelet dysfunction and abnormal bleeding associated with SSRIs *(63)*. This effect appears to be rare and more likely to occur with high doses of SSRIs. A cause-and-effect relationship is yet to be established *(6)*.

2.6.8. Sexual Effects

Among the sexual side effects most commonly associated with SSRIs are decreased or absent libido, difficulty with sexual arousal, erectile dysfunction, delayed ejaculation, painful orgasm, and anorgasmia *(64–68)*. These effects appear to be dose related *(69)*. Most experts agree that SSRIs cause significantly more sexual dysfunction than either TCAs or MAOIs *(65)*. Studies differ regarding the incidence of these effects. For example, the percentage of patients who develop anorgasmia while taking fluoxetine has been reported from 8.3 *(70)* to 75% *(71)*. A recent review article concluded that 30 to 40% of patients on an SSRI will experience some degree of sexual dysfunction *(72)*. A well-designed multicenter prospective study of 344 patients of both sexes found that the frequency of adverse sexual effects was highest on paroxetine (65%), followed by fluvoxamine (59%), sertraline (56%), and fluoxetine (54%) *(69)*. None of the patients in this study had sexual problems prior to initiating SSRI antidepressant therapy, a medical illness, or additional psychiatric disorders. Systematic inquiry by a physician was used to identify sexual dysfunction; this approach was somewhat limited, however, by a lack of randomization to treatment and concurrent medications.

The frequency of SSRI-induced sexual dysfunction is still unknown; however, it is significantly higher than previously reported in premarketing studies and in product labeling of the SSRI *(66,67)*. A possible explanation for this underestimation may be a result of the lack of a structured assessment of sexual dysfunction *(67)*, as well as to underreporting by patients *(65)*.

SSRI-induced sexual dysfunction is a serious problem that often leads to drug discontinuation if it is not properly managed. Several approaches to management are available, including dose reduction, waiting for tolerance to develop, switching to a different antidepressant, a drug holiday, or the addition of other medications *(68)*. Medications that have been studied include α_2-adrenergic antagonist yohimbine, nefazodone, the 5-HT antagonist cyproheptadine, granisetron, mirtazapine, amantadine and pramipexole, methylphenidate, buproprion, the herb ginko biloba, vardenafil, and sildenafil *(65,67,68)*.

Sildenafil citrate has been the most effective agent for the treatment of SSRI-induced sexual dysfunction. In a small open study of sildenafil, investigators found improvement in patients who experienced erectile dysfunction during antidepressant therapy *(73)*. In another open-label trial of 10 female patients who had developed sexual dysfunction as a result of ongoing antidepressant therapy, investigators reported that all patients who took sildenafil as instructed experienced a "complete or very significant reversal" of their sexual dysfunction *(74)*. Finally, in a very recent review of sildenafil efficacy in erectile dysfunction, the results of three randomized, placebo-controlled trials and data from 10 earlier

clinical trials were analyzed *(75)*, and the authors concluded that sildenafil is an effective first-line treatment for either SSRI-induced or depression-related erectile dysfunction. Related agents, such as vardenafil, are also effective.

Another strategy for the management of sexual dysfunction is the addition of or switch to bupropion *(76)*. Some also recommend a weekend drug holiday of 3 d duration (Thursday noon to Sunday noon); this was shown to improve sexual functioning in 30 outpatients who were maintained on an SSRI after recovering from a depressive episode and who had experienced SSRI-induced sexual dysfunction *(77)*. None of the patients experienced a return of depressive symptoms, nor did the mean HAM-D scores increase after the SSRI holiday. Patients who were taking sertraline and paroxetine reported improvement; but patients taking fluoxetine reported no change, which may be associated with the long half life of this drug and its metabolite *(77)*. At the present time, we recommend periodic use of 50 to 100 mg sildenafil (Viagra®) 2.5 to 20 mg vardenafil (Levitra®), or 5 to 20mg tadalafil (Cialis®) as needed to treat SSRI-induced sexual dysfunction.

2.6.9. SSRI Discontinuation/Withdrawal Syndrome

Serotonin withdrawal syndrome, also known as SSRI discontinuation syndrome, can develop when an SSRI is stopped abruptly after long-term use. The symptoms are "flu-like"—patients describe nausea, diarrhea, general malaise, myalgias and paresthesias, dizziness, vertigo, headache, and insomnia *(78,79)*. Vivid dreams, anxiety, and irritability may also be present *(5e)*. The criteria proposed for the diagnosis of SSRI discontinuation syndrome require two or more of the following symptoms developing within 1 to 7 d of discontinuing or reducing the dose of an SSRI after at least 1 mo of therapy that are not accounted for by medical illness: dizziness, lightheadedness, vertigo, paresthesia, anxiety, diarrhea, fatigue, gait instability, headache, insomnia, irritability, nausea or emesis, tremors, and visual disturbances *(79)*.

The syndrome was first noted with paroxetine *(80)*; however, all antidepressants are now known to produce it if the medication is not tapered gradually. Fluoxetine, whose active metabolite has a long half-life, was at first thought to be free of this effect owing to a presumed self-tapering of serum levels; however, the syndrome may still appear after long-term fluoxetine therapy. It had been reported that withdrawal symptoms occur an average of 6.4 d after fluoxetine discontinuation compared with 2 to 4 d after discontinuation of fluvoxamine, sertraline, or paroxetine *(5b)*. In our experience, it has been much less common and not as severe with fluoxetine as with other SSRIs, such as paroxetine. The only treatment for the SSRI discontinuation syndrome is drug reinstitution and then gradual tapering of the offending antidepressant *(78)*.

2.7. Safety

2.7.1. Safety in Overdose

SSRIs are perhaps the safest antidepressants on the market with respect to the risk for overdose, owing to a very high therapeutic index *(5d,39)*. In a recent study of SSRI overdose cases analyzed published cases, data from the American Association of Poison Control Centers, and reports to the FDA adverse event database *(81)*, investigators concluded that SSRI antidepressants were far safer than the TCAs in terms of risk for overdose and that there was no difference among SSRIs with respect to morbidity or mortality. In general, mild to moderate overdose cases in which the individual took up to 30 times the usual daily dose were asymptomatic or associated with mild symptoms and the patients recovered fully without sequelae. Larger overdoses—up to 75 times the prescribed daily dose—were associated with drowsiness, tremor, nausea, and vomiting. More serious consequences—including seizures and electrocardiogram (ECG) changes—were associated with the largest overdoses, and fatalities have occurred with doses exceeding 150 times the usual daily dose. Almost all fatalities occurred in patients who took SSRIs and other substances, usually alcohol, benzodiazepines, or other drugs *(81)*.

The reporting of overdoses has been sporadic, making it impossible to accurately calculate the true incidence of morbidity and mortality. More data are available on fluoxetine and citalopram because they have been in clinical use for a relatively long time. Some evidence has suggested greater toxicity with an overdose of citalopram compared with that of other SSRIs. Six fatalities resulting from a citalopram overdose have been reported *(82)*; however, as was pointed out by Glassman *(83)*, five of the reported deaths occurred in individuals who took citalopram with either alcohol or sedative drugs and the amounts of drugs ingested were quite high. In the only reported case of overdose with citalopram taken alone, the patient took 4000 mg of the drug, which, at the usual daily dose of 20 mg, represents a 6-mo supply. On the other hand, the didemethyl metabolite of citalopram, which has demonstrated cardiotoxicity in animals, may reach high enough levels in an overdose to cause morbidity.

2.7.2. Safety in Pregnancy and Lactation

SSRIs are unique among antidepressants, in that some may be safe for use during pregnancy and lactation. A prospective multicenter controlled cohort study of the risk of SSRI-induced teratogenicity involved the infants of 267 women exposed to SSRIs (fluvoxamine, paroxetine, and sertraline) during pregnancy and

infants of 267 controls *(84)*. Investigators did not find an increased risk for major malformations or higher rates of miscarriage, stillbirth, or prematurity in infants born to mothers treated with SSRIs during pregnancy, nor did they detect any differences in birth weights or gestational age at delivery between the two groups.

To assess the long-term effects of SSRIs on infant development, Nulman and associates *(85)* prospectively studied a cohort of Canadian women, 80 of whom took TCAs during pregnancy, 55 fluoxetine, and 84 control subjects who did not take any agent known to affect a fetus. They detected no differences between children born to the antidepressant-exposed women vs controls with respect to IQ, language development, or behavioral development at 16 and 86 mo.

The authors concluded that *in utero* exposure to either TCAs or fluoxetine did not affect the neurodevelopment of the child. A more recent study by the same authors supported their earlier finding; neither TCAs nor fluoxetine taken throughout gestation affected IQ, language, or temperament in the child *(86)*. For more on this topic, *see* Chapter 8.

2.8. Efficacy

As a class, the SSRIs have been proven effective in a wide range of psychiatric disorders; mood disorders, including dysthymia *(87)*, OCD *(88,89)*, panic disorder *(90)*, social phobia *(91–93)*, eating disorders *(94)*, PMDD *(95)*, and generalized anxiety disorder *(96)*.

In his review article of available pharmacological treatments for PTSD, Davidson cites evidence from large, long-term clinical trials of SSRI antidepressant efficacy in patients with this disorder *(97)*. In individuals with chronic PTSD, we have found that the combination of SSRI and atypical antipsychotic has the best effects (*see* also Chapter 9).

A recent review found fluoxetine to be effective for depression associated with a medical illness. Fluoxetine proved to be significantly better than placebo in the treatment of depression in patients with HIV/AIDS, diabetes mellitus, or stroke *(98)*. The long half-life of fluoxetine and norfluoxetine, as well as their potential for interactions with other medications via P450 isoenzyme activity, may limit their usefulness in medically ill patients. Sertraline and escitalopram appear to be better choices for the medically ill, owing to a lower likelihood of pharmacokinetic interactions *(99)*.

SSRIs are currently being studied for their potential in treating individuals with subtypes of alcohol dependence, based on early and late onset of alcoholism and current or past depression (*see also* Chapter 6) *(100,101)*. At present, there are no widely accepted typologies that can be used to predict SSRI response in alcohol-dependent subjects.

Equivalent efficacy between SSRIs and TCAs is a matter of some debate. In a meta-analysis of approx 300 double-blind, randomized, controlled clinical trials, researchers found that most antidepressants are similar in efficacy and that MAOIs, SSRIs, and TCAs all have response rates of 60 to 68%, as defined by a 50% improvement in the HAM-D or the Montgomery-Asberg Depression Rating Scale (MADRS) score *(102)*. These findings concur with those of another study, in which SSRIs were deemed to be no more efficacious or faster acting than TCAs in patients with MDD *(38)*. In another study, fluoxetine appeared to be no better than imipramine for treatment of atypical depression *(103)*. These results held true in many reviews of specific SSRIs and in other studies *(39,104)*. In one study, investigators found that sertraline, but not other SSRIs, was as effective as TCAs in patients with melancholic depression *(105)*, although this remains a controversial issue. In a 1-yr, double-blind study of suicidal behavior in patients with a history of repeated suicide attempts, investigators found that paroxetine significantly reduced suicidal behavior *(106)*, although the issue of suicidality remains controversial. Others have questioned the equivalency of SSRIs and TCAs (*see* discussion on TCAs).

SSRIs may lose their efficacy during maintenance therapy. In a recent study, investigators found a return of depressive symptoms in 9 to 57% of patients during maintenance therapy; most of these patients had been treated with an SSRI *(107)*. In another double-blind study, researchers reported a relapse into depression in 26 of 77 patients taking a maintenance dose of 20 mg of fluoxetine per day *(108)*. In these cases, it is recommended to increase the dose, switch to a different class of antidepressant, or add an augmenting agent to the regimen.

To summarize, the SSRI antidepressants remain the first-line treatment for major depression, dysthymia, generalized anxiety disorder, panic disorder, OCD, social phobia, PTSD, and bulimia. They have a favorable side-effect profile compared with older antidepressants, better patient tolerability, ease of administration, and well-proven safety in terms of risk of overdose. Drug interactions involving some SSRIs may be significant; therefore, it is prudent to use an SSRI with lowest potential for drug–drug interactions (e.g., citalopram, escitalopram, or sertraline) when treating patients with other medical or psychiatric comorbidities. Interactions mediated by the induction or inhibition of transporters such as P-gp are not yet well defined, but should be considered as potential confounders of clinical effects and risk for toxicity.

3. CYCLIC ANTIDEPRESSANTS

3.1. History

Imipramine was the first TCA to be used in clinical practice. After unsuccessful trials as a potential antihistamine and antipsychotic *(3)*, its efficacy in the

treatment of depression was finally reported in 1957, by Roland Kuhn in Switzerland *(109)*. Some years later, Klerman and Cole demonstrated the superiority of imipramine to placebo in depressed patients by analyzing pooled data from 23 published studies; 65% of patients in those studies improved clinically while taking imipramine compared with only 31% of patients taking placebo *(110)*. For three decades, TCAs were the first-line agents for the treatment of depression.

Desipramine is the demethylated metabolite of imipramine, and like its parent drug, it has antidepressant activity. Amitriptyline was also introduced in the 1960s; its secondary amine metabolite, nortriptyline, was marketed later. The TCAs offer advantages over MAOIs in that they pose less of a risk for drug interactions and require no food restrictions. However, they case some troublesome adverse effects in many patients. They also have a low therapeutic index, which can present problems in patients with suicidal risk. Heterocyclic and other types of antidepressants were introduced to the market over the past 20 yr, but none have demonstrated efficacy superior to that of the TCAs.

The following tricyclic and heterocyclic compounds are currently approved by the FDA for the treatment of depression in the United States: amitriptyline (Elavil®, Vanatrip®), amoxapine (Asendin®), clomipramine (Anafranil®), desipramine (Norpramin®), doxepin (Sinequan®, Zonalon®), imipramine (Tofranil®), maprotiline (Ludiomil®), nortriptyline (Aventyl®, Pamelor®), protriptyline (Vivactil®), and trimipramine (Surmontil®). Among these, amoxapine and maprotiline are less commonly used. The tricyclic chemical structures are shown in Fig. 3, and the chemical structures of amoxapine and maptrotiline are shown in Fig. 4.

3.2. Pharmacology

The basic tricyclic structure is similar to that of chlorpromazine and related to that of the phenothiazines, which have a six-member central ring that joins two benzene rings, resulting in a planar molecule. Most classifications of TCAs distinguish between tertiary and secondary amines. The tertiary amine tricyclics, such as imipramine and amitriptyline, consist of two benzene rings linked by a central imino ring. The seven-member central ring distorts the molecule, causing it to become nonplanar. Imipramine and amitriptyline are tertiary amines, because three carbon substituents are located on the terminal nitrogen of their side chains. Desipramine is a demethylated metabolite of imipramine and, thus, a secondary amine; it has two carbons on the terminal nitrogen of its side chain. Similarly, nortriptyline is the demethylated metabolite of amitriptyline.

Doxepin, trimipramine, and protriptyline all contain the three-ring structure of imipramine, with some minor differences. Recently developed drugs in this family may have a different molecular structure (tetracyclic or heterocyclic, or structurally unrelated compounds). Amoxapine, which was introduced in 1980,

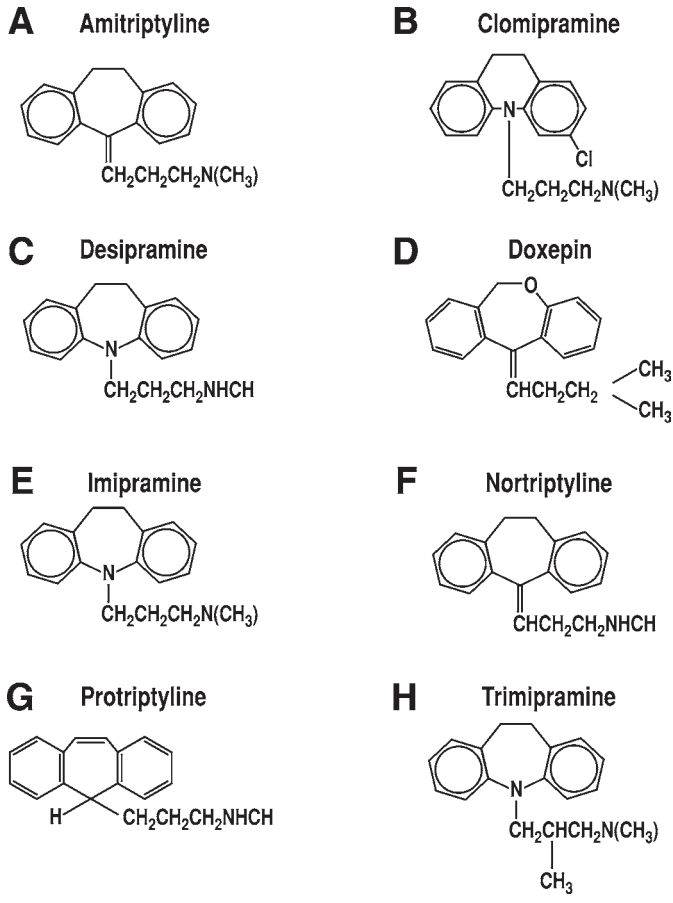

Fig. 3. TCAs: chemical structures.

for example, contains the three-ring structure of imipramine, but has a fourth ring as a side structure. Maprotiline is a tetracyclic compound whose central portion consists of four rings. Both amoxapine and maprotiline are often classified as "TCA-like," because they share the same activity, efficacy, and side-effect profile *(111)*. Thus, the term "TCA,"—which is still commonly used in clinical practice and literature to denote all drugs in this family—is inaccurate, and such terms as "cyclic," "atypical," and "mixed action" are sometimes used. Other classification schemes use such terms as "nonselective serotonin and norepinephrine reuptake inhibitors" (NSNRI) and "selective norepinephrine reuptake inhibitors" (SNRI) to maintain consistency with SSRI terminology. However, none of these approaches is entirely satisfactory or precise.

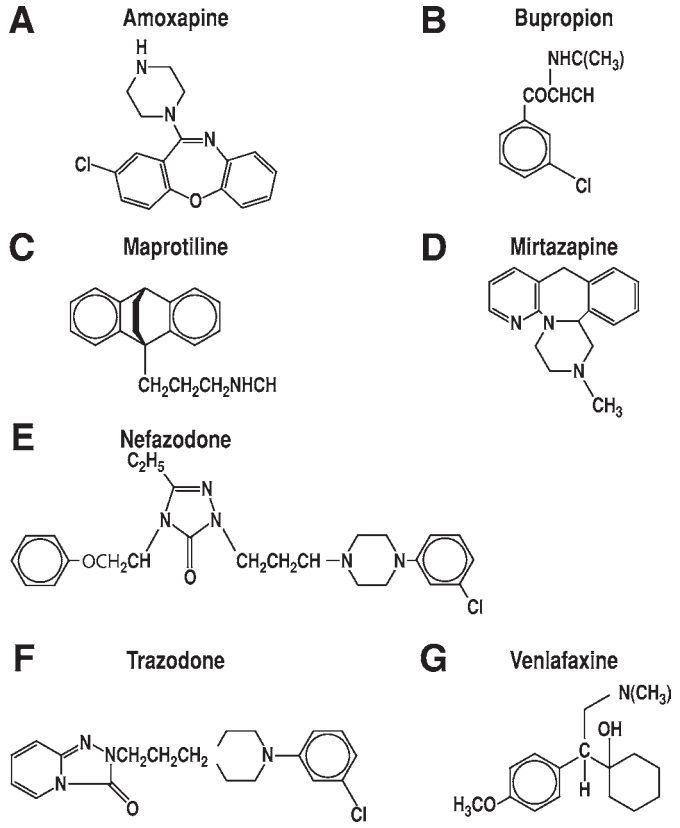

Fig. 4. Mixed-action agents and heterocyclic antidepressants: chemical structures.

3.3. Pharmacokinetics

TCAs are highly lipophilic and well absorbed from the GI tract, with a large volume of distribution and relatively long half-life *(112)*. TCAs are bound to α1-acid glycoprotein and albumin. Because they are highly protein bound, they are subject to drug interactions caused by their displacement from protein-binding sites and factors such as medical illnesses that can alter the amount or activity of binding proteins and change the free fraction of active drug that enters the brain at least transiently. TCAs are metabolized in the liver by means of demethylation, hydroxylation, or both, which is followed by conjugation with a glucuronide *(112)*. TCAs may also be metabolized within the brain. There is wide inter-individual variation in the hepatic metabolism of TCAs. The presence of active

metabolites complicates the interpretation of the therapeutic and adverse effects of these agents. Metabolites differ from the parent compound in terms of pharmacokinetic characteristics and effects on different neurotransmitter systems. Among the tertiary amines, imipramine is demethylated to desipramine and hydroxylated to 2-hydroxyimipramine and 2-hydroxydesipramine. Imipramine is 86 to 93% protein bound and has an elimination half-life of 15 to 30 h. The metabolism of amitriptyline is complex, because its hydroxy metabolites and those of its demethylated metabolite nortriptyline exist as isomers. Amitriptyline is 95% protein bound and has an elimination half-life of 9 to 25 h. Desipramine is 85 to 90% protein bound and has an elimination half-life of 12 to 36 h. Nortriptyline is 92% protein bound and has an elimination half-life of 18 to 33 h. During treatment with either amitryptiline or nortriptyline, the metabolite *E*-10-OH-nortriptyline reaches greater plasma and cerebrospinal fluid (CSF) concentrations than the parent drug *(112)*. In contrast, 2-OH-desipramine plasma levels are less than half that of the parent drug during desipramine administration *(113)*. Hydroxy metabolites cross the BBB and contribute to the pharmacodynamic effects of the parent drug. Cyclic antidepressant metabolites are shown in Table 6.

The pharmacokinetic properties of TCAs have several clinical implications:

1. Within the usual therapeutic range, an increase in dose will result in a proportional increase in the drug plasma level.
2. Correlation between clinical outcome and plasma level has been difficult to establish, in part because of the failure of some studies to consider the effects of metabolites, free drug levels, the activity of transporter proteins (e.g., P-gp), and failure to assay for isomers; still many clinicians believe that the response to nortriptyline is optimal when it reaches a plasma level of 50 to 150 ng/mL, whereas other TCAs (e.g., desipramine) require a minimal plasma concentration, exhibiting the classical sigmoidal response curve.
3. First-pass metabolism by the liver is genetically determined and is the major factor in large interindividual variability in plasma levels
4. Metabolites contribute to therapeutic and toxic drug effects and may reach higher plasma levels than the parent compound.
5. Renal clearance is an important mechanism of elimination for hydroxylated metabolites, and factors such as age and disease may impair excretion.
6. Impaired elimination in the young and elderly is believed to be related to renal function.
7. Differences in metabolism between the sexes have not been consistent, although increased metabolism and plasma volume during pregnancy may require dose adjustments.

Cyclic antidepressants are subject to pharmacokinetic drug–drug interactions as a consequence of being metabolized by means of the hepatic CYP system.

Table 6. Selected Non-SSRI Antidepressant Metabolites

	Metabolites	*Cytochrome Substrates*
(TCAs)		
Tertiary Amines		
Amitriptyline	Nortriptyline 10-OH nortriptyline (*cis, trans,* +, –), 10-OH amitriptyline (*cis, trans,* +,–)	1A2, 2C19, 2C9, 2D6, 3A4
Imipramine	Desipramine 2-OH desipramine 2-OH imipramine	2C19, 2C9, 1A2, 3A4, 2D6
Clomipramine	Desmethylclomipramine 8-OH clomipramine 8-OH desmethylclomipramine	3A4, 2D6 (also inhibits 2D6), 2C19
Trimipramine	Desmethyltrimipramine Didesmethyltimipramine 2-OH trimipramine 2-OH desmethyltrimipramine	2C19, 1A2, 3A4, 2D6
Doxepin	Desmethyldoxepin	2C19, 3A4, 1A2, 2C9
Secondary Amines		
(TCAs)		
Nortriptyline	10-OH nortriptyline (*cis, trans,* +, –)	2D6
Desipramine	2-OH desipramine	2D6
Protriptyline	2-OH protriptyline Desmethylprotriptyline *N*-acetylprotriptyline	2D6
Bupropion	Hydroxybupropion Threohydrobupropion Erythrohydrobupropion	2B6 (also inhibits 2B6), 2D6 (also inhibits 2D6)
Mirtazapine	Desmethylmirtazapine (8-OH mirtazapine) (Mirtazapine *N*-oxide)	3A, 2D6, 1A2
Maprotiline	Desmethylmaprotiline	2D6, 1A2
Venlafaxine	*O*-desmethylvenlafaxine	2D6
Trazodone	mCPP	3A4
Nefazodone	Hydroxynefazodone Meta-chlorophenylpiperazine mCPP Triazole-dione	3A4 (also inhibits 3A4), 2D6

Pharmacokinetic drug–drug interactions involving TCAs can be anticipated with knowledge of the cytochromes that are involved in metabolism and familiarity with drugs that induce or inhibit these enzymes. The most commonly encountered clinical situations involve combination therapy using antidepressants and drugs that inhibit or induce cytochromes involved in antidepressant metabolism. It is also possible to encounter an interaction with other drugs that are substrates for the same cytochromes if those drugs have a higher affinity for binding sites.

For example, some TCAs compete for the enzyme CYP2C19 and alter phenytoin metabolism. The following discussion focuses on the most common pharmacokinetic interactions involving TCA. It is meant to outline some of the principles of these interactions, rather than serve as an exhaustive list of all interactions.

Whereas *N*-demethylation of TCAs is catalyzed by CYP1A2, CYP2C19, and CYP3A4, the contribution of active hydroxy metabolites makes the hydroxylation step, mediated by CYP2D6, extremely important. Approximately 7 to 10% of Caucasians are poor CYP2D6 metabolizers (PM), whereas fewer than 1% of Asians are PM. Several antipsychotic agents and SSRI antidepressants (*see* the SSRI section), as well as moclobemide (an MAOI marketed outside the United States) are the most common psychotropic agents that can impair CYP2D6-mediated metabolic activity. Other drugs that can impair CYP2D6 activity include cimetidine, ranitidine, methadone, metclopramide, amiodarone, celecoxib, and ritonavir. Ritonavir and other antivirals (indinavir, nelfinavir, saquinavir, and delaviridine), antifungals (e.g., ketoconazole and itraconozole), macrolide antibiotics (erythromycin and clarithromycin), ciprofloxacin, and the calcium channel blocker diltiazem inhibit CYP3A4 activity. Fluoroquinolines inhibit CYP1A2. Enzyme inducers—such as modafenil (1A2), barbiturates (3A, 2B6, 2C9), rifampin (2D6, 3A, 2C19, 2B6), carbamazepine (2C19, 3A), tamoxifen (3A) and chronic ethanol—may lower plasma levels of cyclic antidepressants. Some foods, such as grapefruit juice, may also reduce CYP3A4 and CYP1A2 activity.

3.4. Mechanism of Action (Table 7)

The antidepressant activity of TCAs is a result of their ability to inhibit NE and 5-HT reuptake, thereby increasing concentrations of these monoamines in the synaptic cleft. Downregulation of postsynaptic receptors and subsequent changes in gene expression (*see* SSRI section and Chapter 1) are ultimately responsible for the antidepressant effect. TCAs inhibit NE and 5-HT in different proportions. In general, secondary amines, e.g., desipramine and nortriptyline, are much more selective and preferentially block NE reuptake. Thus, desipramine, nortripytyline, and protriptyline, are primarily NE reuptake inhibitors, exhibiting only limited inhibition of 5-HT uptake. Conversely, clomipramine inhibits 5-HT reuptake much more than it does NE reuptake. Imipramine, amitriptyline, doxepin, and trimipramine inhibit NE and 5-HT reuptake equally, although the effect of their metabolites must be considered, because together with the parent compound, they produce a mixed noradrenergic-serotonergic effect. Nortriptyline, amitriptyline, and clomipramine are also antagonists of the 5-HT_2 receptor, although the clinical significance of this effect is not known.

Adverse effects of TCAs occur a result of their activity as agonists at α_1-adrenergic receptors (orthostatic hypotension), H_1-histaminic receptors (seda-

Table 7. Relative Drug Potencies at Receptors

	Relative Potencies					
	5-HT$_{2A}$	*5-HT$_{1A}$*	*H$_1$*	*α_1*	*α_2*	*Muscarinic*
Nefazodone	++++	+++	+++	++++	+++	+
Hydroxynefazodone	++++	+++	+++	++++	+++	–
Triazoledione	++	+	+++	++	+	–
mCPP	++	+++	++	+++	++	+
Trazodone	+++	+++	+++	+++	++	–
Amitriptyline	++++	++	++++	++++	++	++++
Desipramine	++	+	+++	+++	+	+++
Paroxetine	+	–	–	++	+	+++
Sertraline	+	+	+	+++	+++	++
Fluoxetine	++	+	++	+	+	++
Venlafaxine	–	–	–	–	–	–

none; +/–, uncertain; +, weak; ++, mild; +++, moderate; ++++, strong.
Italics indicate a metabolite.
Adapted from refs. *1-5*. Readers are encouraged to review these experimental studies to understand how different profiles emerge from various techniques.

tion and weight gain), and anticholinergic receptors (dry mouth, urinary retention, constipation, blurred vision, and memory problems). The TCAs with the least clinically significant anticholinergic effects are desipramine and nortriptyline. Nortriptyline has the weakest α_1-adrenergic antagonistic effect; desipramine has a somewhat stronger effect, but not as strong as that of the tertiary amines. Amitritpyline, doxepin, and trimipramine have the strongest histaminergic (H_1) antagonistic effect in their group.

3.5. Adverse Effects

TCAs have strong anticholinergic (antimuscarinic) activity, which may cause constipation, dry mouth, urinary hesitancy/retention, blurred vision, dyspepsia, and confusion *(5d,114)*. More severe effects—e.g., tachycardia, confusion, agitation, or even delirium—may occur in elderly patients at therapeutic doses *(115)*. Although rare, these severe complications may occur when a patient takes another anticholinergic drug concomitantly with a TCA; neuroleptics, antiparkinsonian agents, antihistamines, antispasmodics, and over-the-counter sleeping pills are commonly involved.

Initial management of mild to moderate symptoms should include lowering the TCA dose or slowing the rate of dose escalation. In patients who still have troublesome symptoms, 25 to 50 mg of oral bethanechol three or four times a day

may relieve peripheral cholinergic symptoms. CNS symptoms may be reversed by administering intravenous physostigmine; however, this should be done by an experienced clinician because of a risk for tremors, vomiting, and seizures if it is administered too rapidly or at too high a dose. Some clinicians recommend 4% pilocarpine eyedrops for blurred vision and a 1% solution for dry mouth; however, we have found bethanechol to be as effective and more convenient for patients. In a patient who cannot tolerate the anticholinergic effects of these drugs, switching classes is the best approach.

3.5.1. Cardiovascular: Orthostatic Hypotension

Direct peripheral α-adrenergic receptor blockade causes orthostatic hypotension, dizziness, and drowsiness *(116,117)*. This effect does not directly correlate with the patient's age or dose of TCA, although the consequence can be disastrous in the elderly or cardiac-impaired patient. Following the onset of orthostatic hypotension, further dose increases do not produce a greater decline in blood pressure (BP) *(116)*. In many patients, the severity of orthostatic hypotension will prohibit TCA use; up to 10% of otherwise medically healthy patients and up to 25 to 50% of patients with preexisting cardiac disease will require a dose alteration or discontinuation of the medication *(118)*. Orthostatic hypotension is of special concern in the elderly, in whom a fall may result in physical injuries such as fractures or significant lacerations. Injuries resulting from falls may occur at a rate of up to 4% of patients treated with imipramine *(116)*. Nortriptyline may offer some advantages over other TCAs. Lack of postural effect was reported in a study of 32 patients, two-thirds of whom were taking nortriptyline *(119)*. Nortriptyline was found to be significantly less likely to cause orthostatic hypotension than imipramine, desipramine, clomipramine, or amitriptyline. This property makes it the TCA of choice in the elderly population *(119,120)*.

3.5.2. Cardiovascular: Conduction Effects

One of the most serious adverse effects of TCAs is a consequence of their effects on cardiac conduction. ECG changes are well known and consist of flattening of the T wave and lengthening of the P-R interval and the QRS complex *(119)*. TCAs slow cardiac atrioventricular conduction, lengthen the QT interval, and are associated with arrhythmias, especially in cases of overdose and in patients with preexisting cardiac disease *(121)*. TCAs are class 1A anti-arrhythmics (similar to quinidine), which exert their clinical effect by slowing conduction through the His-Purkinje system and myocardium *(121)*. This class of anti-arrhythmics can actually produce an arrhythmia after a myocardial infarction (MI).Cardiac mortality associated with TCA use is a matter of some controversy. Findings of studies conducted prior to the introduction of antidepressants indicated a higher mortality in severely depressed patients compared to the general population, and

a cardiovascular disorder was eight times more likely to be the cause *(122)*. Recently, Witchel and associates *(121)* proposed that TCA-induced prolongation of the QTc interval (>440 ms) may be responsible for their proarrhythmic effects and sudden death. Drawing comparisons to genetic forms of Long QT Syndrome (LQTS), these investigators suggested that TCAs may induce QT-interval prolongation through direct effects on ion channels within myocardial fibers. Identification of the genes that code for these ion channels and defective functioning of these channels in patients with LQTS led to the hypothesis that TCAs (and other drugs) may alter their function, especially in individuals who have "silent mutations." These authors also stressed that the multiple additional effects of TCAs—e.g., monoamine reuptake inhibition, anticholinergic activity, antihistamine effects, as well as blockade of calcium and potassium channels—influence the risk of a prolonged QTc interval *(121)*. In cases of TCA overdose, TCA-induced QT interval prolongation has been linked with torsades de pointes (TdP), complete heart block, and sudden cardiac death. The risk of arrhythmia is especially high in patients with preexisting cardiovascular disease or conduction abnormalities, patients taking high doses of a TCA, and those who take an overdose of these drugs (*see* discussion that follows) *(118)*.

Although cardiac toxicity in overdose cases was well known when TCAs were first used clinically *(123)*, the prevailing clinical opinion has been that few cardiovascular adverse effects arise during TCA therapy in patients who did not have a preexisting cardiovascular pathology *(116)*. As noted previously, in some cases the TCAs proved to have antiarrhythmic properties, suppressing ectopic pacemakers and premature ventricular contractions *(124)*. On the other hand, it was also recognized that these drugs should not be used by patients with a known cardiac illness, e.g., preexisting conduction delays, second-degree heart block, bifascicular heart block, sick sinus syndrome heart failure, or bundle branch disease *(125)*. The risks of TCA-induced impairment of left ventricular function remain unresolved *(126)*.

The Cardiac Arrhythmia Suppression Trial (CAST) evaluated the effect of antiarrhythmic therapy in patients who developed either mildly symptomatic or asymptomatic ventricular arrhythmias after an MI. The CAST study was stopped prematurely when a significantly higher death rate in the groups treated with either encainide or flecainide (and eventually moricizine) vs placebo was detected *(127,128)*. The results of that study indicated that both class 1C and 1A antiarrhythmic agents, the latter of which includes TCAs, had a proarrhythmic effect after an MI. When cardiac tissue becomes anoxic or ischemic, class 1 antiarrhythmics become proarrhythmic *(117)*. Thus, SSRI are the preferred antidepressants for these patients. Most cyclic antidepressants are associated with a risk for arrhythmia, including amitriptyline, amoxapine, clomipramine,

desipramine, doxepin, imipramine, maprotiline, and nortriptyline. Doxepin, once thought to be safer in patients with cardiac disease, has a cardiac risk comparable to that of other drugs in this class *(129)*.

3.5.3. Sexual Dysfunction

Sexual dysfunction has not been well studied in patients taking TCAs, but it is generally believed these drugs are associated with decreased libido, erectile or ejaculatory dysfunction, delayed orgasm, anorgasmia, and, less commonly, impotence *(64–66)*. No reliable data are available to indicate how often these effects occur; many studies refer only to "decreased or impaired sexual function." Several investigators have used clomipramine, a strong serotonergic TCA, as a comparator with SSRI and found equivalent rates of sexual dysfunction. In one study, clomipramine was associated with anorgasmia in approx 90% of patients with OCD *(130)*. The most often quoted numbers for depressed patients who experience decreased sexual function and libido while being treated with clomipramine are 14% for females and 26% for males *(66)*; however, women may be less likely to report sexual side effects *(65)*. On the other hand, an increase in libido with imipramine and amoxapine has been known to occur *(66)*. These disparate findings highlight the difficulty involved in separating sexual dysfunction associated with depression and that resulting from drug therapy.

3.5.4. Other Adverse Effects

Other common adverse effects associated with TCA therapy include tremors, mycolonus, and perspiration. Maprotiline has been associated with seizures at high therapeutic doses. All TCAs lower the threshold for seizures, but this is usually only a problem in patients with a seizure disorder or in cases of overdose. Amoxapine has been associated with EPSs.

3.6. Overdose

TCAs have a relatively low therapeutic index and serious consequences in overdose. For most TCAs, the therapeutic dose is about 3 to 4 mg/kg per day and a potentially lethal dose is 15 to 20 mg/kg per day. The potentially fatal dose is only the equivalent of a 5-d supply of medication. This creates an obvious problem in the treatment of depressed patients, many of whom have suicidal ideation. Epidemiological data from the 1970s to mid-1980s—prior to the entry of SSRIs into the US market—provide the richest data on TCA overdose. During that period, the annual incidence of TCA overdose in United States was estimated at 500,000 *(111)*. Approximately 1500 to 2000 patients a year committed suicide by taking a TCA *(116)*. TCAs became the most commonly ingested drugs among suicidal patients and the third most common cause of drug-related deaths, closely follow-

ing alcohol–drug combinations and heroin overdose *(131)*. In 1983 and 1984, TCAs were the most common drug involved in overdose deaths. Additionally, 70% of patients who took a TCA in a suicide attempt died before reaching the hospital *(111)*; a substantial number died within 5 to 6 h of admission to a hospital *(131)*. More recently, some have opined that the risk of an overdose has been exaggerated. For example, it has been argued that only 5% of suicidal patients use their prescribed antidepressant medications for that purpose *(51)*. Still, most clinicians are unwilling to take any risk as long as safer alternatives are available.

The clinical presentation of a TCA overdose is an extension of their pharmacodynamic actions. Frommer and associates *(111)* describe the initial symptoms as primarily anticholinergic, including mydriasis, blurred vision, urinary retention, dry mucous membranes, decreased peristalsis, tachycardia, general CNS excitation with increased reflexes, hyperactivity, and insomnia. CNS toxicity includes confusion, agitation, hallucinations, and seizures. CNS depression may begin as drowsiness or lethargy and progress rapidly to coma and respiratory arrest in the most severe cases *(111)*. Cardiac abnormalities may include hypotension and arrhythmias, e.g., sinus tachycardia; supraventricular and ventricular tachycardia; prolongation of P-R, QRS, and QT intervals; bundle-branch or second- or third-degree heart block, or sudden death *(4)*. Death is caused by an intractable myocardial depression or cardiac arrhythmia, such as ventricular tachycardia or fibrillation *(111)*. Generalized seizures are associated with increased mortality and often occur immediately prior to cardiac arrest. The progression from mild symptoms to death can be extremely rapid, and often does not follow a predictable pattern.

In terms of individual differences among cyclic antidepressants, amoxapine has been associated with the least amount of cardiotoxicity in large overdoses *(111,132)*; however, it has significant CNS toxicity and has been known to cause status epilepticus and coma in cases of overdose *(132,133)*. Maprotiline, a tetracyclic compound, was reported to possess greater cardiac and CNS toxicity (seizures) than other agents *(134)*.

Treatment for a TCA overdose includes activated charcoal lavage, fluids, and supportive measures. Several authors have proposed specific therapies for hypotension, seizures, and arrhythmias; however there are substantial variations in approach. Regardless of the specific approaches used, all patients should be hospitalized in a cardiac or intensive care unit. Some clinicians recommend physostigmine, but this may precipitate seizures and cardiac arrhythmias in some instances *(134)*.

3.7. Clinical Use (Table 8)

In a study published in 1993, investigators analyzed data on antidepressant use provided by three National Ambulatory Medical Care Surveys conducted in

Table 8. Adult Doses and Formulations of Antidepressants (*See* Table 4 for SSRIs)

	*Usual Starting Dose**	*Maximal Dose**	*Formulations*	*Available Dosages*
Tertiary Amines				
Amitriptyline	25 mg tid	300 mg qd	Suspension, Tablet	Suspensions: 10 mg/mL Tablets: 10, 25, 50, 75, 100, and 150 mg
Imipramine	25 mg tid	300 mg qd	Tablet, Capsule	Tablets: 10, 25, and 50 mg Capsule: 75, 100, 125, and 150 mg
Clomipramine	25 mg qd	250 mg qd	Capsule	25, 50, and 75 mg
Trimipramine	75 mg qd	300 mg qd	Capsule	25, 50 mg, 100 mg
Secondary Amines				
Nortriptyline	25 mg qd	150 mg qd (monitor plasma levels)	Capsule, Solution	Capsule: 10 mg, 25 mg, 50 mg, 75 mg Solution: 2 mg/mL
Desipramine	25 mg bid	250–300 mg qd	Tablet	10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg
Protriptyline	15 mg qd	60 mg qd	Tablet	5 mg, 10 mg
Amoxapine	50 mg bid or tid	120–300 mg qd	Tablet	25 mg, 50 mg, 100 mg, 150 mg
Buproprion	100 mg bid (IR) 150 mg qd (SR)	150 mg tid (IR) 200 mg bid (SR)	Tablet, SR tablet	Tablet: 75 mg, 100 mg SR Tablet: 100 mg, 150 mg
Mirtazapine	15 mg qhs	45 mg qd	Tablets, Dissolving tablets	15 mg, 30 mg, 45 mg
Maprotiline	75 mg qd	225 mg qd	Tablet	25 mg, 50 mg, 75 mg
Venlafaxine	75 mg bid	375 mg qd	Tablet, SR Capsule	Tablet: 25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg SR Capsule: 37.5 mg, 75 mg, 150 mg
Trazodone	50 mg tid	400–600 mg qd	Tablet	50 mg, 100 mg, 150 mg, 300 mg
Nefazodone	100 mg bid	600 mg qd	Tablet	50 mg, 100 mg, 150 mg, 200 mg, 250 mg

* Lower doses should be used in the elderly.

1980, 1985, and 1989 *(135)*. They found that TCAs were the most widely prescribed type of antidepressant in office-based practices throughout the 1980s,

and were still widely used at the time of publication. TCAs have become second-line agents in the United States, but in other countries they remain first-line agents. This is especially true in Europe, where many psychiatrists believe in the superior efficacy of tertiary amines, such as clomipramine and amitriptyline, over other antidepressants *(5d)*. In the United States, however, newer antidepressants, such as SSRIs, have replaced TCAs as first-line agents, primarily because of the belief of equivalent efficacy, greater safety, improved tolerability, and relative ease of dosing.

Most clinicians believe that data support the equivalent efficacy of all TCAs, although some argue for the superior effectiveness of clomipramine. Estimates indicate that up to 80% of heterogeneous depressed patients will experience clinically significant improvements in depression when treated with adequate doses of a TCA *(114)*.

There remains some disagreement on the issue of superior efficacy of TCAs compared to SSRIs. In a review of 186 randomized controlled trials that compared amitriptyline with other antidepressants—including SSRIs, heterocyclics, and other tricyclics—Barbui and Hotopf *(136)* concluded that amitriptyline was more efficacious in the treatment of depression than SSRIs, heterocyclics, or other TCAs. A small but statistically significant higher response rate was found with amitriptyline *(136)*. Boyce and Judd *(137)* have argued that the TCAs are not only more effective in melancholic depression and in-patients with depression, but also that the tolerability and safety of SSRIs have been overstated.

There is support for the position that TCAs should remain a first-line treatment for patients with severe depression (sometimes referred to as endogenous or melancholic depression). The Danish University Antidepressant Group found that clomipramine was superior in efficacy to citalopram, paroxetine, or moclobemide *(138)*. In another study, nortriptyline was found to be superior to fluoxetine for treating depression in hospitalized elderly patients, especially those with a melancholic subtype of depression *(139)*. In a review of six controlled trials, Perry *(140)* concluded that TCAs are more effective in the treatment of "endogenous depression or major depression with melancholic features" compared to SSRIs. On the other hand, clinicians should be aware that investigators have found these two drug classes to be "equivalent" in many studies, although they did not distinguish among melancholic subtypes of depression in most of them.

TCAs have a broad spectrum of efficacy. In addition to major depression and dysthymia, they are effective in panic disorder, social phobia, other anxiety disorders, bulimia nervosa, PTSD, attention deficit-hyperactivity disorder (ADHD), and, in young children, enuresis. The toxicity of TCAs in children has been a matter of some controversy. Some reports have linked desipramine with sudden death in children, but a review by a leading authority in this area did not find such an association *(141)*. As a precaution, children taking TCAs should

undergo ECG monitoring. Clomipramine is approved for treatment of OCD. Adult as well as childhood ADHD responds well to TCAs, with most data available for imipramine and desipramine *(142,143)*. TCAs are sometimes used for chronic pain syndromes and migraine headaches, but more effective medications have largely supplanted their use in these illnesses.

Gender differences in the therapeutic response to TCAs have been studied, but have produced inconsistent findings. In a 12-wk, double-blind, randomized prospective study, investigators found that depressed men were significantly more likely to show a favorable response to imipramine (a TCA) than to sertraline (an SSRI), whereas the reverse was true for women. This difference was most apparent in premenopausal women; postmenopausal women had equal rates of response to these two agents *(144)*. In general, women had a slower response to imipramine and poor tolerability of the TCA. The reasons for the sex differences are unclear, but may include the presence of SSRI-responsive subtypes of depression in women (e.g., atypical, premenstrual dysphoric disorder) an, interaction between antidepressants and female sex hormones, or both. Complicating the interpretation of this study are high dropout rates for women taking imipramine and for men taking sertraline *(145)*.

In a retrospective study in which data for 1746 patients who had been treated with TCAs (imipramine, desipramine), SSRIs (fluoxetine), MAOIs (phenelzine, tranylcypromine, L-deprenyl), or placebo over a 20-yr period were analyzed *(146)*, the authors found no difference in response rates to TCAs and fluoxetine between male and female patients of all ages studied, but women had a statistically significant superior response to MAOI antidepressants. The authors also failed to find a clinically relevant difference in treatment response of women in older age groups, suggesting a lack of influence by menopausal status.

3.8. Other Antidepressants

A number of new antidepressants have been marketed over the last decade. Venlafaxine (Effexor®) and duloxetine are NSNRIs, although duloxetine has greater potency. Neither compound has significant anticholinergic or antihistaminic effects. Mirtazapine (Remeron) is a noradrenergic α_2 antagonist at auto- and heteroreceptors; thus, it enhances 5-HT release. It is also a 5-HT_{2A}- and 5-HT_3-receptor antagonist. Nefazodone (Serzone®)—which is a 5-HT_{2A} antagonist—and trazodone (Desyrel®)— an SSRI—are phenylpiperazine derivatives. Bupropion (Wellbutrin®) is an aminoketone that may block NE reuptake in vivo through its active metabolite hydroxybupropion and increase DA activity by an unknown mechanism. Reboxetine is an SNRI that is currently used in Canada and Europe to treat mood disorders, but is not yet available in the United States. These newer antidepressants offer some advantages over the older agents in

terms of tolerability. Perhaps more importantly, they have different mechanisms of action and, thus, may serve as alternatives for patients who do not respond to other antidepressants. Their chemical structures are shown in Fig. 4.

3.8.1. Bupropion

Bupropion is an aminoketone that was introduced in the United States in 1989 amid concerns about its seizure-inducing potential—a factor that caused a delay in its being marketed after originally gaining FDA approval in 1985.

In the interim, the findings of a large study established that the seizure risk from bupropion at the usual therapeutic doses was similar to that of the cyclic antidepressants. Bupropion has three active metabolites: hydroxybupropion, threobupropion, and erythrobupropion. The relative contribution of each metabolite to its clinical or adverse effects is unclear; however, they reach plasma levels higher than that of the parent compound. The plasma half-life of bupropion after chronic dosing is about 20 h, and it is 80% protein bound. The half-life of hydroxybupropion, an NE reuptake inhibitor, is longer—about 22 h *(148)*.

Bupropion is believed to exert its antidepressant action by inhibiting NE reuptake and enhancing DA activity. It has no serotonergic, anticholinergic, or antihistaminergic effects, nor does it interact with monoamine oxidase *(148)*. There is still some uncertainty concerning its mechanism of action, owing to differences in bupropion activity in vivo and in vitro. Bupropion is a potent DA reuptake inhibitor as well as a moderately potent NE reuptake inhibitor in vitro. In vivo, it is twice as potent as an NE reuptake inhibition compared to its DA reuptake inhibition *(149)*. Although bupropion has demonstrated DA uptake inhibition in vitro, the concentrations required to do so may not be clinically relevant. Additionally, homovanillic acid is increased during bupropion treatment—indicating enhanced DA activity—although its levels are not associated with a positive antidepressant response. Hydroxybupropion is associated with downregulation of postsynaptic β-adrenergic receptors in animal models.

The immediate-release (IR) formulation of bupropion (buproprion IR) carries a relatively higher risk for lowering the threshold for seizures compared to SSRIs. Bupropion IR carries a risk for seizures of 0.4% at doses up to 450 mg/d, which is about two to four times higher than the incidence seen with SSRI therapy (0.1–0.2%) *(150)*. The risk for seizures is strongly related to dose and the rate of dose escalation. Even with modest increases in dose up to 450 to 600 mg/d, the seizure risk increases 10-fold. An extended-release (XR) formulation has lowered the risk of seizures to a level comparable to that of other antidepressant classes. A seizure rate of 0.1% was associated with a sustained-release (SR) formulation of bupropion 300 mg/d and 0.4% with 400 mg/d *(150)*. Clinicians should be aware that Wellbutrin® and Zyban® are both bupropion, and inadvertent overdoses

have occurred when both have been prescribed for the same patient to treat depression and for smoking cessation.

Because of the dopaminergic and adrenergic actions of bupropion, it can be excitatory and may cause overstimulation, agitation, nausea, nervousness, and insomnia, as well as tremors and palpitations *(148,150,151)*. It can induce mania in bipolar patients, however, bupropion-induced mania tends to be milder and has a shorter course than either spontaneous mania or mania elicited in patients by TCAs or SSRI antidepressants *(47)*. Bupropion has a favorable cardiovascular profile and does not cause orthostatic hypotension or delay conduction. Some patients may have elevated BP with bupropion.

Because bupropion does not interact with serotonergic receptors, it is associated with an extremely low incidence of sexual side effects, which are common with SSRIs and most other antidepressants *(66,150,151)*. Bupropion is a reasonable alternative to SSRIs when sexual adverse effects limit their use. Bupropion is not associated with weight gain.

A case report described bupropion-induced erythema multiforme in a 31-yr-old woman after 3 wk of treatment with bupropion SR. This or other dermatologic adverse effects are rare, but may include urticarial and pruritic rashes *(152)*.

3.8.2. Venlafaxine

Venlafaxine is a bicyclic phenylethylamine derivative marketed as a racemic mixture of its *R*-and *S*-enantiomers; the *R*-enantiomer is more potent of the two *(153)*. Venlafaxine is only 27% protein bound and has a half-life of 4 to 5 h. It undergoes first-pass metabolism to *O*-demethylvenlafaxine (ODV), which is an active metabolite and just as potent as its parent compound, with an elimination half-life of 11 h. Clearance of both venlafaxine and ODV is decreased by 55% in patients with severe renal disease and by 33% in patients with cirrhosis *(154)*. Recently, an XR formulation of venlafaxine became available. Pharmacologically, it is quite similar to the original IR formulation of venlafaxine; the differences are increased time to peak plasma concentration and lower plasma concentrations for the XR formulation *(155)*.

Venlafaxine inhibits both serotonergic and NE reuptake at higher therapeutic doses (≥225 mg). At lower doses it affects mainly 5-HT, making it comparable to SSRI; however, as the dose increases, it becomes a potent inhibitor of the synaptic reuptake of NE *(148,153,154)*. At low doses, its rate of inhibition of 5-HT reuptake is about three- to fivefold higher than its rate of NE reuptake *(5d,154)*. Venlafaxine also possesses weak affinity toward the DA receptor *(154)*. It rapidly downregulates β-adrenergic receptors, a property that some contend supports the studies that have found a more rapid onset of antidepressant effect with venlafaxine compared with other agents. It has minimal or no interactions

with muscarinic, histaminic, or α-adrenergic receptors, which accounts for the low incidence of adverse effects with this drug *(153)*.

Most common adverse effects include those associated with SSRI, such as nausea, vomiting, sexual dysfunction, somnolence, and sweating *(148,151,156)*. The incidence of sexual dysfunction is thought by some to be lower than with SSRIs, but there is no consensus on this point *(72,151,157)*.

Of most concern has been elevated BP, which occurs at higher doses of venlafaxine (101 and 300 mg/d) and returns to normal after drug discontinuation *(39,148)*. BP changes are dose related, with an incidence of about 5% at doses less than 200 mg daily and 13% at doses exceeding 300 mg daily. Preexisting hypertension does not appear to be a risk factor for this effect. If the dose cannot be reduced, BP should be treated pharmacologically, using standard drug algorithms.

Discontinuation syndromes upon abrupt discontinuation of venlafaxine have been reported *(158)*. The most common symptoms are dizziness or lightheadedness, excessive sweating, irritability, dysphoria, and insomnia, which are similar to the symptoms comprising SSRI discontinuation syndrome *(158)*. A slow taper of the medication usually prevents this syndrome. On rare occasions, it may be necessary to reinstitute the medication or switch to a long-acting SSRI, such as fluoxetine.

Venlafaxine is one of the few antidepressants that have been studied during pregnancy. In a recent prospective study of 150 pregnant women receiving venlafaxine, investigators found no significant difference in effect between women taking venlafaxine during pregnancy and those taking either an SSRI antidepressants or a known nonteratogenic drug *(159)*. The rate of major neonatal malformation in all groups was the same as the baseline rate for the general population (i.e., 1 to 3%).

3.8.3. Nefazodone and Trazodone

Nefazodone and trazodone are closely related antidepressants. Nefazodone is a phenylpiperazine derivative of trazodone with lower α_1 activity. Trazodone is a triazolopyridine derivative developed in early 1980s as an alternative to TCAs, but its efficacy has always been questioned. Its most common use today is to promote sleep. Its antidepressant properties are believed to be related to its 5-HT_2 receptor antagonism and only partially from its weak 5-HT reuptake inhibition *(5d,153)*. Aside from its therapeutic actions, trazodone is a weak to moderate histamine H_1 receptor antagonist and an α_1-adrenergic antagonist, which makes it similar to TCAs in terms of undesired side effects *(153)*.

Nefazodone has three pharmacologically active metabolites: hydroxynefazodone (OHN), triazoledione, and *m*chlorophenylpiperazine (mCPP). Both

triazoledione and OHN contribute to the antidepressant effect of nefazodone. Like nefazodone, OHN is a very potent inhibitor of 5-HT_{2A} receptors and 5-HT reuptake. The triazoledione metabolite has weak 5-HT_{2A} antagonism. *m*CPP acts as an agonist at the 5-$HT_{1A,1B,1C,1D}$ and 5-HT_{2C} receptors, but is not considered to have a significant impact on overall nefazodone activity *(148,155)*. Nefazodone antagonizes and downregulates postsynaptic 5-HT_{2A} receptors; this, in turn, leads to enhanced 5-HT_{1A} receptor-meditated postsynaptic neurotransmission *(160)*. Nefazodone is a moderate presynaptic 5-HT reuptake inhibitor that also inhibits presynaptic NE reuptake, but to a much lesser degree; *(160)* this, however, probably does not contribute to its therapeutic actions *(148)*. Nefazodone is a weak α_1-adrenergic antagonist and has very little, if any, interactions with α_2-adrenergic, antihistaminic, or DA receptors *(153,161)*.

As discussed previously, trazodone is a histamine H_1-receptor antagonist and an α_1-adrenergic antagonist, which makes it similar to TCA drugs in terms of undesired side effects *(153)*. Despite isolated case reports of conduction delay and arrhythmias with trazodone (especially in overdoses), researchers have not found this effect even in patients with preexisting cardiac disease. Anticholinergic and antihistamine effects are negligible *(148,153)*. Because of its α_1-adenoreceptor-blocking properties, trazodone may cause orthostatic hypotension *(39)*. The most serious adverse effect of trazodone therapy in male patients is priapism, which is a urologic emergency *(162)*. The incidence of trazodone-induced priapism is unknown, although estimates range from 1 in 1000 to 1 in 10,000 patients. It tends to occur early in treatment, usually within the first month, but has also been reported after 18 mo of treatment. It can occur at doses as low as 50 mg/d. Approximately one-third of patients require surgical intervention. Priapism is believed to be a result of α-adrenergic blockade.

Nefazodone has weak α_1-adrenergic and cholinergic receptor antagonism and causes virtually no α_2-adrenergic, dopaminergic, or histaminic blockade *(148,156)*. Nefazodone does not cause sexual dysfunction and is a reasonable alternative to SSRIs when this effect is of concern *(66,72)*. It has not been associated with priapism, despite its structural similarity to trazodone *(6,39)*. The most frequent side effects observed for nefazodone compared to placebo during clinical trials are nausea (21% vs 14%), somnolence (19% vs 13%), dry mouth (19% vs 13%), dizziness (12% vs 6%), constipation (11% vs 7%), lightheadedness (10% vs 4%), and blurred vision (6% vs 3%) *(161)*. It should be noted that nausea and GI distress in patients taking nefazodone or trazodone is usually less severe than that produced by either SSRI or venlafaxine *(151)*.

A recent study of hepatotoxicity with the newer antidepressants using the Spanish Pharmacovigilance System database reported a high incidence of hepatotoxicity with nefazodone, with 28.96 cases per 100,000 patient-years, compared with 1.28 for sertraline and 4.0 for clomipramine *(42)*. The Canadian

Adverse Drug Reaction Monitoring Program found 32 cases of nefazodone-associated hepatotoxicity, with 26 cases classified as severe *(163)*. Patients were aged 30 to 69 yr and taking 100 to 600 mg/d. Of these, 68.8% were women and 88% developed toxicity within 6 mo of beginning the drug. Toxicity is hepatocellular in such cases, with high serum aminotransferase levels and increased total bilirubin. Withdrawal of nefazodone may lead to improvement in liver function; however deaths have also been reported *(42,164)*. It is likely that both pharmacovigilance studies suffer from underreporting *(42)*. If this is so, the incidence of hepatotoxicity associated with nefazodone may be even higher. In the United States, nefazodone now carries a "black box" warning concerning hepatotoxicity, and some countries have removed it from the market.

3.8.4. Mirtazapine

Mirtazapine is a 6-aza-analog of mianserin, but has a different pharmacologic profile *(165)*. Mianserin is a more potent noradrenergic reuptake blocker and 5-HT_2 antagonist than mirtazapine *(165)*. Mirtazapine is an effective antidepressant and antianxiety agent, and some authorities believe it has a more rapid onset than other antidepressants.

The mechanism of antidepressant action for mirtazapine is believed to be related to enhanced 5-HT and NE neurotransmission through potent and direct blockade of α_2-adrenergic autoreceptors and heteroreceptors *(165,166)*; this results in increased noradrenergic transmission which, in turn, stimulates α_1-adrenergic receptors on the serotonergic cell body. Blockade of the α_2-adrenergic heteroreceptor on the 5-HT nerve terminal prevents this receptor from "turning off" the increased 5-HT activity *(165,166)*. Mirtazapine is also a weak agonist of the 5-HT_{1A} receptor and causes some enhancement of 5-HT_{1A}-mediated serotonergic transmission through this mechanism *(166)*. Another major effect of mirtazapine is postsynaptic inhibition of 5-HT_2 and 5-HT_3 receptors, which some authorities believe limits the incidence of adverse effects that are usually associated with increased 5-HT activity and may also contribute to the anxiolytic and hypnotic effects of this drug.

Mirtazapine is marketed as a racemate of *R*-and *S*-enantiomers *(153)*. The *R*-enantiomer is more active, reaches higher plasma concentrations, and has a longer half-life than the *S*-enantiomer. Mirtazapine is rapidly absorbed from the GI tract after oral administration and has high bioavailability. It is 85% plasma protein bound and has an elimination half-life of 20 to 40 h *(167)*. Its major metabolite is demethylmirtazapine, which has only weak activity compared to the parent compound. Hepatic and renal impairment may cause a 30 and 50% decrease in oral mirtazapine clearance respectively, necessitating a dose adjustment in some patients *(167)*.

Mirtazapine is associated with dry mouth, drowsiness, and sedation in about 25% of patients *(31,165)*. Because of its antihistaminic activity, this drug may also cause weight gain in approx 10 to 20% of patients. A similar percentage of patients have elevated cholesterol and somewhat fewer have elevated triglycerides. Mirtazapine has a low incidence of sexual side effects *(72)*.

A causal relationship between mirtazapine and severe neutropenia (absolute neutrophil count <500/μL 3) has been reported in three cases. Of these, two patients developed agranulocytosis. All three patients recovered on discontinuation of the drug. It is therefore recommended that mirtazapine be stopped if any signs of infection with a low white cell count occur *(167)*.

3.9. Overdose

As a group, the antidepressants introduced since 1985 appear to be safer in terms of risk for overdose compared with the cyclic antidepressants. Although reports of mortality in overdose can be found for most of these agents, fatal overdoses usually occur when they are combined with other agents. One review reported 16 cases of overdose with up to 6750 mg of venlafaxine, either alone or with other medications and/or alcohol, without any deaths *(167)*. The most common problems were somnolence and sinus tachycardia. On the other hand, in a cohort study of 538 deliberate antidepressant overdoses, investigators found that both venlafaxine and SSRIs were more likely to cause serotonin syndromes, but less likely to cause coma, compared with TCAs *(168)*. They also found that 7 of 51 (14%) venlafaxine patients had seizures. No deaths were reported. In a study from the United Kingdom, investigators calculated the rate of fatal toxicity from antidepressants using the number of deaths per million prescriptions *(169)*. A rate of 13.2 was reported for venlafaxine, which placed it at the low end of TCA death rates (5.5–200.0), but higher than SSRI death rates (0.7–3.0). These data must be interpreted with caution because they do not take into account selection bias. For example, patients with a high suicide risk may be prescribed drugs that clinicians believe are safer (e.g., venlafaxine and SSRIs) or that are used preferentially in severe depression and avoid those with a low therapeutic index (e.g., TCAs) or those that may not be as effective in endogenous depression (e.g., SSRIs).

Data on the safety of mirtazapine in overdose are limited. One review reported eight patients in clinical trials who took an overdose of mirtazapine either alone in doses of 100 to 315 mg or with a benzodiazepines or "pain killer" *(156)*. No fatalities or ECG changes occurred. In another study, investigators analyzed six cases of overdose with mirtazapine, including that of a 3-yr-old child and a 90-yr-old man, which occurred during postmarketing surveillance and in clinical trials *(170)*. Again, no serious sequelae were reported. Mirtazapine safety in overdose appears to be comparable to that for SSRIs.

Seven cases of overdose with nefazodone, with or without the co-ingestion of other medications or alcohol, have been reported *(161)*. The symptoms of overdose included nausea, vomiting, and somnolence. All of the patients recovered with general supportive care *(161)*. The American Association of Poison Control Centers reported 1338 cases of nefazodone poisoning that were not associated with the use of other drugs *(171)*. There were no deaths, and the most serious effect was hypotension, which occurred in 1.6% of cases. More common symptoms included drowsiness (17.3%), nausea (9.7%), and dizziness (9.5%), which resolved within 24 h.

A fatal overdose of trazodone was reported in European literature. The patient developed arrhythmias (torsades de pointes and complete atrial valve block) and multiple organ failure, and died within 24 h after admission to an emergency department *(172)*.

Buproprion has been associated with fatalities when ingested with other medications or taken at very high doses. In one report, a overdose of 23 g resulted in death *(173)*. In another report, a patient recovered after grand mal seizures and sinus tachycardia occurred following the intentional ingestion of 9 g of bupropion *(174)*. A 3-yr, multicenter, retrospective study of bupropion overdoses reported to poison control centers described 58 cases of bupropion ingestion alone and 9 cases involving the ingestion of bupropion and a benzodiazepine *(175)*. There were no fatal outcomes among these patients, but many developed sinus tachycardia, hypotension, hypokalemia, lethargy, tremors, and seizures *(175)*. The seizure risk with bupropion increases with dose *(150)*; higher seizure rates are seen in bulimic patients, with approximately one-third of overdoses with bupropion IR resulting in seizures in these individuals *(6)*.

3.10. The Role of Newer Antidepressants in Therapeutics

Recently marketed non-SSRI antidepressants are considered by most clinicians to be second-line therapeutic options for treatment-refractory patients. Because these agents act on different neurological systems, they comprise a rational choice for nonresponders *(148)*. They are also used as adjuncts to SSRIs to augment the effect of SSRIs in partial responders. Their overall efficacy as antidepressants is comparable to that of the standard antidepressant drug classes, e.g., SSRIs, TCAs, and MAOIs; some data indicate they are superior to SSRIs in depression with melancholic or endogenous features. They are second-line agents primarily because of cost, however, not efficacy.

In addition to their use in depression, studies support their efficacy in anxiety disorders (especially venlafaxine, mirtazapine, and nefazodone) and ADHD (venlafaxine and bupropion). The role of bupropion in smoking cessation is well recognized *(176)*; it has also been used to treat patients with neuropathic pain *(177)*. It is commonly the agent of choice when SSRI-induced sexual dysfunction

limits continued SSRI treatment. Although some have added it to SSRI therapy in patients with sexual dysfunction, we have found sildenafil to be more effective.

Trazodone has a limited role, but may be useful in promoting sleep in patients taking energizing antidepressants or as an augmentation agent. Nefazodone is a very effective antidepressant, but its use has declined because reports of hepatotoxicity have appeared. Mirtazapine is also an effective antidepressant and antianxiety agent, but its adverse-effect profile may be problematic. It is frequently used in combination with other antidepressants as an augmentation strategy and to improve sleep.

The possibility of a more rapid onset of clinical effect for agents that have mixed actions, mirtazapine and venlafaxine in particular, has been the subject of much debate. At present, data are insufficient to support such a claim.

3.11. Antidepressants in Development

3.11.1. Reboxetine

Reboxetine is an SNRI approved for use as an antidepressant in Canada and Europe; it is not yet available in the United States. It is a racemic mixture of two stereoisomers, consisting of (*S*, *S*)-(+)- and (*R*,*R*)-(–)-reboxetine; the (*S*,*S*) enantiomer is more potent as an antidepressant and has greater affinity to the NE receptor *(178,179)*.

Women have a 30% higher ratio of *S*,*S* to *R*,*R* than men *(180)*. Reboxetine downregulates β-adrenergic receptors *(178)*. Although it is somewhat less potent as a NE reuptake inhibitor than desipramine and nortriptyline *(153)*, it has a very low affinity for α-adrenergic and muscarinic cholinergic receptors and no affinity for serotonergic or dopaminergic receptors *(178)*.

Reboxetine has linear pharmacokinetics with either single or multiple oral doses. Its elimination half-life is approx 12 to 13 h; its absolute bioavailability is 94.5%. Reboxetine is rapidly absorbed, reaching its maximal concentration within 2 h after administration *(178,179)*. It is 97% bound to plasma proteins, particularly α_1-acid glycoprotein *(178,179)*. The suggested dosage for reboxetine is 8 to 10 mg/d in divided doses. *(181)* It has no active metabolites. Plasma concentrations of reboxetine are increased in patients who are elderly or have hepatic or renal insufficiency *(178,179)*. The recommended dose for such patients is 4 to 6 mg/d. Reboxetine is metabolized hepatically by cytochrome P450 CYP3A4, but has no known inhibitory or inducing effect on any of the CYP isoforms.

3.11.1.1. Adverse Effects (Table 9)

Clinical trials have established the safety of reboxetine *(181,182)*. The most frequent adverse effects seen with this drug include dry mouth, constipation, increased diaphoresis, insomnia, and urinary retention *(153,183–185)*; most of

Table 9. Reported Side Effects of Reboxetine

Common	*Less Common*
Dry mouth	Headache
Insomnia	Palpations
Constipation	Tachycardia
Increased sweating	Decreased appetite
Hypotension	Dizziness
Blurred vision	Abnormal sensation in penis/scrotum
Urinary hesitancy	

these appear to be dose-related *(181,184)*. Clinically insignificant orthostatic hypotension has been reported *(183)*. Also, headache, palpitations, tachycardia, decreased appetite, dizziness, and abnormal sensation in the genitals have been reported with reboxetine use; the incidence of all side effects, except tachycardia, was dose-related *(184)*.

Reboxetine did not alter cardiac conduction in healthy volunteers in a randomized, open-label, placebo-controlled study designed specifically to test its effect on cardiac repolarization at different plasma concentrations, including those exceeding the normal therapeutic range *(184)*. ECGs indicated no change in QTc, P-R, and QRS intervals as a result of reboxetine treatment *(184)*; however, reboxetine resulted in an increase in heart rate by 8 to 11 beats per minute at doses of 8 mg/d or higher *(184)*.

3.11.1.2. Efficacy

In several double-blind, randomized clinical trials conducted mostly outside the United States, investigators demonstrated the superiority of reboxetine to placebo and established antidepressants (e.g., fluoxetine) in patients with moderate to severe MDD. During a 6-wk, randomized, double-blind, placebo-controlled study of reboxetine, investigators found that both improvement in the mean HAM-D-21 total score and the response rate (defined as the percentage of patients achieving ≥50% reduction in HAM-D-21 total score) were significantly greater in hospitalized patients with MDD who were treated with reboxetine than in those who took placebo *(183)*.

In an 8-wk, double-blind, randomized, placebo- and active treatment-controlled, multisite clinical trial of 381 in-patients and outpatients with MDD and baseline HAM-D-17 scores of 22 or higher, investigators found reboxetine 8 to 10 mg/d to be as effective as fluoxetine 20 to 40 mg/d (as judged by a similar percentage of patients achieving ≥50% reduction in HAM-D scores) *(185)*. Both active drugs were shown to be significantly superior to placebo *(185)*. Efficacy in severe depression was also found and replicated by Montgomery and associ-

ates *(186)*. Some investigators have found reboxetine to have a faster onset of action than other antidepressants, as improved HAM-D scores have been obtained as soon as 10 d after treatment begins *(182)*.

3.11.2. Duloxetine

Duloxetine hydrochloride is an antidepressant that inhibits both 5-HT and NE reuptake and is more potent in this effect than venlafaxine *(187)*. The recommended dose is 60 to 120 mg/d in a single dose. Duloxetine is a CYP2D6 inhibitor. Adverse effects include nausea, insomnia, headache, somnolence, dry mouth, tremor, hypertension, and tachycardia. It appears to be similar to venlafaxine in terms of its adverse effect profile.

3.11.3. Mifepristone

Mifepristone is a progesterone-receptor antagonist and glucocorticoid antagonist which, in preliminary studies, has been effective short-term as monotherapy for patients with psychotic major depression (PMD) at doses of 600 to 800 mg/d *(188,189)*. Adverse effects include fatigue, anorexia, and nausea. A maculopapular erythematous cutaneous eruption has also been reported *(188,189)*.

3.11.4. Substance P

In recent studies, investigators have examined compounds that inhibit substance P (SP)-neurokinin-1 (NK_1) receptor pathways as potential antidepressants *(190)*. SP and NK_1 receptors are located in brain regions that regulate mood and are associated with neurotransmitter pathways thought to play a role in depression. In one postmortem study, higher concentrations of SP were found in the CSF of depressed patients compared with controls *(191)*. Aprepitant and Compound A, which are SP-NK_1 antagonists, have a high affinity and selectivity for the NK_1 receptor, but have not been shown to inhibit other depression-related neurotransmitters. Both compounds have been studied for the treatment of depression, with mixed results.

4. MONOAMINE OXIDASE INHIBITORS

4.1. History

MAOIs were the first antidepressants in clinical use. Iproniazid, the isopropyl derivative of isoniazid, was developed by Herbert Fox at Roche Laboratories in 1951 for the treatment of patients with tuberculosis *(192)*. The drug proved ineffective for tuberculosis, but did have a mood-elevating effect in some patients *(193)*. Its antidepressant properties are believed to be the result of the inhibition

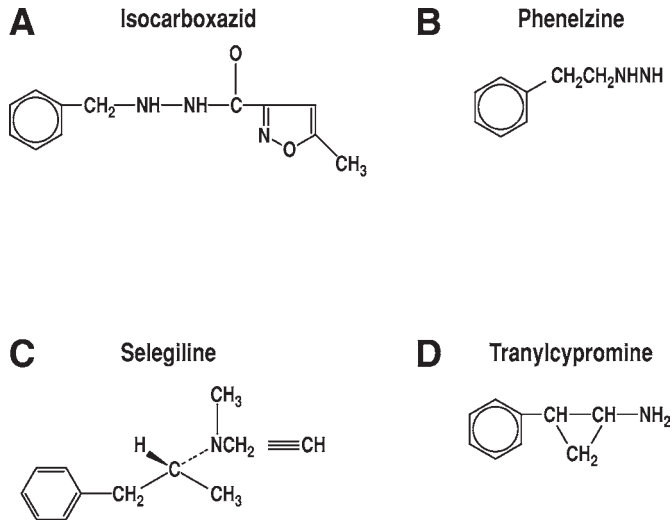

Fig. 5. MAOIs: chemical structures.

of monoamine oxidase (MAO), the enzyme that catalyzes the oxidative deamination of monoamines such as DA, epinephrine, NE, and 5-HT, thereby rendering the amine inactive *(5c,194–196)*. Inhibition of these enzymes results in increased availability of the biogenic amines by preventing their breakdown. Unfortunately, most US clinicians who have entered practice during the last two decades have little experience with MAOIs for the treatment of patients with depression. The efficacy of SSRIs in atypical and mixed depression accounts in part for this phenomenon. However, as described in an upcoming section, the pharmacological activity of MAOIs is unique and they should still be considered alternative agents when other antidepressants are not effective.

During the 1950s and 1960s, MAOIs comprised a primary form of treatment for patients with depression. At their peak, there were five hydrazines (isocarboxazid, nialamide, mebanazine, phenelzine, and pheniprazine), one-indole (etryptamine), and one-cyclopropyla-mine (tranylcypromine) in clinical use *(5c)*. The first MAOI, iproniazid, and then pheniprazine were withdrawn from the market because of hepatotoxicity *(5c)*. As clinical experience grew, the serious adverse effects of MAOIs, combined with the introduction of safer antidepressants, led to a decline in their use. Currently, only three MAOIs are approved by the FDA for the treatment of patients with depression in the United States: isocarboxazide (Marplan®), phenelzine (Nardil®), and tranylcypromine (Parnate®). Their chemical structures are shown in Fig. 5.

4.2. Pharmacology

A clinically relevant classification of MAOIs is based on three characteristics: a hydrazine vs nonhydrazine structure; selectivity for MAO-A or MAO-B; and reversibility of MAO inhibition. Phenelzine and isocarboxazid are hydrazines. The nonhydrazine MAOIs tranylcypromine and selegiline (Eldepryl®) are arylalkamines (*see* Fig.5). Hydrazine derivatives may be associated with hepatotoxicity; thus, patients taking this drug require liver enzyme monitoring during treatment.

The MAO enzyme is located principally on the outer membrane of the mitochondria. Its role is oxidative deamination of monoamines, many of which modulate mood states. The development of substrate-selective MAOIs during the 1960s provided evidence for the existence of two forms of the enzyme: MAO-A and MAO-B. MAO-A selectively deaminates 5-HT, NE, and epinephrine, whereas MAO-B selectively metabolizes tyramine, phenylethylamine, phenylethanolamine, and benzylamine. Both forms are involved in tyramine, tryptamine, and DA metabolism, although some authorities believe DA is the preferred substrate for MAO-B. Both MAO-A and MAO-B are widely distributed in the human body, with some cells containing both forms while others contain only one. Human brain MAO is 70 to 95% MAO-B; in other species (e.g., rodents), MAO-A may predominate in the brain. In humans, gut and platelet MAO is primarily type A.

Although selegiline (referred to as L-deprenyl in older research literature) has selectivity for MAO-B at low doses; as the dose increases, it affects both forms of the enzyme. It is approved for use as an anti-Parkinson agent, but has also shown promise as an antidepressant at doses higher than those used for parkinsonism. Pargyline, a drug that is no longer marketed but was once used as an antihypertensive, is selective for MAO-B. All other clinically available MAOIs inhibit both MAO-A and MAO-B. An interesting compound is TV-3326, a cholinesterase inhibitor that affects both MAO-A and MAO-B but inhibits Type A differentially in the brain and does not inhibit Type A in the gut of rabbits *(197)*. The reason for this selectivity is unclear, but is possibly related to metabolites. It suggests that it may be possible to develop irreversible MAOIs that do not induce a hypertensive crisis when taken with tyramine-containing foods. Another intriguing strategy to avoid the tyramine-hypertensive reaction is a transdermal delivery system for selegiline that permits high brain concentrations of the drug to block both type A and type B MAO in the brain without affecting intestinal MAO-A. Inhibition of MAO type A in the brain is necessary for antidepressant effects, whereas gut inhibition causes the tyramine reaction.

Drug-induced MAO inhibition may be reversible, as is the case with moclobemide and brofaromine (neither of which is marketed in the United States). This class of MAOIs is referred to as RIMA (reversible inhibitors of monoamine oxidase-A). The advantages of the reversible agents include fewer

risks for interactions with tyramine-containing foods, because tyramine is able to displace RIMA from MAO binding sites. In contrast, the agents available in the United States are classified as irreversible or "suicide enzyme inhibitors" because they form covalent bonds at specific sites on the enzyme. Phenelzine inhibits the flavin group and phenelzine the sulfhydryl group. There is some evidence that MAO activity may return more quickly following discontinuation of tranylcypromine (3–5 d) compared with phenelzine. There is considerable variability among patients; therefore, most clinicians follow the manufacturer's guideline of a 10- to 14-d interval after discontinuing an MAOI prior to starting a drug that has the potential for an adverse interaction.

The pharmacological properties of available agents have not been well studied, although there has been renewed interest in the area *(198)*. Phenelzine (Nardil®) is rapidly absorbed after oral administration and reaches maximum concentrations 2 to 4 h after the dose. It has a short elimination half-life (1.5–4.0 h), but its pharmacodynamic effects are long lasting—the result of irreversible MAO inhibition. Its metabolic pathways *(198)* are not well known; however, it is both a substrate and inhibitor of MAO, and this pathway may lead to the production of phenylacetic acid. Thus, the intermediate metabolites may be phenylethylidene hydrazine and 1,2-phenylethyldiazene, also resulting from the action of MAO. Another metabolite is believed to be phenylethylamine (PEA), substantial levels of which may be derived both from the metabolism of phenelzine and inhibition of endogenous metabolism (PEA is a substrate of MAO). Another pathway probably involves ring hydroxylation leading to the formation of *p*-hydroxyphenelzine and via MAO to *p*-hydroxyphenylacetic acid. Contrary to the findings of early studies, it is now generally believed that despite its structural similarity to isoniazid, phenelzine acetylation is only a minor pathway, but low levels of *N*-acetyl phenelzine have also been reported. The contributions of the metabolites to clinical effects are not known.

Tranylcypromine (Parnate®) is also rapidly absorbed, reaching peak plasma levels 1 to 2 h after an oral dose. It too is rapidly eliminated, with a half-life of less than 2 h; however, a single 10-mg dose can produce MAO inhibition lasting as long as 1 wk. Metabolic pathways in humans remain uncertain. Perhaps the most controversy over this drug has centered on the issue of whether it is metabolized to amphetamine, which was detected in the plasma of a patient who took an overdose of tranylcypromine *(199)*. In more recent studies, investigators have not detected amphetamine after any dose of tranylcypromine in humans or animals *(200,201)*. Most of the information on tranylcypromine metabolites is derived from animal studies, and their clinical relevance is not established. Tranylcypromine is marketed as a racemic mixture, and studies indicate that *S*-tranylcypromine is absorbed and metabolized more slowly, and reaches higher blood levels than *R*-tranylcypromine *(202,203)*. *R*-tranylcypromine is a more

potent inhibitor of MAO, but is less potent in inhibiting catecholamine reuptake than *S*-tranylcypromine *(198)*.

We are unaware of published studies on the human pharmacokinetics of isocarboxazid (Marplan®).

Selegiline (Eldepryl®) has antidepressant effects at oral doses of 40 to 60 mg/d, although it is not approved by the FDA for this use. Its absorption is increased by food; Its elimination half-life is 2 h after a single dose, but 10 h at steady state. The elimination half-life of selegiline delivered using the transdermal delivery system ("patch") is 18 h after a single dose and 22 to 30 h with chronic dosing. Time to reach steady state with the patch is 4 to 5 d. With oral administration, there is wide variability in selegiline metabolism among individuals. Its primary metabolite, desmethylselegiline, possesses MAO-B inhibiting activity; although it is less potent than the parent compound, it is present in higher concentrations. Other metabolites include L-amphetamine and L-methamphetamine; however the concentrations of these metabolites are thought to be too low to contribute to the therapeutic effects of the drug. Even at the 10-mg oral dose used to treat parkinsonism, MAO-B selectivity is not absolute, and hypertensive reactions have occasionally been observed after the ingestion of tyramine-containing foods. As the dose increases, selectivity is lost, and although the exact dose at which selectivity is lost varies, at doses exceeding 30 mg daily, tyramine restrictions should be instituted. The transdermal delivery system has been studied most widely in a 20-mg dose, however, some authorities believe higher doses may be needed to consistently demonstrate antidepressant efficacy. Tyramine-restricted diets are not necessary with the patch. The concentration of metabolites is 50 to 70% lower with the patch than with the oral formulation.

RIMAs include moclobemide and brofaromine, both of which have proven antidepressant efficacy and are considered as effective as and even better tolerated than the TCAs *(39,204–206)*. RIMAs are also thought to have a much improved side-effect profile owing to their reversibility and selectivity. Although not entirely free of risk, they may be less likely to be associated with the serotonin syndrome based on the significantly smaller number of reported cases compared with traditional MAOIs *(207)*. At this time, brofaromine is not being developed as an antidepressant for reasons unrelated to its adverse effects or efficacy. It had been studied as a possible treatment for patients with panic disorder, and clinical improvements in anxiety symptoms and subsequent reduction in agoraphobic avoidance have been found *(208)*.

Moclobemide is widely used throughout much of the world, except the United States *(5c,209)*. Moclobemide was found to be comparable to the SSRIs in both efficacy and tolerability *(205)*. It was also found to be better tolerated, with an earlier onset of antidepressant activity compared to clomipramine in a UK-based study *(206)*.

Conventional explanations of the mechanism of antidepressant activity for MAOIs are consistent with the biogenic amine hypothesis of depression, attributing their effect to the inactivation of an enzyme responsible for the catabolic metabolism of these amines, which results in increased concentration of NE, DA, and 5-HT and trace levels of amines in the brain *(3)*. In turn, these effects lead ultimately to changes in gene expression (*see* SSRI section, and Chapter 1, in this volume). Although an integrative theory has appeal, it should not be misinterpreted to mean that all MAOIs act identically. At least three related mechanisms have been identified that may contribute to the therapeutic actions of MAOIs: (1) inhibition of the metabolism of brain biogenic amines, including trace amines such as phenylethlylamine, tyramine, and octopamine; (2) enhanced neurotransmitter release, blockade of synaptic reuptake, and/or direct receptor effects; and (3) inhibition of other enzymes, thereby altering other neurotransmitters.

Both phenelzine and tranylcypromine have direct effects on the reuptake of DA, noradrenaline, and, to a lesser extent, 5-HT. They have been reported to downregulate β_1, β_2, and α_2 adrenoreceptors, and the 5-HT somatodendritic autoreceptor. Tryptamine receptors are reduced in rat cortex after chronic tranylcypromine administration and 5-HT_2 receptors are decreased. Phenelzine and/or its metabolites inhibit γ-aminobutyric acid (GABA) and alanine transaminases (leading to an elevation in brain GABA and alanine levels), DA β-hydroxylase, tryptophan pyrolase, aromatic amino acid decarboxylase, and tyramine amino transaminase.

4.3. Clinical Use

MAOIs are now considered second- or third-line agents in depression because of the potential for drug–drug and drug–food interactions. They have established efficacy in atypical depression, bipolar depression, and dysthymia, and in some studies they have even been found to be superior to other established antidepressants *(206,208,210–214)*. MAOIs have also been effective in the treatment of depression in the elderly *(215)*. MAOIs were as effective as the TCAs in all recent controlled studies of depressed patients with either typical (unipolar) or atypical depression. Phenelzine superiority to imipramine, for example, was demonstrated in atypical depression *(216)*. Other studies support MAOI advantages for the treatment of patients with atypical depression *(211,212)*. Some have argued that higher-than-usual doses of the MAOI may be needed in severely depressed patients and those who failed treatment with a TCA *(217)*.

The use of MAOIs in patients who failed trials of other antidepressants is well supported *(212,217–219)*. In a double-blind crossover trial, phenelzine was effective in up to 67% of depressed outpatients who were not responding to treatment with imipramine *(210)*. Tranylcypromine in combination with lithium was effective in treating depression in 12 treatment-refractory patients *(218)*. Tranyl-

cypromine was found more effective than imipramine for bipolar depression and is often used to treat patients during the depressive phases of the illness *(220)*. In bipolar patients who developed manic states associated with antidepressant treatment, those treated with MAOIs experienced milder and shorter manic episodes than those treated with SSRIs or TCAs *(47)*.

MAOIs are also effective in dysthymia, anxiety, and phobic disorders *(213)*. Some reports of its efficacy in individuals with PTSD and personality disorders have been made, although the data are conflicting *(97,221–223)*.

4.4. Adverse Effects

The older MAOIs have been limited in use as a consequence of their potential for toxicity. Of greatest concern have been drug–drug interactions with sympathomimetic amines and the food–drug interaction with tyramine, both of which may cause a hypertensive crisis. Another serious adverse effect is the serotonin syndrome, which can occur when MAOIs are coadministered with SSRIs *(53)*. Other significant side effects include dizziness, hypotension, liver toxicity, dry mouth with GI upset, blurred vision, urinary retention/hesitancy, headache, fatigue late in the day, skin rashes, weight gain, pedal edema, and paresthesias. Muscle pain and paresthesias may respond to 100 mg/d vitamin B_6 (pyridoxine). Phenelzine is known to cause sedation, especially late in the day, and tranylcypromine can cause insomnia. Hypotension, particularly orthostatic hypotension, is a major concern when treating elderly patients because it increases their risk for falls and fractures. We have not found a consistently effective way to manage orthostatic hypotension, although some clinicians recommend increased fluid and salt intake, 0.3 to 0.8 mg/d of fludrocortisone , and support hose.

Sexual dysfunction—e.g., decreased libido, erectile dysfunction, and inhibition of ejaculation in males and anorgasmia in females—has been reported *(66)*. These are common problems and have been shown to occur with all of MAOIs. Some of these are known to resolve over time; for example, spontaneous remission of MAOI-induced anorgasmia has been reported *(224)*. It is also worth noting that rates of sexual effects with MAOIs seem to be equivalent to those seen with TCA drugs and significantly lower than those seen with SSRIs *(65)*.

4.4.1. Hypertensive Crises

During the 1960s, there were several case reports of a sudden emergence of hypertension in patients taking MAOIs who were exposed to aged cheese. The name "cheese reaction" was coined by Asatoor and associates in 1963, who hypothesized that the combination of MAOIs with the pressor tyramine in cheese was responsible for this reaction*(225)*. Dietary precautions to limit the ingestion of tyramine-containing foods has greatly increased the safety of MAOI therapy. It is generally accepted that more than 10 mg of tyramine must be ingested to

produce a clinically significant interaction. Symptoms may include severe headache, nausea, neck stiffness, diaphoresis, mydriasis, neuromuscular irritability, occasionally cardiac arrhythmias, and severe hypertension *(225–227)*. Hypertensive crises are managed with intravenous phentolamine in closely monitored medical settings. Some clinicians advise patients to take oral nifedipine 10 mg if hypertension develops.

Our dietary recommendations are shown in Table 10

4.4.2. Drug–Drug Interactions

Serotonin syndrome has been reported with concurrent administration of MAOI and drugs that increase 5-HT activity. The most common drug interactions associated with serotonin syndrome were combinations of an MAOI and L-tryptophan (removed from the US market because of an independent association with eosinophilia–myalgia syndrome) and fluoxetine *(53)*. There is also a report of serotonin syndrome in patients who were started on clomipramine 4 wk after discontinuation of clorgyline (an MAO-A inhibitor) *(53,228)*. A fatal case of serotonin syndrome occurred after combined moclobemide and citalopram intoxication in a Belgian patient with a history of depression and suicide attempts *(55)*. The serotonin syndrome consists of confusion or hypomania, agitation or restlessness, tremor, hyperreflexia, myoclonus, fever, diaphoresis, diarrhea, incoordination, and shivering. In general, treatment for serotonin syndrome should be the immediate withdrawal of the offending agent and supportive measures.

Sympathomimetic amines—which are often contained in cold remedies, weight control products, and dietary supplements—can cause a hypertensive reaction when taken with an MAOI. Both indirect-acting sympathomimetics (more dangerous) as well as direct-acting (less dangerous) sympathomimetics may cause a hypertensive crisis when administered with MAOIs. The following indirect-acting vasopressors produce their pressor effects through the release of bound intraneuronal stores of NE and DA: amphetamine, methamphetamine, cyclopentamine, ephedrine, pseudoephedrine, L-dopa, DA, mephentermine, phentermine, metaraminol, methylphenidate, phenylpropanolamine, and tyramine. The indirect-acting agents are generally believed to be more dangerous than the direct-acting amines, with the indirect agents ephedrine, pseudoephedrine, and phenylpropanolamine being especially hazardous *(229)*.

4.5. Overdose

MAOIs are dangerous in overdose, and suicidal patients may exploit their inherent toxicity to commit suicide *(230)*. A fatal dose is considered to be 4 to 6 mg/kg body weight *(39)*. The onset of symptoms usually occurs within 6 to 12 h after the ingestion of a toxic dose, but has been known to be delayed by 24 h. The clinical presentation of a patient who overdosed with an MAOI may include

Table 10. Dietary Restrictions With MAOI Therapy (*See* refs. *350* and *351* for Tyramine Content of Specific Foods)

Contraindicated	*Moderate Restrictions*	*Relative Restrictions*	*Unnecessary to Restrict*
Aged cheese (English Stilton, blue cheese, 3-yr-old white, old cheddar, and others)	Bottled or canned beer (highest content: 1.0–1.5 mg tyramine/serving)	Red or white wine (most have <0.5 mg tyramine/serving)	Bananas
Marmite yeast	Pizza (caution patients about different types of cheeses that may be used	Banana peel or overripe bananas (1.4 mg tyramine per peel)	Chocolate
Sauerkraut		Distilled spirits (most do not contain tyramine, but some MAOI inhibit acetaldehyde metabolism creating a potential for a disulfiram-like effect)	Fresh/mild cheeses
Some aged/cured meats (mg tyramine/30 g meat: salami 5.6, mortadella 5.5, air-dried sausage 3.8)			Fresh meat
Tap beer			Pickled/smoked fish
Improperly stored meats or fish			Yeast extracts, except Marmite
Soy sauce (tyramine content is highly variable)			Chicken Liver (little evidence unless not fresh, by day 5 contains 1.5 mg tyramine/30 g, while undetectable at day 1)
Soybean			
Tofu			
Fava Beans (reactions not related to tyramine content, which is negligible)			

fainting, anxiety, flushing, and sweating, headache, tachycardia, and tremor in the early stages; this will progress to agitation, coma, seizures, severe hypotension, and possibly cardiac arrest *(39)*. Also, physical tolerance and dependence has been reported with tranylcypromine, with one patient taking doses as high as 440 mg daily *(231)*.

5. AUGMENTATION STRATEGIES

5.1. Combinations of Antidepressants

We recommend augmentation approaches only after monotherapy with two different antidepressants has failed; this opinion is based on the observation that at least 50% of out-of-class switches result in a treatment response *(232–234)*. In partial responders who have been taking adequate doses for sufficient time, we are inclined to follow an augmentation strategy. Once a decision has been made to augment, a number of options are available. The most common augmentation strategy is to combine antidepressants from different classes. With an SSRI, our current practice is to add mirtazapine in doses of 15 to 30 mg, a strategy that is supported by the somewhat limited literature on the topic *(235–237)*. Our personal experience has been less favorable with bupropion augmentation, but that may be an artifact of the clinical population we treat. There is a small body of evidence that supports its efficacy in the augmentation of SSRIs *(238–240)*, and survey data indicate that it is the most popular SSRI augmentation strategy among clinicians *(241)*. The addition of low doses of a TCA, such as desipramine or nortriptyline, has yielded mixed results *(242–245)*.

Lithium probably has the best evidence in supporting of its efficacy as an augmentation agent; however, it is less commonly used than other approaches. In studies conducted during the early 1980s, investigators found that the addition of lithium to TCA therapy in nonresponding patients with unipolar depression resulted in improvement in depression *(246,247)* and was comparable to thyroid (T3) supplementation, both of which were better than placebo *(248)*. Other investigators reported similar results, including efficacy in potentiating MAOIs, although a lack of efficacy and toxicity has also been reported *(249–251)*. Most studies have found that lithium is also effective in the augmentation of SSRIs *(243,252–254)*. We suspect that the reasons for less frequent use of lithium are its low therapeutic index and the necessity for monitoring serum levels. Typical augmentation doses are 600 to 1200 mg/d to produce a target serum level of 0.6 to 0.9 mEq/L.

5.2. Buspirone

Conflicting data exist concerning the efficacy of buspirone augmentation. Many open trials have suggested its efficacy as an augmentation strategy *(255–258)*; however, placebo-controlled trials have not fully supported the clinical

report findings. In a study of 102 outpatients with MDD who did not have an adequate response to 6 wk of treatment with fluoxetine or citalopram, buspirone 10 to 30 mg twice a day [bid] or placebo was added after a 2-wk placebo washout period *(259)*. Although buspirone was superior to placebo after 1 wk, based on the MADRS, no difference was found at 6 wk, except in patients with baseline MADRS scores above 30. In another study of 119 patients who failed to respond to paroxetine or placebo after a minimum of 4 wk, buspirone or placebo was added for an additional 4 wk *(260)*. Although the combinations were well tolerated, there was no difference between groups, with both showing a substantial improvement on the Clinical Global Impression Scale (buspirone: 50.9%; placebo: 46.7%). An open-label, 2-wk , follow-up phase with buspirone augmentation produced a response rate of 69.4%. Despite the lack of strong support for its efficacy, we have found that the addition buspirone in doses of 30 to 50 mg/d produces dramatic results in some patients; however, we acknowledge that this may be a placebo effect.

5.3. Psychostimulants

Methylphenidate is a secondary amine stimulant that exists as four isomers, with the marketed preparation contains the d,l-threo racemate, with d-threo racemate isomer believed to be responsible for therapeutic activity. The major metabolite is ritalinic acid (approx 70%); smaller amounts of *p*-hydroxyritalinic acid (1%) and 6-oxoritalinic acid (2%) are also produced. It is believed that only the parent compound contributes to the therapeutic effects. In its standard preparation (Ritalin® immediate release), methylphenidate reaches peak plasma concentrations in 1 to 2 h, has an elimination half-life of 2 to 3 h, and exhibits dose proportionality throughout the therapeutic range *(261)*. Newer preparations of methylphenidate include d-methylphenidate (Focalin®) and long-acting preparations (Metadate CD®, Concerta®, Ritalin-SR®). Dextroamphetamine is available as Dexedrine® and Dexedrine Spansule®. Adderall® and Adderall-XR® contain a mixture of d-amphetamine and l-amphetamine.

The pharmacologic actions of methylphenidate and dextroamphetamine are complex. Both drugs affect DA and NE reuptake, although there may be subtle differences in the mechanism of action. Also, both drugs promote the release of monoamines, but methylphenidate acts on reserpine sensitive storage pools while dextroamphetamine releases them from newly synthesized stores. Both drugs affect α-adrenergic receptors. The effects of stimulants on acetylcholine, 5-HT, glutamate, and GABA result from the influence of DA on these systems and, in some cases, from direct actions at receptors. Their activity in the brain, as observed during PET studies, also suggests differences among stimulants.

There has been a long history of stimulant therapy in depression, both as monotherapy in the medically ill and as an augmenting agent *(262–268)*. In the Boston area, it is not uncommon for stimulants to be prescribed as sole agents or in combination with antidepressants. The scientific literature supporting this practice is weak, but clinical experience and data from surveys of psychiatrists in the United States and Canada provide support for it. The body of new research in this area appears to be growing *(269,270)*.

In clinical practice, methyphenidate therapy can be started with 10 mg/d and increased gradually to 80 mg/d. We use approximately half that dose for dextroamphetamine therapy. Frequent patient monitoring, both for adverse effects and misuse, is necessary. Once the proper dose is achieved, the response is rapid. Modafinil (Provigil ®), a medication for the treatment of narcolepsy, has also been used in doses of 100 to 200 mg/d to augment and hasten the antidepressant response *(271,272)*.

5.4. Thyroid Hormone

In the first of a series of studies of thyroid augmentation of antidepressant response, Prange and associates evaluated imipramine 150 mg plus of triiodothyronine (T_3) 25 μg in 20 euthyroid patients (16 women and 4 men), most of whom had been diagnosed with unipolar retarded depression *(273)*. The reduction in HAM-D score was greater and occurred more rapidly in the T_3 group. Other studies from the same research group found that women with nonretarded depression also responded to T_3 augmentation, but men did not. In a study of T_3 augmentation of amitriptyline, patients who were treated with T_3 40 μg with amitriptyline 100 mg improved more rapidly than those taking T_3 20 μg or placebo; women had better responses than men *(274)*. An open trial of clomipramine had similar results *(275)*. In several other studies, researchers found that patients who were unresponsive to TCAs improved with the addition of T_3 in doses of 25 to 50 μg *(276–279)*. SSRI augmentation with T_3 appears to be efficacious and well tolerated *(280–282)*. However, other studies have indicated a lack of efficacy *(283)* or efficacy only in patients with an elevated thyroid-stimulating hormone response to thyrotropin-releasing hormone *(284)*. It is not clear whether T_3 augmentation is superior to thyroxine (T_4) or lithium augmentation. In one small study, the findings suggested that T_4 augmentation should precede lithium augmentation *(285)*. The weight of evidence suggests that T_3 is more effective than T_4 augmentation; however, some studies suggest that it may be necessary to administer high doses of T_4 for long periods of time to obtain the maximum benefit. In an open-label study of T_4 482 μg/d administered for 8 wk, investigators reported a substantial improvement in depression in more than half of the sample *(286)*.

A meta-analysis of six double-blind, placebo-controlled clinical trials evaluating the coadministration of T_3 and TCAs concluded that adjunctive T_3 therapy led to a more rapid clinical response *(287)*. Women were more likely to benefit from T_3 than men *(287)*. The mechanism of action is believed to be related to the correction of underlying subsyndromal thyroid dysfu≠nction or direct effects on adrenergic activity.

In clinical practice, T_3 (Cytomel®) therapy begins with 12.5 to 25 µg and may be increased weekly up to 50 µg/d. One to 4 wk is considered an adequate trial of T_3 augmentation. It should be used with caution in patients with arrhythmias, hypertension, and cardiac disease. Some authorities believe that the best response occurs in women, patients with mild thyroid abnormalities, and individuals with severe or retarded depression.

5.5. Testosterone

Testosterone supplementation was recently shown to improve depressive symptoms for a subset of male patients with low or borderline testosterone levels and refractory depression. A randomized, double-blind, placebo-controlled trial in 23 patients with a low or borderline serum testosterone level (100–350 ng/dL; normal range: 270–1070 ng/dL) who met the *DSM-IV* criteria for current MDD and were being treated with antidepressant medications prior to and during the trial received either testosterone gel (1% gel, 10 g/d) or placebo for 8 wk *(288)*. There was significantly greater improvement in HAM-D score in the testosterone group compared to placebo in both the vegetative and affective symptom subscales of the HAM-D Scale. Overall, the testosterone gel was well tolerated. One patient in the study experienced exacerbation of benign prostatic hyperplasia, which may be attributed to testosterone supplementation, and was withdrawn from the study. The mechanism of antidepressant action for testosterone is not known.

5.6. Estrogen

The increased prevalence of depression in perimenopausal and postmenopausal women has led to several studies examining the role of estrogen replacement and augmentation therapy in women during these stages of life. Perimenopause is the phase before menopause, which continues until menstruation has ceased for 12 consecutive months. Common symptoms include hot flashes, decreased libido, sleep disruption, and depression. In one study, perimenopausal women with major depression, dysthymic disorder, or minor depressive disorder received transdermal

patches of 17[β]-estradiol 100 μg or placebo for 12 wk *(289)*. Among the women treated with estradiol, 68% had remission of depression compared to 20% in the placebo group *(289)*. In an earlier study, investigators also found that estrogen was superior to placebo in reducing depressive symptoms in perimenopausal women *(290)*. In a small study of 16 perimenopausal women, investigators found that estrogen replacement therapy (ERT) was effective in treating depression *(291)*. Other studies have found that both transdermal patches and sublingual estradiol improved mood in women with premenstrual dysphoric disorder and postpartum depression *(292–294)*. Investigators in other studies have not found efficacy of ERT for depression *(295–297)*. In a review of the literature, Epperson and associates *(298)* reported that five studies found ERT to be more effective than placebo in a group of both perimenopausal and postmenopausal women and five found it as effective as placebo. In one study *(299)*, investigators found that estrogen was superior to placebo in perimenopausal but not postmenopausal women. In an early study, 5 to 25 mg/d of estrogen—which is 5 to 25 times the replacement dose—was more effective than placebo in the treatment of women with depression who were unresponsive to antidepressants *(300)*. In a more recent study in postmenopausal Chinese women, investigators did not find differences between 1 and 2 mg of oral estradiol and placebo on symptoms of anxiety and depression *(301)*.

In addition to ERT as monotherapy, it has also been used as an augmentation strategy in women with menopausal depression. Fluoxetine in combination with ERT proved superior to fluoxetine alone in a single study *(302)*. On the other hand, Oppenheim and colleagues did not find estrogen augmentation effective when administered with imipramine (cf. *298*).

In summary, data are conflicting regarding the efficacy of ERT in perimenopausal or postmenopausal women with depression. Some investigators have attributed inconsistent findings to the use of oral preparations with poor bioavailability, failure to use laboratory measures to confirm menopausal status, and wide variability of diagnostic and outcome measures *(289)*. The mechanism of action of estrogen is unknown; however, a substantial body of evidence indicates that it influences monoamine and GABA systems. There is little evidence to support the use of estrogen augmentation with cyclic antidepressants, although some evidence supports its value in combination with fluoxetine. Its use as an augmentation agent is also limited by the risk of toxicity when it is used in combination with imipramine, which is most likely a consequence of a pharmacokinetic interaction. Increased risk of carcinoma and cardiovascular disease may be associated with ERT *(303–306)*.

6. ALTERNATIVE AND NONTRADITIONAL ANTIDEPRESSANTS

6.1. St. John's Wort

St. John's Wort (*Hypericum perforatum*, available commercially as Hypericum alcohol extract standardized by level of hypericin) has been used as a traditional herbal medicine for more than 2000 yr. Pharmacologically, the plant contains naphthodianthrones (such as hypericin and pseudohypericin), phloroglucinols (such as hyperforin and adhyperforin), flavonoids, phenylpropanols, proanthocyanidins, xanthones, and amino acids *(307–309)*. It remains uncertain which of these constituents are responsible for its antidepressant effects. Although extracts have been standardized for hypericin content, this component may not be able to cross the BBB *(309)*. Consequently, hyperforin has been the focus of recent research. It inhibits reuptake of 5-HT, DA, NE, GABA, and glutamate *(310)*. It also has affinity for opioid receptors and 5-HT_6 and 5-HT_7 receptors. In vitro models have demonstrated that hyperforin inhibits receptor responses of AMPA, NMDA, and GABA, and also inhibits K^+, Na^+, and Ca^{2+} currents *(310a)*. Channels for which ions? Adhyperforin has similar effects on monoamine reuptake. Pseudohypericin inhibits DA-β-hydroxylase. Flavonoids and xanthones inhibit MAO-A; flavonoids also inhibit catechol-*O*-methyl-transferase (COMT). Amentoflavone binds to the benzodiazepine receptor. Similar to synthetic antidepressants, chronic administration of St. John's wort downregulates β-receptors in animal models.

Several standardized extracts are available in Europe; preparations available in the United States may vary in the concentration of active constituents. Of particular importance is that most preparations used in clinical trials have not been standardized to hyperforin. Typical dosages range from 900 to 1800 mg/d of the herb administered in two or three divided doses. Initial doses are usually one-third of the typical dose and increased weekly, as needed, to the maximum dose *(307,308,311–313)*.

6.1.1. Adverse Effects

Extracts of St. John's wort have been well tolerated under the conditions of physician supervision, monotherapy, and controlled doses of standardized extracts used in clinical trials *(308,311,313,314)*. The most common adverse effects reported in clinical trials have been headache, dry mouth, GI upset, nausea, dizziness, sedation, fatigue, and insomnia *(312,315,316)*. Among the more serious adverse effects, which are very rare, are photosensitivity and possible induction of manic symptoms *(313)*. A serotonin syndrome caused by St. John's wort had been reported in patients using St. John's wort together with an SSRI or other antidepressants, such as nefazodone and venlafaxine *(308,317,318)*.

6.1.2. Drug–Drug Interactions

Because of its ability to induce P-gp (a transporter protein in the BBB and intestinal mucosa) *(10,319)* and P450 cytochromes 3A4, 1A2, and possibly 2C9, St. John's wort has the potential to interact with other medications *(308,320)*. St. John's wort can decrease plasma levels of many prescribed drugs, such as anticoagulants, oral contraceptives, and antiviral agents. An interaction between St. John's wort and cyclosporine (metabolized by 3A4) resulted in reduced cyclosporine activity and organ rejection after transplantation *(321,322)*. Interactions with St. John's wort have resulted in a decrease in the international normalized ratio in patients taking warfarin (which is metabolized by CYP2C9 [*S*-warfarin] and CYP1A2 [*R*-warfarin]) *(308,323,324)*, and a decrease in digoxin levels when these drugs are administered concurrently *(325)*. Bioavailability of indinavir, cyclosporine, and digoxin may be altered as a result of P-gp induction *(319)*.

In the United Kingdom and Sweden, where St. John's wort is used extensively for medicinal purposes along with other herbal remedies, clinical interactions between St. John's wort and other licensed medications were deemed serious enough to warrant a change in product labeling for the involved medications and warnings to health care practitioners and patients about potential for such interactions *(320)*.

6.1.3. Efficacy

Numerous European clinical trials examined the efficacy of St. John's wort. Most of these studies have found St. John's wort to be more effective than placebo and at least as effective as a reference antidepressant for short-term treatment of mild to moderate depression *(311,314,316)*.

In a randomized, double-blind, multicenter clinical trial in 263 German outpatients with the diagnosis of moderate depression (according to the *International Classification of Diseases, 10th Revision (ICD-10)*) who were randomized to placebo, 100 mg/d imipramine , or 1050 mg/d St. John's wort extract for 8 wk *(311)*, investigators concluded that the standardized St. John's wort extract was more effective than placebo and as effective as imipramine in reducing HAM-D, Hamilton Rating Scale for Anxiety (HAM-A), and Clinical Global Impression (CGI) scores *(311)*. The authors themselves noted the study limitation of suboptimal dosing of imipramine *(311)*.

Several meta-analyses and systematic reviews have supported the efficacy of St. John's wort in mild depression *(315,326,327)*. Linde and colleagues *(326)* conducted a meta-analysis of 23 randomized clinical trials of acceptable methodo-logic quality that included 1757 outpatients with mild to moderate depression. They found that St. John's wort extract was significantly superior to placebo and as effective as a standard antidepressant (imipramine, amitriptyline, or maprotiline).

Gaster and Holroyd *(315)* reviewed eight randomized, controlled, double-blind trials of acceptable methodological quality and concluded that St. John's wort is more effective than placebo in the treatment of patients with mild to moderate depression. They also noted that there were insufficient data to assess the efficacy of St. John's wort in severe depression or to compare its efficacy with that of other antidepressants.

Kasper and Dienel *(327)* performed a meta-analysis of the original published data from three double-blind, randomized multicenter trials in 544 patients with mild to moderate depression (based on *DSM-IV* diagnostic criteria) who received 900 mg/d St. John's wort (WS 5570 or WS 5572 standardized extracts) or placebo for 6 wk and found that St. John's wort was significantly superior to placebo for mild to moderate depression and was especially effective in reducing the core symptoms of depression.

Serious methodological flaws exist in most published clinical trials of St. John's wort*(312,315,326,327)*. Common problems are failure to use standardized diagnostic instruments or rating scales, short study duration, and administration of ratings by inexperienced investigators *(312,315,326,327)*. The earliest studies were limited by their small size, short duration, lack of either a placebo or active reference drug arm, differences in preparation of the extract, and failure to describe randomization and blinding methods, measure compliance, or report or explain study dropout rates *(308,328)*. In studies using a well-established antidepressant for comparison, the results may have been skewed by underdosing of the reference drug. Doses such as 100 mg/d or less of imipramine or amitriptyline were used without monitoring plasma levels to determine compliance or adequate dosing *(312,326)*. In many studies, the blind may have been transparent if care was not taken to mask the peculiar taste of St. John's wort extract or if a specific constellation of side effects allowed investigators to guess the treatment arm *(312,326)*.

The first major US randomized, double-blind, placebo-controlled clinical trial was conducted by Shelton and colleagues *(312)*. While criticizing prior studies for methodological flaws and biases, these investigators succeeded in conducting a well-designed, large-scale, multicenter clinical trial. They recruited 200 patients through tertiary care centers associated with academic centers in the United States. Participants had a diagnosis of MDD (according to *DSM-IV* criteria) and a baseline HAM-D score of at least 20. Care was taken to enssure similarity in the outward appearance, taste, and smell of both the placebo and the St. John's wort preparations to protect the blind. The study followed a 1-wk, single-blind run-in of placebo, done to minimize the effect of early placebo response, and the treatment arm lasted 8 wk. The outcome measures were a decrease in HAM-D, Beck Depression Inventory (BDI), CGI, or HAM-A scores.

The investigators failed to detect a significant difference in response rates between St. John's wort and placebo after 8 wk of the study; response rates were 26.5% for St. John's wort and 18.6% for placebo. It was concluded that St. John's wort was not effective in treating MDD.

The US and European study populations were quite different. Shelton and associates recruited subjects from tertiary care outpatient clinics affiliated with academic medical centers. These patients had a diagnosis of MDD and a baseline HAM-D score of at least 20, with an average duration of depression of more than 2 yr *(312)*. In contrast, European populations studied came mostly from primary care settings and did not have chronic depression but had either a first or recurrent episode of "mild to moderate" depression with lower baseline HAM-D scores *(312,327)*. These distinctions make the US patient sample quite different from the European populations studied previously; they may also explain the lower response rate in the placebo and active treatment groups. Kasper and Dienel *(327)* suggested that this difference in populations accounted for the disparate US and European study findings, noting that St. John's wort may not be appropriate for the treatment of patients with chronic MDD.

The findings of a randomized controlled trial by the Hypericum Depression Trial Study Group in 340 adult outpatients with major depression and a baseline HAM-D score of at least 20 did not support the use of St. John's wort to treat patients with moderately severe major depression *(329)*. The two primary outcome measures for this trial showed that neither sertraline nor St. John's wort differed significantly from placebo, possibly as a result of the low sensitivity of the trial or inadequate doses of sertraline. The investigators indicated that St. John's wort may be most effective in treating less severe cases of major depression, but that this cannot be supported until additional efficacy trials have been made.

6.1.4. Conclusion

The efficacy of St. John's wort in major depression has not been established. There is some evidence that it may be effective in milder forms of depression. Its clinical use is limited by uncertainty concerning its active components, a propensity for drug–drug interactions, and a paucity of safety data. Currently, no literature is available on St. John's wort in children and adolescents, in patients with major psychiatric comorbidities, or in pregnant or lactating women. The drug–drug interactions associated with St. John's wort limit its use in patients with other medical or psychiatric comorbidities. Its efficacy is not established in moderate to severe cases of major depression. Further research and well-designed clinical trials are needed to determine the efficacy of St. John's wort in the treatment of mood disorders.

6.2. SAMe

SAMe (*S*-adenosyl-L-methionine 1,4-butanedisulfonate) is a dietary supplement that has been used as an antidepressant by European psychiatrists for approx 30 yr *(330)*. It is a naturally occurring compound that acts as a methyl-group donor to multiple substances in the CNS and is involved in synthesis of various neurotransmitters (DA, 5-HT, and NE) as well as nucleic acids and proteins *(330)*. SAMe is synthesized in the brain from L-methionine, an amino acid. Both folate and methylcobalamin (vitamin B_{12}) are necessary for its production *(330)*. Deficiencies in folate and vitamin B_{12} have been linked to some types of depression *(330)*. When low plasma concentrations of SAMe are found in depressed patients, interventions that increase SAMe levels are associated with improved mood *(331)*. Although supporting evidence is lacking, several mechanisms have been suggested to explain SAMe effects in depression. Potentially, SAMe could increase neurotransmitter synthesis (e.g., 5-HT or NE), increase neurotransmitter receptor responsiveness, or increase phospholipid production, which would enhance cell membrane fluidity.

Two meta-analyses of clinical trials of SAMe involving more than 1300 patients concluded that SAMe efficacy was superior to that of placebo and equivalent to that of TCAs *(332,333)*. Recently two multicenter studies were conducted in patients with major depression and a HAM-D score of 18 or higher *(334)*. The first study compared oral SAMe 1600 mg/d to oral imipramine 150 mg/d using a double-blind design. The second study compared SAMe 400 mg/d administered intramuscularly (SAMe has very poor oral availability) with 150 mg/d of oral imipramine. The primary efficacy measures were HAM-D scores and percent responders on clinical global impression scales. Secondary outcome measures were MADRS scores. Responder was defined as a patient who demonstrated a decrease from baseline in HAM-D score by 50% or greater *(334)*. The number of responders in both studies ranged from 50 to 59%, with no statistical difference between oral or intramuscular SAMe and imipramine *(334)*. The failure to include a placebo control group seriously limits the validity of these findings. An earlier study reported that 400 mg/d of SAMe administered intramuscularly produced an antidepressant effect at 7 and 15 d, which is more rapid than conventional antidepressants *(335)*.

A recently published review of the use of SAMe in the treatment of patients with depression concluded that doses of oral or parenteral SAMe from 200 to 1600 mg/d were a safe and effective alternative to TCAs, as they demonstrated a faster possible onset of action and may have a role in the augmentation of traditional antidepressants *(330)*.

6.3. Omega 3 Fatty Acids

The rationale for the use of omega 3 fatty acids (OFA) in the treatment of depression is based on converging evidence from diverse theoretical perspectives that seems to link OFAs and mood disorders. First, epidemiologic evidence suggests that populations with a low intake of dietary OFAs (e.g., fish oils) have a higher prevalence of depression than populations consuming large amounts *(336)*. Second, red blood cell membrane OFAs are lower in patients with depression compared to healthy controls *(337,338)* and are correlated with the severity of depression *(339)*. Third, fatty acids are involved in signal transduction in the brain *(340)*.

OFAs in the brain consist of 6-OFAs (e.g., arachidonic acid) and 3-OFAs (e.g. decosapentaenoic acid [DPA], docosahexaenoic acid [DHA], and eicosapentanoic acid [EPA]). A preliminary study of 3-OFAs (a combination of 6.2 g EPA and 3.4 g DHA daily) as adjunctive therapy in patients with bipolar disorder found it superior to placebo in improving mood and preventing relapse *(341-343)*. In another study of depressed patients who were not responding to antidepressant therapy, the addition of 1 g/d of ethyl-eicosapentaenoate (ECA) improved HAM-D, MADRS, and BDI scores, whereas placebo and higher doses of ECA did not *(340). I*n both studies, investigators found 3-OFAs were well tolerated, with common side effects including loose stools and breath "fish odor."

The efficacy of OFAs in depression has not been established. Although preliminary evidence suggests that 1 g/d of ECA is effective as adjunctive therapy and most authorities believe that ECA is the active component of the antidepressant response, neither OFA doses nor optimal composition of fatty acids have been established. In our clinical practice, we have not been impressed by clinical responses to OFAs, even when given as adjunct therapy. Many of our patients have been taking OFAs for their cardiac effects, and we have not observed significant changes in mood at the initiation or discontinuation of OFA therapy. On the other hand, OFAs are unlikely to be associated with severe adverse effects, and may be beneficial in preventing cardiovascular disease.

7. CONCLUSION

Appropriate clinical use of antidepressants relies on the ability of clinicians to make an accurate diagnosis, rule out medical conditions or substance-induced mood disorders, and distinguish subtypes of depression (e.g., unipolar vs bipolar). Furthermore, the ability to integrate knowledge of the pharmacology of specific drugs and the neuropathophysiology of depression forms the basis of rational prescribing.

Several multisite clinical trials have established approximate equivalent efficacy of all marketed antidepressants, with the clinically relevant differences related to adverse effects, ease of dosing, and safety. SSRIs remain the first-line agents under most circumstances, with mixed-action, TCA, heterocyclic, and MAOI agents as additional options. Antidepressants are effective across a range of disorders, including depression, PTSD, anxiety, and chronic pain. Combination and augmentation therapies have been developed for types of depression that are resistant to monotherapy, although evidence to date does not favor a specific approach. Novel treatments, whether developed from herbal preparations or new chemical compounds, comprise an exciting area for further research, but data supporting their efficacy and safety are limited.

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3 Antidepressant Treatment of Geriatric Depression

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CONTENTS

1. EPIDEMIOLOGY

The aging of the population has resulted in a new demographic phenomenon: a significant increase in the percentage of elderly. Between 1960 and 1990, the general population in the United States increased by less than 50%, whereas the population of those older than 65 yr increased by almost 100% and those older than 85 yr of age increased almost 250% *(1,2)*.

Known as the "oldest-old," those older than 85 yr comprise the fastest growing segment of our population. They are most likely to be women, to experience poverty, to have less education, and to need far more Medicare and Medicaid services. Life expectancy at age 65 is currently 15.5 yr for men and 19.1 yr for women; thus, reaching the age of 80 yr has become the norm. For those currently

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aged 80 yr or older, life expectancy is greater in the United States than in Sweden, France, England, or Japan, and is increasing *(2–4)*. The inevitable result of this demographic shift is the need to confront common disorders in the elderly, including depression, dementia, and delirium.

The prevalence of depression in the geriatric population has been investigated in various studies, but the results have been discordant. Few large population-based studies have been conducted, and many studies exclude individuals with comorbid medical or psychiatric disorders or those living in institutions. The results range from a point prevalence of 1.6% in one large US study *(5)* to a range of 12 to 15% in others *(6,7)*. For the physically ill or institutionalized, the prevalence of depression is thought to be upwards of 24 to 30% *(7)*. In several studies, the results have suggested that the prevalence of depressive disorders decreases after age 65, but these studies included few individuals older than 80 yr; other reports of studies that included the old-oldest suggest that the prevalence of depression may increase after age 80 *(5)*.

Whatever the rate of depressive disorders in the elderly, no one doubts that treatment for depression in geriatric practice is becoming an issue of increasing concern *(8–10)*. In a recent review, Blazer discussed the relationship between depression and the broader concept of health—i.e., both psychiatric and physical well-being—in later life *(3)*. Patrick and Erickson *(11)* described this as health-related quality of life, which is defined as "the value assigned to duration of life as modified by the impairments, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment, or policy." In two Swedish studies, investigators found that only 27% of centenarians had been diagnosed with dementia, 25% lived in their own homes, and 52% had little or no assistance managing their daily activities *(12,13)*. Function tends to decline with increasing age, but the amount of decline varies widely. According to Blazer *(3),* advanced age with good functioning can mask an increasing vulnerability to a domino-like effect of physical and/or psychiatric problems that can be triggered by the onset of a single physical or psychiatric problem. Such a chain reaction reveals the interrelatedness of psychiatric issues, decline in functioning, medical comorbidity, and quality of life. Depression may be one of these problems and either start a chain of events or result from it.

About half of those older than 85 yr and living the community are frail despite their apparent functional well-being. Blazer defines frailty as a constellation of weight loss, weakness, fatigue, inactivity, decreased food intake, and depression. Failure to thrive is the "end stage of frailty" and results ultimately in death *(3)*.

The interplay of depression, chronic medical illness, and disability is becoming more clear over time. Social and physical disabilities are the shorter term outcomes of depresion, and mortality is a longer term consequence of depression. Depression has a similar, and perhaps stronger, impact on disability than

chronic illness. The reverse is also apparently true, i.e., that chronic illness and disability predict the onset and persistence of depression *(3)*.

In a large ($N = 652$) Netherlands study of the temporal relationship between depression and disability in patients aged 55 to 85 yr, a diagnosis of depression was associated with the development of disability 5 mo later. This association held whether the depression was major or subsyndromal *(14)*.

2. DIAGNOSIS

Depressive disorders to consider in geriatrics should include not only the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) diagnoses of major depression and dysthymia, but also *subsyndromal* depression (also called *minor* depression), which is characterized by depressive symptoms that do not meet the criteria for other *DSM* diagnoses. (Although subsyndromal depression is not included in the *DSM*, some have argued that it should be considered a separate entity *[5]*.) Such depressive conditions have been reported to be more common in the elderly than major depression and may increase in prevalence with age. They should not be considered more benign forms of depression, because they are nonetheless associated with significant morbidity and disability *(5)*. Symptoms presented by older adults may differ from those seen in younger adults, with an increase in somatic and cognitive complaints but fewer affective symptoms, more specifically, lacking a sad mood *(15)*. Such complaints in an elderly person can be considered either symptoms of depression or medical illness and can be a challenge to the diagnosing physician (Table 1).

Standard screening tools can be helpful for clarifying depressive states. The Mini-Mental Status Exam (MMS) is used universally to make a gross assessment of cognitive functioning *(16)*. The self-rated Geriatric Depression Scale *(2,17)* has 30-item, 15-item, and 5-item versions; the 5-item version has been found to have high sensitivity (97%) and specificity (85%) *(18)*. The Center for Epidemiological Studies Depression (CESD) Scale is also used, but it is not specifically designed for medically ill geriatric patients and its many somatic questions may render false-positive results *(7)*. The Hamilton Rating Scale for Depression (HAM-D) is a standard interviewer-administered instrument, as is the Cornell Scale for Depression in Dementia (CSDD). Most research studies also use the Montgomery-Asberg Depression Rating Scale (MADRS). The detection of depressive symptoms is important whether or not a *DSM* diagnosis can be made. Screening tools can help sort out the relative severity of the symptoms, but may fail to detect a significant portion of the depressed elderly in a given population.

Essential elements of the diagnostic workup include a thorough psychiatric history and examination. Important areas of focus are the cognitive exam, the neurological exam, and the assessment of functioning, loss/grief, living situation, and support in the community. The laboratory workup should include the

Table 1. Characteristics of Depressive States in the Elderly *(15)*

- Older patients report a greater number of somatic and cognitive symptoms than affective symptoms ("depression without sadness" *[250]*)
- Suicide occurs twice as frequently among the elderly as in the general population
- Suicide attempts decrease in number with aging but increase in lethality
- Severity of depression is strongly correlated with suicidal ideation
- Depression occurring in the context of medical illness should be treated concurrently with the medical illness
- Late-onset dysthymia is usually not associated with personality disorders; when it is, however, obsessive–compulsive and avoidant personality disorders are most common
- Subsyndromal or minor depression in the elderly is associated with disability and progression to major depression in 25% of cases in existence >2 yr; old-old patients may have longer prodromal periods (3 yr) prior to the onset of major depression

thyroid-stimulating hormone level, a complete metabolic panel, complete blood count with differential, vitamin B_{12}, folate, and urinalysis. Computed tomography (CT) and magnetic resonance imaging (MRI) of the head should be considered, particularly for patients without a prior examination history. A chest x-ray and electrocardiogram (ECG) may also be indicated, depending on the presentation of symptoms.

2.1. Depression Subtypes and Comorbidity

2.1.1. Vascular Depression

Vascular depression is a relatively recent concept based on the relationship between ischemic changes in the brain and late-life depression. There is a growing body of research supporting a neuropathologic basis for a type of depression that is characterized less by depressive ideation and more by subcortical dysfunction resulting in apathy, and psychomotor change *(19–25)*. Alexopoulos and associates *(19)* studied 33 elderly patients diagnosed with vascular depression and 32 patients with nonvascular depression based on the Cumulative Illness Rating Scale–Geriatrics. The symptoms of vascular depression in these patients included cognitive dysfunction, disability, retardation, and lack of insight; depressive ideation was limited. Although the underlying pathology is unknown, the resemblance of this set of symptoms to the frontal lobe syndrome led these investigators to suggest that vascular depression is related to the disruption of striato-pallido-thalamo-cortical pathways, but they also pointed out that lesions in other brain areas could produce symptoms of vascular depression. One of their most intrigu-

ing suggestions was for further study of nontraditional agents for the treatment of vascular depression, including "anticholinesterinemic and antiplatelet agents, free radical scavengers, calcium channel blockers, glutamate *N*-methyl-D-aspartic acid receptor antagonists, gangliosides, aminosteroids, and amphetamine" *(19)*. They also stressed the fact that antidepressants may differ in their ability to promote neurologic recovery after ischemic lesions. Krishnan and colleagues *(26–28)* have also described hyperintensities in subcortical white matter assumed to be of vascular origin in the pathogenesis of late-life depression. Several investigators have identified changes in the medial orbital frontal cortex (OFC) during late-life depression, with smaller OFC volumes associated with late-life depression *(29–34)*. In a postmortem study, inflammatory changes consistent with cerebral ischemia were found in dorsolateral prefrontal cortex tissue taken from elderly patients with depression compared with controls *(35)*. Tupler and associates *(36)* suggested that lesions in left-sided white matter are associated with depression with an older age of onset, whereas lesions in right anterior white matter and left subcortical tissue are associated with melancholia. MRI imaging revealed deep white matter hyperintensities, which are markers of ischemic change, particularly in the dorsolateral prefrontal cortex.

The efficacy of drug therapy in late-onset depression remains controversial. There are some indications that sertraline may be effective *(37)*. In one study, investigators found an absence of an association between the severity of subcortical hyperintensities and sertraline response *(38)*. Microstructural white matter abnormalities located 10 and 15 mm above the anterior–posterior commissural plane, which is located lateral to the anterior cingulate, were associated with a poor response to citalopram *(39)*. These investigators hypothesized that such abnormalities interfere "with the reciprocal regulation of dorsal neocortical–ventral limbic structures and lead to a 'disconnection syndrome' with poor antidepressant response."

2.1.2. Psychotic Depression

Psychotic depression, a variant of major depression, is characterized by paranoia, delusions, and hallucinations in addition to symptoms meeting the criteria for major depression. It can be difficult to distinguish this diagnosis from that for dementia with depression and psychosis. Fortunately, the treatment is often the same for both conditions, i.e., concurrent antidepressant and antipsychotic therapy. Electroconvulsive therapy (ECT) is an effective alternative treatment (*see also* Chapter 5 for a discussion on the pharmacotherapy of psychotic depression.)

2.1.3. Suicidality

Suicidality is of particular concern in the elderly, who have the highest risk of any age group. The rate is almost twice that for the general population and even

higher among white males over 65 yr. Among the elderly, suicidal ideation is almost always associated with depression. More than 75% of those who committed suicide had seen a primary care physician within a month of their death, which demonstrates the need for better diagnostic approaches and more aggressive treatment *(40)*. A screening tool that is widely used to assess suicidal ideation is Beck's Scale for Suicide Ideation (SSI) *(41)*.

2.1.4. Depression With Concurrent Substance Abuse

Depression with concurrent substance abuse is a complicated comorbid condition ("dual-diagnosis"). Substance abuse by itself can cause depression and, conversely, depression can lead to substance abuse. It is this bidirectional relationship that can make diagnosis and treatment difficult. Community-based surveys indicate that the prevalence of alcohol-use disorders among elderly individuals with depression is three to four times greater than among elderly individuals without depression. A past history of a major depressive disorder in individuals aged 65 yr or older is associated with an alcohol-use disorder prevalence of 13.3%, compared with 4.5 % among the elderly without a history of a major depressive disorder *(42)*. In cohorts of elderly with current depression, the comorbidity rate is even higher, with 15 to 30% also having an alcohol-use disorder *(43,44)*. Typically, there is a lower rate of a family history of alcoholism for elderly patients with late-onset substance abuse disorder compared with those with an early onset of this disorder. In some studies, a worse prognosis was found for elderly depressed patients with an alcohol use disorder *(44,45)*.

As a society, we tend to not suspect the elderly of substance abuse or dependence and excuse them for "nipping at the bottle" or needing a benzodiazepine to "steady their nerves." This may lead us to miss an underlying cause for a patient's mood disorder. Therefore, substance abuse screening should be a routine part of any depression workup. The usual screening tools—such as the CAGE questions (*c*ut down, *a*nnoyed by criticism, *g*uilty about drinking, *e*ye-opener drinks)—can be applied, and information from family members or caretakers can be invaluable.

2.1.5. Depression With Anxiety

In a sample of elderly patients in psychiatric and primary care, 23% of those with major depression were diagnosed with an anxiety disorder at the time of the interview and 35% met criteria for lifetime anxiety disorder *(46)*. Using less rigorous criteria, other investigators found that 50% of 336 elderly patients with major depression had symptoms of anxiety based on rating scales, but only 2.5% met the criteria in the third edition (revised) of the *DSM* (*DSM III-R*) for any anxiety disorder *(47)*. The latter study has been criticized for excluding patients with generalized anxiety disorder, which is believed to have a high prevalence in the geriatric population *(48)*; however, other studies have provided evidence sup-

porting a low rate of anxiety disorders in elderly depressed patients *(49–51)*. Comorbid anxiety disorders do not seem to diminish the response to treatment with antidepressants in the elderly *(52)*; however, few studies have examined this issue.

2.1.6. Comorbidity and Personality Disorders

Kunik and associates *(53)* reported that 24% of a series of elderly in-patients had comorbid personality disorders, mainly Cluster C category disorders (avoidant, dependent, obsessive–compulsive, and passive–aggressive disorders). Devanand and associates *(54)* reported that in a series of 76 elderly patients, 31.2% had concurrent personality disorders (obsessive–compulsive, 17.1%; avoidant, 11.8%; borderline, 5.3%; narcissistic, 2.6%; and schizoid, 2.6%; and no cases of antisocial or histrionic personality disorder), which are associated with an earlier age of onset of depression *(42)* and a history of recurrent depressive episodes *(55)*. The findings of some studies suggest a poorer prognosis for patients with major depression and personality disorders compared with major depression alone *(56)*. Other studies have found a poor response to psychotherapy *(57)*, but not to somatic therapies *(55)*.

2.1.7. Depression and Dementia

The relationship between depression and dementia is an area of rapidly expanding research, but it remains a common and difficult diagnostic challenge in geriatrics. Depression often occurs before (and during) dementia. What is the relationship between these two diseases? Does depression predispose to dementia? The findings of some recent studies have suggested that depressive symptoms are risk factors for Alzheimer's dementia. In particular, disinterest, low energy, and poor concentration—rather than mood symptom—have been correlated with the future development of dementia *(58)*.

In a study of 243 patients with probable Alzheimer's disease (AD) compared with 151 controls, Zubenko and associates found that the concurrence of major depression and AD ranged from 22.5 to 54.4%, even when a common, reliable methodology (the Clinical Assessment of Depression in Dementia Interview) was used by an expert consortium *(59)*. The findings of this study—in which 18.5% of patients with AD reported symptoms of premorbid major depression—also supported published evidence that major depressive episodes arising prior to cognitive impairment are associated with an increased risk for AD. Depressive symptoms differed significantly between the two groups: patients with AD were more likely to report indecisiveness or an inability to concentrate than controls, but less likely to report sleep disturbances and feelings of worthlessness or guilt *(59)*. As the severity of dementia increased, psychotic symptoms worsened. The investigators argued that the validity of depression in AD is supported by their findings that the onset of major depressive symptoms developed during the early stages of cogni-

tive impairment and that there were differences in the clinical features of mood disturbance in patients with AD compared with controls *(59)*. This major depressive mood syndrome may affect nearly one-third of all patients with AD, which would make it one of the most common mood disorders in the elderly *(59)*.

Depression alone can present with significant cognitive deficits, also called pseudodementia (the latter term is now less commonly used than the former); such deficits are treated with antidepressants. In patients with established dementia, major or subsyndromal depression may develop as a part of the dementia. Treatment of depression in these contexts should not include anticholinergic antidepressants such as tricyclic antidepressants (TCAs) because they may cause the cognitive status to worsen.

In terms of medical history and clinical course, the onset of depression tends to be demarcated and readily progressive, and the patient usually has a history of depression, a recent life stressor, or both. Persons with dementia have a longer, more insidious onset that tends to remain unrecognized for a period of time and a psychiatric history that is often unremarkable. In terms of clinical behavior, individuals with depression often emphasize disability wth detailed complaints of cognitive dysfunction. They communicate a strong sense of distress, but on questioning often give a "don't know" answer consistent with poor motivation. Task performance is variable. At night the symptoms are not usually worse.

In contrast, individuals with dementia often do not complain — or only vaguely — of cognitive loss. They are more likely to conceal their disability and confabulate answers. Task performance is consistently poor. Night worsening of symptoms is common *(60,61)*.

2.1.8. Depression and Medical Illness

Comorbidity of depression and medical illness presents a diagnostic challenge, because the criteria used in psychiatry to diagnose depression rely on physical symptoms common to both depression and illness. For example, even though the fourth edition of the *DSM* (*DSM-IV*) specifies not including "symptoms that are clearly caused by a medical condition," the criteria for major depression include significant weight loss and fatigue or loss of energy. Four major approaches to distinguishing psychiatric and medical symptoms have been proposed and often appear in the geriatric psychiatry literature *(15,62,63)*:

1. *Inclusive approach:* All depressive symptoms, somatic or psychological, are considered evidence of a mood disorder. Thus, in a patient with anemia, a complaint of "poor energy" would be considered a symptom of depression. If there are enough symptoms to meet the criteria for depression, the diagnosis is made. The problem with this approach is its over-inclusiveness, which can result in poor specificity.

2. *Exclusive approach:* Physical or medical symptoms are not considered symptoms of a depressive disorder. In the patient described in Item 1, "poor energy" would not contribute to a diagnosis of depression. The problem with this approach is its over-exclusiveness, leading to poor sensitivity.
3. *Substitutive approach:* Physical symptoms are "translated" into psychological symptoms, e.g., back pain is considered equivalent to hopelessness. If enough psychiatric equivalents are identified, a diagnosis of depression can be made. The problem with this approach is that no evidence has been found that can be used to validate the concept of "psychological equivalents."
4. *Etiological approach:* The clinician evaluates each symptom independently and makes a subjective determination of whether it is related to depression or a medical illness. The problem with this approach is that it relies on decisions that are not evidence based and has poor interrater reliability.

Other approaches to distinguishing depression from medical illness have included combinations of the approaches listed or the use of the Hospital Anxiety and Depression Scale, the shortened version of the Geriatric Depression Scale, and even a one-item questionnaire ("are you depressed?"), an approach used in one study that proved to be the most sensitive and specific tool. The conundrum in finding the best diagnostic method is that there is no gold standard by which to compare results, and further epidemiological research is needed. Given the tolerability and safety profile of today's antidepressants, it may be best to initiate pharmacotherapy when depression is suspected.

3. TREATMENT OF GERIATRIC DEPRESSION

3.1. Pharmacological Treatments

The elderly face barriers to effective pharmacological treatment for depression. As a group, they experience both a low rate and low intensity of treatment. Antidepressants are often prescribed in subtherapeutic doses, and many geriatric patients simply stop taking their medications *(10,64)*. These difficulties may be related to a relative lack of clear guidance in identifying the most effective treatments for this population; there have been relatively few studies in this area, and many problems are associated with conducting such studies as well as measuring the outcome of interventions. Despite this, it is clear that treatment for depression is effective in the majority of patients.

When elderly patients present with a persistent sad mood, it is rarely difficult to make a diagnosis. However, mood disorders can also present solely with anxiety, impaired cognitive function, medical symptoms, decreased activity, social isolation, or reduced motivation. Overemphasis on depressed mood results in failure to recognize treatable depression in the elderly *(65)*.

It may be clinically relevant to subtype late-life depression. In an interesting study of a group of oldest-old patients in a nursing home ($N = 50$; mean age: 89 yr), investigators compared antidepressant responses to fluoxetine, sertraline, and paroxetine *(66)*. At 12 wk, a significant overall decline in HAM-D scores was seen, with 42% of these patients demonstrating at least a 50% decline in score. There was no difference in efficacy among the three medications, although four kinds of depression responded quite differently: major depression (93%), AD plus depression (8%), vascular depression (6%), and other central nervous system (CNS) disorders with depression (83%). This difference in response rates between those with "simple" major depression vs cognitive impairments with perhaps an underlying vascular etiology has been shown in other studies as well. Clearly the challenge is to find effective treatments for diagnostic subgroups *(66)*.

3.2. Physiology of Aging

The physiology of aging is an important consideration when prescribing psychotropic medications. A number of well-documented and potential changes occur involving three interrelated areas of physiologic function: homeostasis, pharmacokinetics, and pharmacodynamics *(67–70)*.

Human beings have a reserve physiological capacity to deal with stress or acute events; this reserve capacity diminishes with age. If an individual is faced with a physiological stress that is beyond this reserve capacity, decompensation of the involved organ system(s) occurs. Therefore, even a minor stressor can result in the downward cascade of events referred to earlier in this chapter. In the elderly, the cardiovascular, CNS, and musculoskeletal systems are particularly vulnerable. Examples of homeostatic impairments include orthostatic hypotension and other signs of autonomic nervous system dysregulation (e.g., loss of body temperature regulation, bowel and bladder dysfunction, and ambulatory instability), as well as cognitive decompensation (e.g., confusion and disorientation) *(71)*.

3.2.1. Pharmacokinetics

Pharmacokinetics—the action of a drug in the body over time—changes with age *(72,73)*. Specifically, the pharmacokinetic subcategories of absorption, distribution, metabolism, and excretion each undergoes well-known age-associated changes. Individuals age differently, however, and so do the organ systems in a given individual. Additionally, it may be difficult to distinguish signs of normal aging from those of "pathological aging."

Absorption is the pharmacokinetic function that seems to be least affected by age. Despite an increase in gastric pH and a decrease in gastrointestinal (GI) blood flow and gastric motility, the bioavailability of most antidepressants does not appear to change to a meaningful degree *(74)*. Medications that require active transport may be more poorly absorbed with aging. Because the rate of first-pass metabolism is

decreased in aging, serum levels of drugs such as morphine and propanolol are higher in the elderly than in younger individuals given the same dose *(75)*.

The distribution of medication in the body varies with body composition. In the elderly, there is an increase in body fat and a relative decline in lean body mass and total body water. This means that the volume of distribution for water-soluble drugs, such as lithium, may decrease and the plasma concentration may increase. For lipophilic drugs, such as the benzodiazepines, an increase in volume of distribution is seen along with a longer elimination half-life *(76)*. Distribution is also a function of plasma protein binding, particularly for agents that are transported by albumin and α_1-acid glycoprotein *(77)*. Serum concentrations of such drugs can be altered by changes in the serum level of these proteins, which, in turn, alter the ratio of bound–free drug. The clinical relevance of increased levels of free nortriptyline in the elderly is unknown *(78)*. Alterations in plasma protein binding that occur with aging are not thought to be as clinically important as declining hepatic or renal function or decreased cardiac output *(79)*.

The rate at which antidepressants are metabolized in the liver may decrease in the elderly as a consequence of reduced blood flow to the liver and reduced activity of the cytochrome P450 oxidative enzymes. CYP2D6 appears to be less affected by aging than CYP2C19 or CYP3A4 *(80)*. Antipyrine clearance, a general marker of oxidative metabolism, declines with age. In one study, the cytochrome P450 content of biopsied livers was lower in patients aged 40 to 49 yr compared with those aged 20 to 39 yr, but similar to those obtained from patients aged 50 to 69 yr; only in samples taken from patients older than 70 yr was the cytochrome P450 content lowered further *(81)*.

With respect to specific isoenzymes, surprisingly few data are available from studies comparing in vitro findings with the human pharmacokinetics of known substrates. Probes for 1A2 and 3A4 isoenzymes have indicated impaired functioning with aging *(82,83)*. Substrate challenges of 1A2 using caffeine and theophylline have demonstrated decreased clearance in the elderly *(67)*. The rate of metabolism for debrisoquine (a 2D6 substrate) did not change with aging in other studies *(84,85)*. Both age- and sex-related differences have been found with CYP3A4 substrates; aging reduces the clearance of erythromycin *(86)*, nifedipine *(87)*, and nefazodone *(88)*.

The kidneys provide the primary route of elimination for many drugs. The glomerular filtration rate is thought to decline with age, although many elderly do not show such a decline. Medications such as lithium depend on renal function, and serum levels (which are critical in lithium therapy) can be affected by it *(89)*. Alterations in renal function may lead to higher levels of hydroxymetabolites of nortriptyline, desipramine, and imipramine, which are potentially cardiotoxic *(10,90,91)*.

The determination of age-related changes in the pharmacokinetics of antidepressants relies on animal experiments, in vitro modeling, and direct drug administration to humans. Von Moltke and colleagues *(68)* reviewed data for older antidepressants and found a lack of consistency, which was most likely the result of large interindividual variation in the rate of metabolism of TCAs, inappropriate use of control groups, and failure to distinguish clinical importance from statistical significance. Despite these shortcomings, they concluded that the data provided evidence that clearance rates for amitriptyline and imipramine were reduced in the elderly, but the rate for desipramine was not significantly affected by aging *(74)*. Nortriptyline clearance does not seem to be affected either, except in the presence of medical illness. The clinical implications of the comparatively lower levels of free nortriptyline observed in the elderly are not known *(78)*. TCA hydroxymetabolites are likely to accumulate in elderly patients who have reduced renal function. The trazodone clearance rate may also be decreased in the elderly *(74)*.

Several pharmacokinetic studies of selective serotonin reuptake inhibitors (SSRIs) in the elderly have been published. The citalopram clearance rate is reduced in individuals older than 60 yr, resulting in a higher steady-state concentration and a prolonged elimination half-life *(92,93)*. Initial doses of citalopram in the elderly are half those prescribed for younger individuals. The area under the curve and elimination half-life for escitalopram increase by approx 50% in patients aged 65 yr or older; therefore, the initial dose should be reduced to 10 mg in these patients. In a study of 22 healthy volunteers, sertraline and desmethylsertraline plasma levels were similar in elderly men and both elderly and young women, the mean concentration for all groups being approx 25% higher than in young men *(94)*. These differences are probably not clinically meaningful.

Studies of 20 to 40 mg of paroxetine in elderly and nonelderly patients have had two clinically important findings: mean steady-state plasma concentrations were 40% higher in the elderly than in younger patients, and older patients may be more sensitive to the nonlinear pharmacokinetics of paroxetine, which may result in a disproportionate increase in plasma-level response to dose escalation *(95–98)*. Most clinicians initiate paroxetine therapy in the elderly at 10 mg/d, rather than the 20-mg/d dose used in the non-elderly.

Data on fluvoxamine are contradictory, with one study revealing only an insignificant increase in elimination half-life in the elderly (mean: 25 vs 22 h in young adults) *(99)*. While the drug was still under patent in the United States, Solvay Pharmaceuticals reported in its 2002 product information brochure that single-dose studies of 50 and 100 mg in elderly (aged 66–73 yr) and young (aged 19–35 yr) study participants demonstrated a 50% higher maximum concentration (C_{max}) in the elderly. In multiple-dose studies, the elimination half-life after

a steady state was achieved following a 50- and 100-mg dose, was 17.4 and 25.9 h in elderly patients compared with 13.6 and 15.6 h in young adults, respectively. Fluvoxamine clearance may be reduced by 50% in the elderly.

In a study of fluoxetine, investigators found no clinically significant difference in pharmacokinetics in patients aged 65 to 77 yr compared to younger patients with a single 40-mg dose *(80)*. In a study of adults aged 60 yr or older, researchers found that 6 wk of 20 mg of fluoxetine therapy produced steady-state fluoxetine and norfluoxetine levels of 209.3 ng/mL, which is comparable to that seen in younger adults and adolescents *(100)*.

In a study of venlafaxine in elderly (aged 60–80 yr) vs young (aged 21–44 yr) patients after a single 50-mg dose, which was followed by 50 mg every 8 h for 5 d, investigators did not observe any difference in pharmacokinetics following the single dose and only a modest increase in steady-state concentration after long-term dosing in the elderly, making it unlikely that a dose reduction is necessary in most elderly depressed patients *(101)*.

A small study of bupropion suggests that the dose should be reduced in the elderly *(102)*. Elevated plasma levels of bupropion and its metabolites suggest that a dose reduction of 25 to 50% may be necessary. Even more significant pharmacokinetic changes in the elderly have been reported for nefazodone *(88)*, and most clinicians begin treatment in the elderly with no more than half the dose normally used to initiate therapy in younger adults. Mirtazapine clearance was reduced 40% in elderly men compared with younger men taking 20 mg/d for 7 d, but reduced only 10% in elderly vs young women.

3.2.2. Pharmacodynamics

Pharmacodynamics—the response of the body to a drug acting at a particular site—is altered in the elderly, possibly resulting in a heightened response or "sensitivity" to that drug *(72)*. Benzodiazepines are good examples of this, and there is evidence that the elderly are sensitive to the CNS effects of this class of drugs *(76,103–105)* as well as opiates *(106)*. Conversely, the elderly exhibit a reduced response to other medications used in psychiatry, such as β-adrenergic antagonists *(89)*.

Altered sensitivity can lead to adverse effects other than those associated with an increase in plasma levels. Several reviews have summarized the common adverse effects of antidepressants that may be the consequence of altered metabolism, receptor function, or signal transduction mechanisms *(10,65,71,107,108)*.

3.2.3. Anticholinergic Adverse Effects

Elderly patients often take other prescribed and over-the-counter medications that have anticholinergic activity; therefore, clinicians should be aware of potential drug–drug interactions. Older individuals are more sensitive to the anticho-

linergic effects of TCAs; even low doses may produce urinary retention, severe constipation, xerostomia, glaucoma, and tachycardia. More severe anticholinergic effects include mild confusion, memory impairment, worsening of depression, and delirium. The lack of muscarinic effects makes SSRIs and some newer mixed-action agents more appropriate as first-line agents in depressed elderly individuals. Among the SSRIs, only paroxetine has substantial anticholinergic activity; however, in vitro studies suggest a greater effect is seen experimentally than clinically. Using sera from patients aged 60–95 yr treated with either nortriptyline (plasma level: 100 ng/mL) or paroxetine 20 to 30 mg/d, investigators showed that paroxetine had only one-fifth the anticholinergic activity of nortriptyline *(109)*. Salzman and colleagues found no adverse effects with paroxetine in patients aged 80 yr or older *(10)*. In a more recent 8-wk, double-blind, placebo-controlled study of paroxetine in nursing home patients ($N = 24$; mean age: 87.9 yr) *(110)*, investigators found two patients in the paroxetine group who had experienced delirium; they also found that the patients taking paroxetine had lower MMS scores. Patients with higher HAM-D-17 and CSDD scores in the paroxetine group experienced greater improvement than those taking placebo (based on the Clinical Global Impression of Change [CGI-C] scale, an interview-based outcome measure). In contrast to other study findings, they found no clinically significant difference in serum anticholinergic activity for paroxetine vs placebo. Therefore, if cognitive impairment does occur in elderly patients treated with paroxetine, its relationship to anticholinergic activity has not been unequivocally established.

3.2.4. Cardiovascular Effects

As discussed in Chapter 2, cardiovascular mortality is increased in patients with depression *(111–113)*. Surprisingly few studies have specifically addressed the association between these conditions in the elderly. The relationship between depression and heart failure was studied in 2501 community-dwelling individuals aged 65 yr or older who were free of heart failure at baseline *(114)*. During a 14-yr follow-up period, depression in women, but not men, was associated with a greater risk for heart failure. Between 11 and 19% of the elderly living in the community reported depressive symptoms above the cutoff criterion for clinical depression on the CESD Scale *(115–118)*. In a cohort study of antihypertensive therapy, an increase in depression over time predicted stroke and myocardial infarction (MI) in individuals aged 60 yr or older *(119)*, rather than baseline depression scores. In the Cardiovascular Health Study, investigators prospectively examined the relationship between depressive symptoms and coronary heart disease (CHD) in 4493 Americans aged 65 yr or older who were free of cardiovascular disease (CVD) at baseline *(120)*. Depression was an independent risk factor for CVD and mortality: the more severe the depressive symptoms, the

greater the risk for CVD. Similar findings were reported by Pratt and associates *(113)* for the general population older than 18 yr, i.e., the odds ratio for having an MI associated with dysphoria was 2.07 (95% CI range: 1.16–3.71) and 4.54 (95% CI range: 1.65–12.44) with major depression. Given these findings, the role of antidepressant pharmacotherapy in older patients has substantial public health implications.

We are unaware of any strong evidence suggesting that intervention with antidepressants or psychological treatments reduces the risk for CHD in elderly patients with depression; however, a growing body of evidence in the literature supports their safety, even in patients with CVD. In the general population, mortality rates are lower in depressed individuals who receive adequate treatment for depression *(121)*. Furthermore, preliminary data in adult smokers aged 30 to 65 yr who were hospitalized with a first MI revealed a lower recurrence of MI in patients treated with SSRIs than in those who did not receive an SSRI *(122)*; SSRIs may not confer the same benefit in individuals without a prior MI, however *(123)*. In a study of the effects of treatment for depression after a recent MI in 2481 patients (mean age: 61 yr), antidepressant therapy was associated with a lower risk for death or nonfatal MI compared with the risk in patients who had not received antidepressant therapy, although the differences in depression scores were small and of questionable clinical significance *(124)*. The potential cardioprotective effects of SSRIs, such as platelet serotonin receptor blockade, complicate the interpretation of these findings.

Early concerns about the cardiac effects of TCAs were raised in a report by Rodstein and Oei *(125)*, who described 32 geriatric patients, 10 of whom received amitriptyline 20 to 75 mg daily for a mean of 53 wk, 21 of whom received imipramine 20 to 100 mg for a mean 40 wk, and 1 who received two 10-mg doses of nortriptyline. T-wave inversions and "evidence of acute coronary insufficiency" were noted in the patients taking amitriptyline. Intermittent left bundle branch block, acute coronary insufficiency with node dysfunction, T-wave inversion, and tachycardia were reported for patients taking imipramine. The single patient taking nortriptyline had an acute MI after the two doses of this drug. Current opinion is that TCAs present the greatest risk in patients with an ischemic myocardium, a conclusion inferred from the Cardiac Arrhythmia Suppression Trials (discussed in Chapter 2). In the presence of myocardial ischemia, TCAs and other Class 1A antiarrhythmic agents have proarrhythmic properties. Several studies now confirm that SSRIs—including fluoxetine *(126,127)*, sertraline *(128)*, paroxetine *(10,129–132)*, and citalopram *(133)*—have greater cardiac safety than TCAs. Similarly, cardiac profiles for bupropion, venlafaxine, and mirtazapine are superior to those for TCAs, although venlafaxine is associated with hypertension in a dose-related fashion. Autonomic dysfunction, indicated by a decrease in heart rate variability, may be greater in patients with depression

(134), and anticholinergic antidepressants (e.g., TCAs) may present a greater risk for cardiac events *(135)*.

3.2.5. Orthostatic Hypotension and Falls

Experienced clinicians have long been aware of the risk for orthostatic hypotension associated with TCAs and monoamine oxidase inhibitors (MAOIs). As described in Chapter 2, this is most likely a consequence of α-adrenergic blocking activity. Among the TCAs, nortriptyline is least likely to have this effect. One of the most surprising findings in SSRI research in the elderly is that SSRIs are also associated with falls and fractures. In a study of 8127 elderly women living in the community and followed for an average of 4.8 yr, investigators discovered that 15% had experienced a nonspinal fracture, including 4% with a first hip fracture *(106)*. Women taking narcotics and antidepressants were at greatest risk for any nonspinal fracture. Women taking SSRIs and TCAs had a 1.7-fold increased risk for hip fracture. There was no independent association between benzodiazepine or anticonvulsant therapy and hip fracture. Other studies have also found an increased risk for falls in patients taking SSRIs, especially when therapy is initiated; some evidence suggests that patients develop a tolerance to this effect *(136–138)*. Studies of body sway in patients taking sertraline or paroxetine have not clarified the underlying mechanism of SSRI-associated falls *(139)*. In a study of 104 individuals aged 69 yr or older who received paroxetine, psychotherapy, and augmentation therapy (with bupropion, nortriptyline, or lithium), investigators found that 38% of patients had fallen, about half of them within the first 6 wk of treatment *(140)*. Memory impairment and orthostatic hypotension were risk factors for falls.

3.2.6. Other Adverse Effects

Other adverse effects have been reported in single cases or in a case series. Although the frequency of these effects cannot be determined from available studies, it has been our experience that they do appear more commonly, albeit still infrequently, in the elderly. Extrapyramidal symptoms (EPSs) associated with SSRIs have been reported and appear to be related to a reduction in dopaminergic tone that accompanies aging and the effects of serotonin on dopamine activity. We believe that all SSRIs can produce EPSs in susceptible individuals and that the increased number of reports with fluoxetine is related to greater clinical experience. To put this risk in perspective, Coulter and Pillans *(141)* reviewed the charts of 5555 patients treated with fluoxetine and found 15 cases of EPS, only 7 of which involved patients who had received fluoxetine as the sole psychotropic agent. Others have suggested a lower incidence of EPS with sertraline therapy, citing its weak dopamine reuptake-inhibiting activity; however, there have been reports of EPS with that drug, as well *(142–144)*.

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is an infrequent but serious adverse effect of antidepressant therapy that is more common in the elderly. Liu and colleagues *(145)* reviewed published and unpublished data (1980–1995) on SIADH observed in patients taking fluoxetine, fluvoxamine, paroxetine, or sertraline. They found a total of 736 cases: 75.3% involving fluoxetine, 12.4% involving paroxetine, 11.7% involving sertraline, and 1.5% involving fluvoxamine. Although most reports involved fluoxetine, this finding is probably an artifact of its greater clinical use. The median time to onset of hyponatremia was 13 d (range: 3–120 d). There are reports of SIADH with citalopram *(146,147)*, fluvoxamine *(148–150)*, paroxetine *(150–153)*, sertraline *(154–156)*, and venlafaxine *(151,157)*, as well as with TCAs *(158–165)* and MAOIs *(166)*. Although the exact mechanism for this effect is unknown, clinicians should be vigilant for changes in sodium levels, especially early in treatment. Lethargy, disorientation, and muscle cramps are early signs of hyponatremia, with delirium and coma possibly arising in the late stages of this disorder *(71)*. Management involves discontinuation of the offending agent, fluid restriction, and, in severe cases, hypertonic saline. When the condition clears, an alternative antidepressant may be started; however, there have been reports of recurrences. In patients with a severe case of depression, clinicians should consider ECT.

The elderly may be more sensitive to other adverse effects that younger people are able to tolerate. Bupropion, for example, may cause agitation in the elderly, and lower-than-usual doses of venlafaxine may cause an elevation in blood pressure. Sedative effects of antidepressants are also enhanced in the elderly. Serotonin syndrome has also been reported in elderly patients receiving mirtazapine as monotherapy *(167,168)* or in combination therapy with fluoxetine *(169)*, as well as combination therapy with paroxetine and risperidone *(170)*.

3.3. Treatment of Major Depression

In several reviews, investigators concluded that SSRIs are first-line antidepressant agents for geriatric major depression *(65,171,172)*. Virtually all available SSRIs have been compared with TCAs or mixed-action agents, and investigators in most studies have found equivalent efficacy with fewer adverse effects than are seen with tertiary amine TCAs *(173)*.

3.3.1. SSRIs

All SSRIs are effective for late-life depression. Minor variations in adverse effects (e.g., paroxetine has a greater sedative effect, and fluoxetine a more stimulatory effect) may influence the choice of medication. At times, these effects may be significant. In one study, for example, elderly patients with depression who were also medically ill lost more than 5% of body weight when treated with fluoxetine compared with TCA (with which no weight was lost) *(174)*.

Some SSRIs also strongly inhibit hepatic metabolizing enzymes and, thus, may affect blood levels of other medications. Because elderly individuals are likely to be taking several drugs concurrently, an SSRI such as citalopram, which does not influence hepatic enzyme activity, may be selected for treatment.

In one study of citalopram (20–40 mg/d) vs amitriptyline (50–100 mg/d) in elderly patients with depression, investigators found their efficacy to be equivalent, based on MADRS, HAM-D, and CGI scores, although a greater number of adverse effects and a higher discontinuation rate were seen in the amitriptyline group *(175)*. In another comparison study in patients aged 65 yr or older, investigators found citalopram (20–40 mg) to be equivalent in efficacy to mianserin (30–60 mg) and less likely to cause fatigue and somnolence, although it was more likely to cause insomnia *(176)*. In a study of patients aged 60 yr or older with unipolar major depression who were randomized to flexible-dose nortriptyline or citalopram, investigators noted a better response in the nortriptyline group, especially in endogenous or psychotic patients By "endogenous or psychotic patients," do you mean "patients with somatic or psychotic disorders"? *(177)*. Although discontinuation rates associated with adverse effects were similar between groups, autonomic effects were more common in the nortriptyline group. Citalopram was superior to placebo in terms of providing prophylaxis against recurrent depression during a 48-wk trial of maintenance therapy in outpatients aged 65 yr or older *(178)*. Keller *(133)* reported the pooled data from eight double-blind, placebo-controlled studies to assess the tolerability of citalopram 10 to 80 mg daily in patients younger and older than 60 yr. Of the 1891 patients in that study, 265 were older than 60 yr. The only adverse effect more common in the elderly taking the active drug vs placebo was increased sweating (7.3 vs 1.2%, respectively). In a 6-wk study in elderly patients with depression and dementia, investigators found early adverse effects (fatigue and emotional indifference) associated with citalopram, although by the fourth week no differences between the active drug and placebo were detected *(179)*.

Although not limited to data from studies in the elderly, the adverse-effect profiles of citalopram and escitalopram indicate that they would be good candidates for the treatment of depression in older individuals. In younger patients, somnolence, dry mouth, and nausea have occurred at rate 5% or greater than with placebo, although some evidence exists indicating that tolerance to these effects may develop. Cardiovascular risk is low with all SSRIs, including citalopram, which causes a small decline in heart rate (4–8 beats per minute [bpm]) and a low incidence of bradycardia (1%), even in the elderly. The issue of cardiotoxicity for the didemethyl metabolite of this drug is relevant for humans only at very high plasma levels (>1000 nM), which would require a massive overdose. With one exception, all of the fatalities reported as a result of a citalopram overdose involved

very high doses (840–3920 mg) in combination with alcohol or sedatives. The one fatality caused by citalopram alone involved the ingestion of 4000 mg.

Another extremely important advantage for both citalopram and escitalopram over most other SSRIs is the low incidence of pharmacokinetic interactions associated with these drugs. In a review of in vitro studies, Greenblatt and colleagues *(180)* reported that citalopram inhibits CYP1A2 only slightly and has virtually no effects on CYP2C9, CYP2C19, CYP2D6, or CYP3A4 activity (*see also* Chapter 2 for a discussion of antidepressant metabolism). With the possible exception of an interaction between citalopram and metoprolol (a 2D6 substrate), studies in humans confirm the low incidence of pharmacokinetic interactions with citalopram *(133)*. Pharmacodynamic drug interactions of citalopram and escitalopram are probably equivalent to those seen with other SSRIs; therefore, efforts should be made to avoid concomitant administration with MAOIs, other SSRIs, meperidine, tramadol, and other medications that increase serotonin activity.

Sertraline—another SSRI commonly prescribed for elderly patients with depression *(181,182)*—also has the advantage of a low incidence of pharmacokinetic drug interactions *(180)* and good tolerability. Bondareff and colleagues *(183)* compared sertraline to nortriptyline in patients with major depression (210 outpatients aged 60 yr or older with a mean illness duration of 3 yr and an HDRS-24 score of 18 or greater). In a completer analysis, efficacy was similar for both groups, with a 71.6% response rate among patients taking sertraline (mean dose: 96 mg/d at 12 wk) vs 61.4% among those taking nortriptyline (mean dose: 78 mg/d at 12 wk). Based on an intent-to-treat (ITT) analysis using the last observation carried forward, response rates (≥50% reduction in HAM-D score) were not as robust, but were still similar in both groups. Time to response was also similar for both groups, with 75% of improvement seen by week 6. Patients aged 70 yr or older who were taking nortriptyline did not respond as well as younger patients; however, age did not appear to influence the response to sertraline. An additional finding of this study was a beneficial effect of sertraline on cognitive functioning (assessed by the Profile of Moods State, confusion factor, MMS, Wechsler Adult Intelligence Scale [WAIS], and Shopping List Task [SLT]). The finding of improved cognitive function is supported by another study in which small improvements in cognitive function with sertraline (but not paroxetine) were observed in normal elderly volunteers *(184)*.

In another study, investigators found only modest improvements in cognitive function in response to sertraline *(185)*. In this study, 39 patients aged 50 yr or older with depression (major depressive disorder, dysthymic disorder, or depression not otherwise specified, with a HAM-D-17 score ≥8) and cognitive impairment without dementia (i.e., intellectual impairment lasting 6 mo to 10 yr and

impaired neuropsychological test performance [≥1 standard deviation below standardized norms] on at least one test from a brief neuropsychological battery) participated in a 12-wk open trial of sertraline up to 200 mg/d. Antidepressant response was defined as a 50% or greater decline in HAM-D score from baseline and improved CGI score. Of the 26 patients who completed the study, 17 were responders and 9 were nonresponders. Responders were younger, with a mean age of 66.8 yr vs 82.3 yr for nonresponders. The only cognitive measure for which a significant (albeit slight) difference was found was the WAIS-R digit symbol substitute test (a measure of attention and executive function) Please provide *P* value to support significance. . No difference was found for another test of attention, the WAIS-R digit span.

The findings of another study also suggested cognitive improvement in elderly patients treated with sertraline *(186)*. In this double-blind study, 236 outpatients aged 60 yr or older with major depression completed a 1-wk placebo wash-in period and were then assigned to 12 wk with sertraline (50–100 mg/d) or fluoxetine (20–40 mg/d). Response—defined as a 50% or more reduction in HAM-D score from baseline—was comparable for both groups (sertraline: 73%; fluoxetine: 71%), with patients with a high severity of depression responding more quickly in the sertraline group. Equivalent responses were also seen on the CGI, MADRS, and the Hamilton Rating Scale for Anxiety (HAM-A). The sertraline group demonstrated greater improvement in verbal learning and recall, as measured by the SLT and the WAIS-R digital symbol substitution test. Improvement in cognitive functioning did not appear to be correlated with improvement in symptoms of depression. During a 12-wk clinical trial of patients younger than 70 yr who had a diagnosis of a major depressive disorder, Finkel and colleagues found no statistically significant difference in the occurrence of adverse effects in patients taking sertraline vs fluoxetine *(187)*.

Inconsistent data on cognitive improvement with antidepressant treatment is not limited to sertraline. Citalopram and moclobemide have been associated with cognitive improvement, while findings for TCAs and paroxetine have been mixed *(7,110,179,186,188–190)*.

Despite the controversy surrounding the clinical significance of cognitive changes seen with sertraline, evidence for its antidepressant efficacy and tolerability in elderly patients has been consistent. Its equivalence to TCAs remains unresolved, however. In a study of depressed patients younger than 60 yr taking 50 mg/d of sertraline vs 150 mg/d of imipramine, investigators found that the response to treatment—defined as a 50% decrease in the MADRS scale score—was similar between groups. Although the group of patients who completed the study and the ITT group had lower MADRS scores with imipramine, these differences did not reach statistical significance. Also of interest is that the dropout rate in the imipramine group was 44.4% compared with 28.6% in the sertraline

group. Although the difference in rates was not statistically significant, it does suggest better tolerability for sertraline *(191,192)*. Montgomery and associates *(193)* suggested that the improved tolerability of SSRIs compared with TCAs is most evident when the comparator drug is amitriptyline or imipramine. This finding seems to be supported by those of an open-label trial of sertraline in doses up to 100 mg daily in nursing home residents, in which no difference in tolerability was found, although sertraline was less effective for the treatment of depression *(194)* (the dose may have been too low).

Many sertraline efficacy trials suffered from the use of an inadequate dose and inadequate duration of treatment. In a study of elderly nursing home residents with significant residual depression, an increase in sertraline dose—from 100 to 200 mg/d—resulted in an improved response, and it was well tolerated *(195)*. Efficacy studies that used nortriptyline as a comparator drug were complicated by the interaction of plasma levels, depression, and cognitive function observed for this drug. For example, in a double-blind, 10-wk clinical trial of regular (60–80 mg/d) vs low (10–13 mg/d) doses of nortriptyline, investigators found greater improvement in symptoms of depression in cognitively intact patients taking a regular dose and greater improvement in symptoms of dementia in patients taking a low dose *(196)*. In depressed patients without cognitive impairment, a curvilinear plasma response relationship was demonstrated; however, the therapeutic window may be somewhat lower (i.e., the curve shifted to the left) compared with that seen in younger adults.

Sertraline is effective in patients with depression associated with dementia. In a double-blind, placebo-controlled efficacy and safety study of sertraline in 22 patients with depression and AD, investigators found that sertraline was superior to placebo in terms of reducing depression *(197)*. The sertraline group also demonstrated significantly greater declines in the CSDD scores.

Paroxetine has been widely used in geriatric patients with depression. In a 6-wk study comparing the efficacy of short-term nortriptyline vs paroxetine in 80 elderly patients (mean age: 75 yr) with a major depressive episode, investigators found neither significant differences in dropout rates nor a relative decrease in HAM-D scores *(132)*.

In an 18-mo open continuation trial of the efficacy of 24.5 mg/d of paroxetine vs 51.3 mg/d of nortriptyline (mean blood level: 85.5 ng/mL) in 40 patients aged 70 yr or older with major depression, no or mild cognitive impairments, and mild to moderate chronic medical illnesses *(198)*, paroxetine was comparable to nortriptyline in terms of its ability to delay relapse and recurrence of major depression and may be better tolerated for maintenance.

Bump and associates *(199)* compared paroxetine and nortriptyline in a larger, two-phase, open-label continuation trial that began with a 12-wk, short-term treatment period. Elderly patients ($N = 116$) with major depression were treated

with either paroxetine or nortriptyline and were openly switched to the comparator if they did not respond to the original drug (response was indicated by a HAM-D-17 score ≤10 that was maintained for 3 wk). Patients in whom depression remitted were given the opportunity to enter the second phase of the study, an 18-mo follow-up trial of the medication to which they responded. During follow-up, the paroxetine group ($n = 83$) and the nortriptyline group ($n = 21$) demonstrated similar relapse rates and a similar duration of time to relapse. The nortriptyline group experienced both lower residual depressive symptoms and adverse effects than the paroxetine group during the second phase of the study. Investigators found that in the elderly, paroxetine and nortriptyline have similar efficacy in terms of rates of relapse and recurrence.

The efficacy and tolerability of mirtazapine vs paroxetine were evaluated more recently in a double-blind study of 255 elderly patients aged 65 yr or older with major depression without dementia *(200)*. The study consisted of an 8-wk acute phase followed by a 16-wk extension phase. Mirtazapine exhibited more notable antidepressant effects than paroxetine, with a greater mean change from baseline in HAM-D-17 score and a greater reduction in HAM-D Factor I (anxiety/somatization) and Factor VI (sleep disturbance) scores. Patients in the mirtazapine group also experienced better drug tolerability during the acute phase and a more rapid onset of action, with a median of 26 d compared with 40 d for the paroxetine group.

Cassano and associates *(201)* performed a 1-yr, double-blind, parallel-group study of paroxetine (20–40 mg/d) vs fluoxetine (20–60 mg/d) in 242 elderly patients (mean age: 75.4 yr) with depression without dementia. Participants were assessed for cognitive performance (using the Buschke Selective Reminding Test, Blessed Information and Memory Test, Clifton Assessment Schedule, Cancellation Task Test, and Wechsler Paired Word T Test) and mood function (using the HAM-D test and the Clinical Anxiety Scale). Both paroxetine and fluoxetine were well tolerated. Most patients in both groups experienced improved cognitive function. Both groups also exhibited good antidepressant efficacy, as indicated by the percentage of responders.

In an acute, 12-wk, double-blind study *(202)* of nortriptyline vs paroxetine in 116 elderly in-patients and outpatients (mean age: 72 yr) with either major or melancholic depression, investigators found that both drugs were efficacious. Although paroxetine did show greater tolerability, indicated by a significantly lower discontinuation rate associated with adverse effects, the ITT analysis indicated no significant differences in response rates in between groups.

In a double-blind French study *(203)* comparing the efficacy, safety, and tolerability of paroxetine (20 mg/d) with that of mianserin (30 mg/d) in 116 elderly hospitalized patients aged 60 yr or older with major depressive disorder, investigators identified improvement in both treatment groups for all assessment criteria,

except MMS. Patients taking paroxetine exhibited significantly greater improvement in the Covi anxiety scale (CAS). This study provides evidence of the therapeutic value and efficacy of paroxetine in a geriatric population with depression, especially when it is accompanied by anxiety.

The efficacy of reboxetine and imipramine was assessed during an 8-wk, double-blind multicenter trial in patients aged 65 yr or older with a diagnosis of depression or dysthymia, in which patients were assigned to 4 to 6 mg/d of reboxetine (n = 176) or 50 to 100 mg/d of imipramine (n = 171) *(204)*. The reduction in HAM-D score was similar between treatment groups, with a modest but clinically significant difference favoring imipramine in terms of the change in HAM-D and CGI scores. Tolerability was comparable for the two groups, with 68% of the reboxetine group and 71% of the imipramine group reporting adverse effects. The incidence of hypotension and cardiovascular effects was lower with reboxetine, whereas insomnia was less common with imipramine *(204)*.

In a 6-wk study comparing mirtazapine (15–45 mg/d) with amitriptyiline (30–90 mg/d) in 115 patients aged 60 to 85 yr with depression, investigators found similar reductions in total HAM-D and MADRS scores *(205)*. Analysis of HAM-D factors revealed a statistically significant advantage for amitriptyline in terms of the cognitive disturbance factor for weeks 2, 4, 6, and endpoint, and for the retardation depression factor at week 6. Both drugs were well tolerated.

In a double-blind study comparing bupropion SR with paroxetine in 100 elderly outpatients with depression, investigators determined that both treatment groups demonstrated similar improvement in HAM-D and CGI scores, but the side-effect profile was more favorable for bupropion *(206)*. Significantly more patients in the paroxetine group reported somnolence and GI disturbances compared with the bupropion SR group. Both groups reported dry mouth, nausea, and agitation at rates of 12 to 15%. Headache was reported by 35% of patients taking bupropion SR and 19% of patients taking paroxetine. In a naturalistic study (a study that "allows the treating geriatric psychiatrist to choose appropriate treatment for the patients using clinical judgment and treatment guidelines") of bupropion SR, elderly patients with major depression and medical comorbidity responded well to bupriopion SR alone or in combination with other medications *(207)*.

3.3.2. TCAs

Although TCAs are no longer considered the first-line pharmacologic choice for the treatment of depression, they comprise the most extensively studied class of antidepressant medications prescribed for the elderly. Numerous published reports indicate the efficacy of these medications for treating depression *(172,208)*. TCAs are subdivided into two groups: tertiary amines and secondary amines (the pharmacology of TCAs is described in detail in Chapter 2). The

tertiary amines—which include amitriptyline, clomipramine, doxepin, imipramine, and trimipramine—are not recommended for elderly patients because of the frequency and intensity of their side effects. The secondary amines, especially desipramine and nortriptyline, are still widely used to treat elderly patients with depression, but usually as a second-line medication for those who have not responded adequately to a non-TCA.

The most recent studies of TCAs in geriatric patients have examined nortriptyline, which is often used as a comparator drug in late-life depression treatment studies *(125,132,177,183,194,196,198,199,202)* and has been assessed in both short-term and maintenance therapy. During a 7-yr, double-blind, placebo-controlled, maintenance study of the efficacy of nortriptyline (80–120 ng/mL) and interpersonal therapy (IPT) in 187 elderly patients (mean age: 67.6 yr) with recurrent major depression (HAM-D-17 score >17 and MMS score ≥27) *(209)*, investigators found that the rate of recurrence was lower in all active treatment groups compared with placebo, with rates of 20% seen in the nortriptyline/IPT group, 43% in the nortriptyline/medication clinic visit group, 64% in the placebo/IPT group, and 90% in the placebo/medication clinic visit group. Please define "medication clinic visit group." Combination therapy with nortriptyline and IPT had a clinically significant effect on recurrence, which was most pronounced during the first year of maintenance therapy in patients older than 70 yr.

In a 3-yr, double-blind study, Reynolds and associates *(210)* compared the efficacy of two fixed plasma levels of nortriptyline (80–120 ng/mL and 40–60 ng/mL) in 41 elderly patients with a history of recurrent major depression. The difference in rate of recurrence between the group taking 80 to 120 ng/mL (mean age: 67.7 yr) and the group taking 40 to 60 ng/mL (mean age: 66.3 yr) was not significant. Compared with the group taking 40 to 60 ng/mL, significantly fewer patients in the group taking 80 to 120 ng/mL had HAM-D scores in the subsyndromal range (6 vs 25%), but they experienced constipation more frequently (33 vs 5%). With the proper management of adverse effects, the researchers found the 80- to 120-ng/mL dosages to be more efficacious.

During a more recent, 1-yr maintenance trial of nortriptyline and IPT in patients with major depression, investigators assessed the social adjustment of study participants ($N = 49$; mean age: 66.8 yr, with a HAM-D score ≥17 or an MMS score ≥27) *(211)*. The Social Adjustment Scale (which measures performance, interpersonal behavior, friction, and satisfaction domains) was administered every 3 mo until depression recurred. The investigators found that the patients treated with nortriptyline and IPT "maintained treatment-attributable improvements" in Social Adjustment Scale scores, whereas those in either monotherapy group exhibited declining scores. According to Lenze and associates, combination therapy improved "not only the length but the quality of recovery."

The severity of adverse effects experienced with nortriptyline was examined in a double-blind, placebo-controlled maintenance study of 37 elderly patients (mean age: 67.9 yr) with recurrent major depression treatment over a 2- to 3- yr period *(212)*. Of the 10 side-effect variables monitored, treatment-by-time analysis identified only dry mouth and elevated heart rate (+6–8 bpm) more consistently in the nortriptyline group. Other complaints, identified by using the total Asberg Rating Scale for Side Effects (physical tiredness, daytime sleepiness, and nighttime sleep disturbance), were related to residual depression as opposed to nortriptyline therapy. This trial did not provide evidence in support of reports linking nortriptyline therapy with constipation, weight change, or orthostatic symptoms, but suggests that nortriptyline is a safe and well-tolerated treatment option for late-life major depression.

Dew and associates *(213)* examined initial recovery patterns to determine their potential use as predictors of the outcome of maintenance therapy during a 3-yr study of nortriptyline and IPT in 140 elderly patients (aged ≥60 yr) with recurrent unipolar major depression. After 16 wk of combination nortriptyline/IPT therapy, participants were classified as either "rapid sustained responders," "delayed sustained responders," "mixed responders without sustained improvement," or "prolonged nonresponders," then randomized to either combination therapy with nortriptyline and IPT, monotherapy with either IPT or nortriptyline, or medication clinic visits with placebo. Compared with the placebo group, "rapid responders" assigned to combination therapy or monotherapy demonstrated lower rates of recurrence. In the "rapid responders" group, each form of monotherapy was as effective as the other in decreasing the rate of recurrence. The "mixed responders" only exhibited improved recurrence prevention compared with placebo when they were assigned to combination therapy, and the effect was only moderately superior to that seen in the placebo group when assigned to monotherapy. The "delayed responders" receiving combination therapy exhibited lower rates of recurrence than the placebo group, but their rates were not different from those in the groups receiving monotherapy with either drug or placebo. The "prolonged nonresponders" did not exhibit any benefit from any form of treatment. This study suggests that a patient's initial response to antidepression therapy may predict the possibility of a successful outcome with specific types of therapy.

In a 6-wk, double-blind study of sex-related differences in adverse effects from short-term nortriptyline therapy (60–120 ng/mL) in 78 patients aged 18 to 85 yr (mean: approx 50 yr in each group) with a diagnosis of a major depressive episode, a HAM-D-21 score of 18 or greater, and definite primary unipolar depression *(214)*, investigators observed a significant increase from baseline in supine heart rate in both men and women. In men, the heart rate was significantly

higher between weeks 4 and 6 compared to women; the difference among age groups was not significant. Throughout the trial, a significantly higher percentage of women reported dry mouth, dry lips, or both, while the men only reported significantly greater occurrence of dry mouth during weeks 3 and 5.

In an acute, 6-mo, single-blind study, investigators compared the efficacy and safety of venlafaxine (225–300 mg/d) with that of nortriptyline (50–100 mg/d) in 68 in-patients and outpatients aged 65 yr or older with a current diagnosis of major depression (based on a HAM-D-17 score ≥21) and symptoms lasting at least 1 mo *(215)*. Differences in recurrence or dropout rates were not significant between treatment groups. Patients in the venlafaxine group tolerated the medication slightly better than those in the nortriptyline group. Those in the nortriptyline group reported significantly more episodes of orthostatic vertigo, dry mouth, and impaired accommodation, as assessed using the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale. The findings of this study suggest that venlafaxine and nortriptyline are similar in efficacy in moderate to severe major late-life depression, with venlafaxine exhibiting slightly better side-effect tolerability.

Several other TCAs have been assessed for their efficacy in the treatment of late-life depression. In two acute, double-blind, placebo-controlled studies, investigators compared the efficacy of nomifensine vs imipramine in patients with late-life depression *(216,217)*. In both studies, investigators found the drugs to be comparable in terms of antidepressant effect, and were both superior to placebo. Nomifensine and imipramine were well tolerated in both studies, with the imipramine group experiencing more uncomfortable adverse effects than the nomifensine group. In one study, investigators associated imipramine with a greater incidence of anticholinergic effects *(217)*. In the other study, no statistical differences between the two medications was found, but patients taking imipramine had a tendency to experience drowsiness, nervousness or restlessness, and blurred vision more often than patients taking nomifensine, while those taking nomifensine had a tendency to experience constipation more often *(216)*. In an earlier 4-wk, double-blind, placebo-controlled study of trazodone vs imipramine in 60 patients (mean age: 68.4 yr) with unipolar depression, investigators found that both drugs were superior to placebo and had similar therapeutic effects *(218)*. The imipramine group reported a larger side-effect profile, which included cardiovascular and anticholinergic effects. During an 8-wk comparison study of buspirone vs imipramine in 177 elderly patients (mean age: 72 yr) with major depression (HAM-D score: ≥18), investigators found a clinically significant reduction in total HAM-D scores in the imipramine group and a clinically significant improvement in CGI scores and earlier onset of improvement in that group compared to placebo *(219)*. Imipramine elicited a more robust therapeutic effect than buspirone, with a greater change in HAM-D scores and a significant improvement over placebo beginning at week 2 vs week 8. The rate of improvement in HAM-D and MMS scores was

assessed in an acute, 8-wk, double-blind trial of imipramine in 61 elderly patients with AD (mean age: 72 yr), with and without depression *(188)*. Depressed patients treated with imipramine and placebo exhibited similar rates of improvement in HAM-D score. MMS scores improved in all patients over time, with no difference seen in patients taking imipramine vs placebo and with patients with depression demonstrating significantly more improvement than those without depression.

Investigators assessed the efficacy and tolerability of trazodone (150 mg tid), mianserin (60 mg tid), and amitriptyline (75 mg tid) in 106 elderly patients (mean age: 65.8 yr) with major depression over 5 wk. All three medications exhibited comparable efficacy, as determined by HAM-D and Geriatric Depression Scale (GDS) scores, but the trazodone group experienced fewer adverse effects. Amitriptyline was also compared with mianserin in a placebo-controlled study in 75 patients aged 60 yr or older with depression *(220)*. Investigators found that amitriptyline and mianserin had comparable antidepressant effects, while mianserin exhibited a more tolerable side-effect profile. In a more recent 8-wk, double-blind study comparing the efficacy and tolerability of paroxetine (20–40 mg/d) with that of amitriptyline (75–150 mg/d) in 191 patients (mean age: approx 55 yr) with rheumatoid arthritis and depression *(221)*, investigators found that both medications resulted in similar improvements in MADRS and CGI scores. Paroxetine had a tendency to be better tolerated than amitriptyline, with fewer anticholinergic effects (18.1vs 43.8%, respectively) and fewer sedative effects (9.6 vs 25.0%, respectively).

In a 4-mo study of desipramine, cognitive behavioral therapy (CBT), or both for late-life depression *(222)* in 102 patients aged 60 yr or over with a major depressive disorder, investigators found a significant improvement in the per-session rate of change in HAM-D scores achieved by patients receiving combination therapy compared with those receiving desipramine monotherapy Significantly greater per-session rates of change were also observed for combination therapy and CBT monotherapy compared with desipramine monotherapy, as determined by the Beck Depression Inventory-Short Form (BDI-SF). ITT analyses suggested that the combination therapy group experienced significantly greater improvement than the desipramine monotherapy group, and different measures yielded conflicting results regarding the superiority of CBT monotherapy vs desipramine monotherapy.

3.3.2.1. Clinical Use of TCAs

Before treatment with a TCA is initiated, the elderly patient should be evaluated for cardiac disease, cerebrovascular or degenerative brain disease, glaucoma, and protastic hypertrophy, each of which may be worsened by this drug class The most common adverse effects of TCA therapy are orthostatic hypotension, sedation, and anticholinergic effects (dry mouth, constipation, blurred vi-

sion, urinary hesitancy, and cognitive impairment). TCAs also have quinidine-like properties; thus, high blood levels of these drugs may produce cardiac arrhythmias. For this reason, it is strongly recommended that an elderly patient with depression have a baseline ECG before TCA therapy is initiate, particularly to evaluate the QTc interval (widening of this ECG interval indicates the development of cardiotoxic effects) (*see also* Chapter 2).

Most older patients respond to TCAs within approx 6 to 8 wk—the same length of time as for young and middle-aged adults. However, their response is less complete; therefore, 12 wk or more may be necessary for the remission of the depressive symptoms in elderly patients. Once an older patient has responded to treatment, maintenance therapy should be continued for at least 1 yr, the total duration of therapy depending on the number of prior depressive episodes and the severity of the most recent depressive episode. Elderly individuals who have been extremely ill or repeatedly ill should continue TCA antidepressant therapy as long as possible.

3.3.3. Summary of Antidepressants in Geriatric Major Depression

Available studies indicate that antidepressants are equivalent in efficacy against major depression in geriatric patients. SSRIs are considered first-line agents because of their safety profile, simplicity of dosing, and lack of drug–drug interactions with citalopram and escitalopram. Other drugs that are also effective and well tolerated include sertraline, nortriptyline, venlafaxine, mirtazapine, and bupropion. Some studies indicate that TCAs can be used safely, provided adequate medical monitoring is provided. ECT should always be considered for geriatric patients with major depression *(172)*.

3.4. Antidepressant Response in Patients Without Major Depressive Disorders (MDDs)

3.4.1. Treatment for Dysthymia and Subsyndromal Depression

The approach to patients with subsyndromal (minor) depression depends on the length and severity of symptoms. For patients with an onset of symptoms within the preceding few weeks, the best initial course is psychotherapy and careful follow-up. If this approach fails within a reasonable period of time, the addition of an antidepressant is warranted. No specific antidepressant has demonstrated superior efficacy. However, it should be noted that published trials are not equivalent, because different doses of the same antidepressant, different medications, and variable durations of treatment and follow-up are used. Many of the clinical trials discussed above have included patients with major depression and those with dysthymia. Very few antidepressant studies have limited their enrollment to patients with dysthymia or minor depression.

A notable exception is a study of 415 patients in primary care (mean age: 71 yr) with minor depression ($n = 204$) or dysthymia ($n = 211$) and a HAM-D score of 10 or greater who were randomized to paroxetine (10 mg/d titrated to a maximum of 40 mg/d) or a behavior-based psychotherapy designed specifically for patients in primary care: Problem-Solving Treatment-Primary Care (PST-PC) *(223)*. Paroxetine-treated patients showed a greater decline in the Hopkins Symptom Check-List Depression (HSCL-D) scale score compared with both PST-PC and placebo groups. Improvement in symptoms of depression was greater and more rapid with paroxetine; however, the change would be considered moderate by clinical standards. Patients with dysthymia and those with minor depression both responded to drug therapy in a similar fashion.

The findings of two small open-label trials suggest that sertraline and citalopram are effective in minor depression in the elderly. During a 6-wk, open-label trial of sertraline in nursing home residents with dysthymia ($N = 12$), investigators found no significant side effects and 75% met the criteria for remission *(224)*. In a study of 10 geriatric patients with minor depression who received citalopram 20 mg for 12 wk, investigators found that the participants tolerated the medication well and demonstrated a marked decrease in depressive symptoms *(225)*. Patients with prolonged bereavement have also responded to antidepressant treatment in a small number of studies *(65)*.

3.4.2. Treatment of Depression After a Stroke

Depression is also a risk factor for stroke. In persons over 65 yr, stroke occurs at rates that are 2.3 to 2.7 times greater in persons with more severe depression than in those with relatively mild depression. *(226)*. Approximately 30% of patients are depressed after a stroke *(227)*. Research surrounding the biological treatment of depression following a stroke has focused on the use of antidepressant medications, psychostimulants, and ECT. Confirmation of psychostimulant and ECT efficacy requires more randomized, controlled studies, although both treatments appear to be safe and well tolerated *(228)*. Patients experiencing depression following a stroke respond well to antidepressant drug therapy. TCAs, especially nortriptyline, have been particularly effective, as have most SSRI antidepressants *(229,230)*. Most recent evidence, however, strongly favors the use of SSRIs over TCAs *(231)*.

The efficacy and tolerability of fluoxetine (20 mg/d) for depression after a stroke was examined in a 6-wk double-blind, placebo-controlled study in 31 patients who had experienced a stroke within the preceding 3 mo and had been diagnosed with major depression (as determined by the *International Classification of Diseases, 10th revision,* and a MADRS score <19) *(232)*. The fluoxetine group exhibited a clinically significant improvement in mean MADRS score at week 6 compared with the placebo group (score = 11.8 vs 18.7, respectively). The

fluoxetine group also experienced a significantly greater mean change in MADRS score than the placebo group (mean change = 16.6 vs 8.4, respectively).

Fluoxetine efficacy and safety was also assessed in a 3-mo, double-blind, placebo-controlled study, with an 18-mo, open-label follow-up period *(233)*. Patients ($N = 54$) had experienced a stroke within the preceding 2 wk and had been diagnosed with moderate to severe depression (according to BDI and CGI scores, and a HAM-D score <15). Both groups exhibited significant improvements in HAM-D scores. The difference in scores was not significant at the 3-mo assessment, but at the 18-mo follow-up assessment, patients in the fluoxetine group demonstrated significantly less depression than patients in the placebo group. No fluoxetine-related adverse effects were exhibited. During an 8-wk trial of fluoxetine (20–40 mg/d) vs sertraline (50–100 mg/d) in 45 patients following a stroke who had been diagnosed with major depression, investigators found that both SSRIs could be efficacious *(234)*.

During a 12-wk, double-blind, placebo-controlled study of nortriptyline (25–100 mg/d) vs fluoxetine (10–40 mg/d) efficacy in 56 patients who had experienced a stroke *(230)*, investigators found nortriptyline to be superior to fluoxetine, eliciting a significantly higher response rate (77% for nortriptyline, 14% for fluoxetine, and 31% for placebo). These results appear to contradict those of other studies that suggested that SSRIs are superior to TCAS in post-stroke depression; however, the dropout rate was higher in the fluoxetine group, and the study design was altered mid way because of a high placebo response rate. The fluoxetine group was composed of significantly more patients who failed to respond to placebo than the nortriptyline group, which suggests that the patients taking fluoxetine were more difficult to treat *(228)*.

In a 12-wk, double-blind, placebo-controlled study of nortriptyline (25–100 mg/d) vs fluoxetine (10–40 mg/d) efficacy in the prevention of depression after a stroke in nondepressed patients ($N = 48$) *(235)*, investigators observed a significantly higher rate of depression in the placebo group than in the active treatment groups combined among patients who completed the 12-wk treatment period. The nortriptyline group was significantly more likely to developing depression within less than 6 mo after the treatment period ended, indicating that fluoxetine may have a prophylactic effect.

Research indicates that depression following a stroke can be treated effectively using antidepressants. Both TCAs and SSRIs are well tolerated and effective; however, research findings support the use of SSRIs as first-line agents in the treatment of post-stroke depression.

3.4.3. Treatment of Depression After an MI

Depression increases the risk for ischemic heart disease and mortality following an MI *(227)*. Recent data strongly emphasize the importance of using non-

TCAs to treat patients who develop depression after an MI as well as patients with ischemic heart disease *(236)*. The treatment of depression in patients following an MI is discussed in the section on cardiovascular effects.

3.4.4. Treatment of Vascular Depression

Existing research on the pharmacotherapy of vascular depression does not yield definitive answers for the clinician. As described earlier, sertraline may be effective *(37)*, but the response to citalopram may be lower in patients with vascular depression compared with those who have major depression without ischemic brain lesions *(39)*. Pharmacologic approaches that increase dopamine or acetylcholine levels have an appeal based on theory, but have not been adequately studied. Bupropion, methylphenidate, and dextroamphetamine are often used in clinical settings.

3.5. ECT

Although the primary purpose of this chapter is to review the pharmacotherapy of depression in geriatric populations, ECT should be discussed because it is also a safe and effective treatment. In a review of treatment modalities available for depression in the elderly, Salzman and associates *(172)* reported on 12 publications examining the efficacy of ECT *(237–248)*. They concluded that ECT was efficacious and well tolerated even in patients over 80 yr. They also pointed out that there have been reports of a risk for falls during ECT and isolated cases of delirium or dementia developing after ECT.

3.6. Psychosocial Treatment

A number of psychotherapeutic or psychosocial interventions have proven helpful in treating depression in geriatric patients, including individual, group, and family therapy approaches with or without concurrent antidepressant medication. A large meta-analysis carried out in 1994 revealed the efficacy of various types of individual therapy, including cognitive, behavioral, interpersonal, supportive, reminiscence, and "eclectic" approaches. Both brief and longer forms of psychodynamic therapy have had good results in the elderly. CBT is recognized as an appropriate treatment for patients with both dementia and depression. IPT is also effective, particularly for patients with bereavement issues.

Group therapy includes cognitive-focused, psycho-educational, reminiscence, problem-solving, and goal-focused approaches, which are conducted in inpatient settings, partial hospital programs, and day programs. They have had a good effect, although some studies have shown that patient selection is important because various disabilities need to be taken into account. If a patient has difficulty engaging in group therapy, this difficulty may have a negative effect on the group process.

Family therapy is important, because patients are often first seen after the family has become overwhelmed in trying to take care of its loved one. Family involvement offers the therapist an opportunity to obtain an accurate history on the patient that can be used to better understand the current situation and to educate the family as primary managers of patient behaviors and medicines. It also offers an opportunity to gather information about family dynamics that may help or hinder the patient's progress *(249)*.

4. CONCLUSIONS

The pharmacologic treatment of depression in geriatric patients, although similar to that in younger adults, presents its own distinctive challenges that we must confront in response to the growing number of elderly in our population. A diagnosis of depression may be masked by confounding medical symptoms and comorbid medical illness in this population. Dementia may also mimic some aspects of depression and make the primary diagnosis unclear. Depression with a vascular etiology may prove refractory to the usual forms of treatment and needs to be a focus of research in the future. Despite the fact that antidepressants are effective in late-life depression, treatment rates remain low and drug adherence is a problem.

Evidence of the efficacy of antidepressants is strongest in studies of patients with major depression, but somewhat weaker for patients with minor depression or dysthymia. ECT remains a mainstay of treatment for major depression in geriatric patients *(172)*. Although the safety and efficacy of antidepressants in the medically depressed elderly has been established, the size of the effect is modest. Antidepressant augmentation strategies have not been adequately studied in the elderly. The pharmacokinetics and pharmacodynamics of antidepressants are altered in the elderly, leading clinicians to base their approach on the maxim, "start low, go slow." SSRIs are commonly recommended as first-choice antidepressants because they are presumed to be better tolerated in the elderly, yet most studies show little improvement with SSRIs compared with nortriptyline. The improved adverse-effect profile for SSRIs becomes apparent when amitriptyline and imipramine are used as comparator drugs. There are very few studies on recently introduced agents—such as venlafaxine, bupropion, mirtazapine, and nefazodone—making the selection of agents based on relative efficacy and safety in the geriatric population difficult.

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4 Treatment of Bipolar Depression

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Contents

1. INTRODUCTION

1.1. Scope of Depression in Bipolar Illness

The challenge of treating depression in patients with bipolar illness has been both underestimated and understudied for a variety of reasons. The three major mood stabilizers—lithium, carbamazepine, and valproate—are each better antimanic agents than they are antidepressants. Perhaps not surprisingly, when a large group of intensively treated outpatients was prospectively assessed on a daily basis, it was found that they had three times as many days of depression as they did days of mania, bipolar I disorder being the predominant diagnosis in this group (Post et al., in preparation). Among these patients, 25% remained ill for more than three-fourths of the year, with the majority having ultra-rapid cycling frequencies and 7% having chronic depression. Additionally, 40% of these patients had intermittent illness despite the intensive therapy, with the majority

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having intermittent major depression and full-criteria mania intervening in 9.7%, hypomania in 19%, or no mania in 5.8%; another 5.8% had mostly mania. Disappointingly, only 11.2% were judged symptom-free and only one-third were minimally impacted by their affective illness over the prospective year.

Although illness begins in half of all patients with bipolar disorder (BD) with episodes of depression rather than mania, these patients contribute disproportionately to the population of those with more episodes of mania and more rapid-cycling patterns over the course of their illness.

A very large portion of patients with BD whose illness begins with depression (who will eventually be diagnosed with BD) and the very large group of patients who are misdiagnosed in community settings as having unipolar depression actually have bipolar II disorder (BD II) and undergo extremely long delays before they are properly diagnosed *(1)*. A variety of studies indicate that approx 20 to 40% of unipolar patients, on closer examination, meet the criteria for either full-blown BD or one of a spectrum of BDs, including BD not otherwise specified (NOS) and cyclothymia *(2)*.

Although it is estimated that roughly 1% of the US population will have a diagnosis of Bipolar I disorder (BD I) over their lifetime, current estimates suggest that an additional 2 to 4% will have bipolar spectrum disorder. The vast majority of these will be not be diagnosed. Epidemiological studies indicate that 40% of patients with BD meeting the criteria for BD I are not receiving treatment at the time of the diagnostic interview. In a survey of more than 80,000 US households using a self-rated mood disorder questionnaire—which has been validated as a screening instrument to detect bipolar illness *(3)*—investigators determined that not the majority of patients with BD were not diagnosed as such, and even if correctly diagnosed, were not receiving appropriate treatment. In most cases, treatment involved the use of antidepressants without concomitant mood stabilizers.

Evidence that the depressive components of bipolar illness remain a major contributor to morbidity *(4)* and that the illness is markedly underdiagnosed and undertreated in the community has important ramifications for mortality associated with the illness. It has been estimated that approx 10 to 20% of patients with this diagnosis will die by suicide. The major phases of the illness that drive suicide attempts are the depressive ones, along with dysphoric mania. We have ascertained that patients who have made suicide attempts that require medical treatment have a history of more depressive episodes and demonstrate prospectively on follow-up that they experience more severe depression and more time depressed.

Therefore, there is a tremendous need for a better approach to depression in bipolar illness to prevent both depressive morbidity and mortality by suicide. Additionally, depression is a risk factor for premature death from a variety of

other medical illnesses, such as heart attack and stroke. It is estimated that inadequately treated patients with recurrent unipolar and bipolar depression have an average 7-yr reduction in life expectancy compared with the general population. A reduction in morbidity and mortality can be achieved in this patient population. As discussed later, long-term therapy with lithium reduces the risk of suicide dramatically and normalizes the excess medical mortality that is associated with recurrent affective illness.

1.2. Potential Reasons for Understudy of This Phase of the Illness

Despite the association of BD with a considerable depressive illness burden and the highest rate of suicide among the major psychiatric disorders, the illness in general and BD depression in particular have been disappointedly understudied, for a number of reasons. These include the initial perception that lithium was adequate treatment for the vast majority of patients. It is now recognized that only a minority of patients with BD respond adequately to lithium, whether it is administered as monotherapy or in combination therapy with an antidepressant, antimanic, benzodiazepine, or other type of adjunctive agent. Patients with BD depression have traditionally been excluded from trials of antidepressants for fear of their switching into a manic episode and confounding interpretation of antidepressant responsivity. Thus, there is little information about the efficacy in bipolar illness of antidepressants that are widely used in patients with unipolar illness. Only recently has this need been recognized by the pharmaceutical industry and have they targeted this population for study.

Moreover, almost all drugs now being studied in BD were initially considered for use as antipsychotic agents for schizophrenia or anticonvulsants agents for refractory epilepsy. Additionally, when these drugs were studied in patients with BD, they were almost universally initially considered for the acute treatment of mania, and FDA approval for this indication was rapidly attained. Rarely has a drug been studied initially or at all for its potential efficacy in the acute treatment of bipolar depression, with the recent exception of the atypical antipsychotic olanzapine and the anticonvulsant lamotrigine.

Perhaps the most important issue responsible for the lack of research in bipolar illness is the complexity of its presentation and course, which often confounds the most highly respected investigators in the field and prevents them from impeding agreement on appropriate study methodology and priority for grant funding. Disagreements about optimal research methodology, design, and outcome measures have markedly reduced the number of studies funded. Currently, few studies on the efficacy of pharmacological agents in bipolar illness are even submitted for consideration for funding to the extramural program of the National Institute of Mental Health because of this controversial history.

1.3. Implications for Treatment Recommendations

The limited amount of research into BD therapy has had a considerable effect in the field of clinical therapeutics. In this chapter, we review the systematic literature that exists on treatment of depression in bipolar illness, but acknowledge from the outset that a paucity of information exists in this regard, and that a very large part of clinical practice and treatment of bipolar illness is currently based on uncontrolled clinical observations and clinical intuition, if not clinical wisdom. As such, much of what we discuss and present in this chapter is provisional and subject to revision as more systematic data become available from controlled clinical trials.

Conventional wisdom suggests that therapy for BD depression should begin with combination therapy using an antidepressant and a mood stabilizer *(5)*. Another well recognized option is lamotrigine monotherapy, particularly for BD II depression. Many authorities advocate the avoidance of antidepressants in patients with rapid cycling, continuous cycling, and/or polyphasic episodes, favoring the use of one or more mood stabilizers instead to control the rate of occurrence and reduce mood instability. A considerable diversity of opinion exists regarding the next step when these initial options fail, particularly because of the multiple agents available in each drug class and the wide variety of potential augmentation strategies that can be used.

As the search for agents moves from first-line to second- or third-line options for patients with BD, guidance from controlled clinical trials drops from minimal to virtually nonexistent. A number of possible options and strategies for patients with substantial residual depressive morbidity—which comprise a large percentage of this patient population—are described in later in this chapter.

2. SECOND-GENERATION ANTIDEPRESSANTS

Antidepressants that are widely used in the treatment of BD depression are bupropion, the selective serotonin reuptake inhibitors (SSRIs) and the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine. For several reasons, these agents have generally supplanted the first-generation antidepressants—the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Although the efficacy of first- and second-generation agents is approximately the same, the second-generation antidepressants are much better tolerated. In particular, they have fewer anticholinergic adverse effects and are less likely to induce orthostatic hypotension, both of which are particularly problematic in older individuals and at higher doses. Second-generation antidepressants are also safer in terms of the risk for overdose.

The older agents were highly toxic; even small overdoses could be lethal and could be used to attempt suicide. There is also some evidence that first-genera-

tion drugs may induce a switch to mania or promote rapid cycling *(6)*. For these reasons, the first-generation agents are largely to be avoided, except for MAOIs in patients with refractory bipolar depression and anergic or atypical depressive syndromes *(7—9)*. The efficacy of MAOIs is better than that of TCAs in bipolar depression *(7)*. Additionally, anergic or atypical depressive syndromes are more common in bipolar than unipolar patients *(10)*.

Evidence of the risk for mania induction by antidepressants varies widely across several studies. Mania induction rates of 25 to 50% have been reported for TCAs and MAOIs *(6,11,12)*. Considerably lower rates (range: 2.5–12%) have been reported in studies of acute treatment with second-generation antidepressants *(13,14)* vs placebo (4.2% switch rate) *(14)*. The reversible MAOI moclobemide is effective in BD depression and appears to have lower switch rates than TCAs *(15,16)*. Variables contributing to the variable switch rates appear to be longer observation times for continuation and prophylaxis studies compared with acute studies,
as well as patient population characteristics. Regarding the latter, in studies including patients with rapid cycling or with a greater number of manic episodes *(11)*, switch rates are usually higher than studies that exclude patients with these disorders. In one meta-analysis by Rouillon and colleagues *(17)*, switch rates for placebo and combination therapy using an antidepressant (usually a TCA) and a mood stabilizer yielded both yielded a switch rate of approx 25%. The switch rate rose to approx 50% for antidepressant monotherapy. It is unclear whether the type of concomitant mood stabilizer is a factor in antidepressant-induced switch rates.

2.1. Bupropion

Bupropion was effective for BD depression in two small, controlled studies *(18,19)*. While the SSRIs are most widely used to treat unipolar depression, bupropion is often recommended for patients with BD because of its general tolerability and side-effects profile, which is well attuned to patients with BD, who often have atypical depression with reverse vegetative symptoms. This drug can be slightly excitatory for the anergic patient and may help delay sleep onset for the hypersomnic patient. It is also weight neutral, and few individuals experience sexual dysfunction with this antidepressant compared with SSRIs.

Open clinical trial literature supports the use of combination therapy using bupropion and lithium carbonate, even in those with rapid cycling presentations. It can also be used effectively with valproate or carbamazepine, although carbamazepine induces bupropion to be metabolized to form an active hydroxymetabolite.

While divided and spaced doses are necessary with the bupropion immediate-release preparation, this is less of a concern with the extended-release preparation, particularly when the drug is used in combination with anticonvulsants. The

drug is said to carry approx 0.1% seizure liability, particularly at doses of 450 mg or more. Individual case reports indicate that unexpected switches to hypomania and mania can still occur with this drug, despite its use in combination with mood stabilizers *(20)*.

2.2. SSRIs

The SSRIs have been found effective for bipolar depression, with controlled studies supporting the use of fluoxetine *(21,22)*, paroxetine *(23–25)*, and citalopram *(26)*. SSRIs are well tolerated as a class, although headache, insomnia, and sexual adverse effects can sometimes limit their use. Recent controlled studies of SSRIs as adjuncts to mood stabilizers suggests a rapid switch rate typically in the range of 5 to 10% and in several instances significantly less than the rates for older TCAs. Of note, patients receiving concomitant paroxetine and lithium may develop a serotonin syndrome *(27)*.

Nefazodone is essentially an SSRI with the additional mechanism of blocking 5-HT_2 receptors, an action associated with an increase in slow-wave sleep. This agent has not been studied systematically in bipolar patients, but has been reported particularly effective for sleep disturbance in patients with posttraumatic stress disorder, and may therefore be useful in patients with BD and this comorbidity. Nefazodone has not been associated with the same degree of sexual dysfunction as pure SSRIs, probably because of the 5-HT_2 receptor antagonist properties of this agent.

Venlafaxine was effective for BD depression in a controlled trial *(25,28)*. Because it inhibits the reuptake of both serotonin (5-HT) and norepinephrine (NE), it is thought to have a potency exceeding that of the SSRIs. Two recent meta-analyses support this contention in patients with unipolar depression, although it remains to be determined whether a similar increase in efficacy rate and magnitude of antidepressant response occurs with venlafaxine compared with the SSRIs used in patients with BD depression. For some individuals, gastrointestinal adverse effects are problematic, particularly during the first week of treatment, but these are usually time limited. Venlafaxine has been associated with a small increase in blood pressure, which may be problematic for patients with borderline or frank hypertension.

Mirtazepine exerts actions on both the serotonergic and noradrenergic systems through its blockade of inhibitory noradrenergic α_2-autoreceptors. However, it has substantial sedating properties and is often associated with considerable weight gain, which can limit its utility for patients with BD who present with symptoms resembling those of patients with unipolar disorders, i.e., agitation, insomnia, and anorexia, mirtazepine may be useful, particularly at the lower doses, often providing more sedation.

The newly approved drug duloxetine also inhibits 5-HT and NE reuptake and thus shares the efficacy of venlafaxine in patients with depression and pain.

Pramipexole is a dopamine (DA) agonist with high intrinsic activity and modest selectivity for D3 receptors and, therefore, perhaps for mesolimbic dopaminergic systems, as well. Goldberg and associates found pramipexole to be superior to placebo in 24 patients with BD depression *(29)*. This is consistent with previous case series *(30,31)* and a large controlled study in 174 patients that found pramipexole equal to fluoxetine in unipolar depression *(32)*. It is likely that pramipexole is a unimodal antidepressant, as there have been reports of mania induction. The DA agonist ropinirole may have similar activity *(33)*.

In patients with BD depression, these agents are usually provided as monotherapy for the first day or two to determine their side-effects profiles; thereafter, they may be administered as combination therapy with a mood stabilizer. A variety of soft clinical predictors of response to mood stabilizers are available; when used in conjunction with their side-effects profile, these may be of assistance to the clinician in choosing initial and secondary treatment options.

3. APPROACHES TO DEPRESSION BREAKING THROUGH ONGOING TREATMENT WITH A MOOD STABILIZER

The most typical presentation of depression in bipolar illness is that of breakthrough depression during ongoing treatment with a mood stabilizer that was initiated for the treatment of one or more manic episodes. This involves many of the same issues discussed above, but also introduces the controversial issue of optimal duration of prophylactic antidepressant augmentation therapy in the face of the need to simultaneously limit the risk for mania induction.

Because of the perceived risk of switching patients into a manic episode, inducing cycle acceleration or continuous mood cycling with the unimodal antidepressants, circumscribed use in bipolar illness has generally been recommended. Some authorities recommend only very limited use of antidepressants from the outset and discontinuation as soon as possible after the depressive episode ends to limit the risk for switching. The findings of Frankle and colleagues were consistent with this approach. In a recent retrospective chart review, these investigators found no difference in the length of depressive episodes among 50 patients with BD, whether they received antidepressants ($N = 33$) or not ($N = 17$) *(34)*. One way to limit unimodal antidepressant use is to use combination mood stabilizer therapy; this approach is supported indirectly by data showing that prophylaxis is enhanced with various combinations of mood stabilizers *(35,36)*.

In new short-term and longer-term studies, questions have been raised about this strategy. During a 6-wk study, Young and colleagues *(37)* observed superior

antidepressant effects and no difference in switch rates in patients with BD depression when paroxetine was added to a mood stabilizer vs the addition of a second mood stabilizer. Altshuler and colleagues reported analogous longer-term data *(38)*.

In two studies of patients who remained stable for 2 mo while taking antidepressants—a retrospective chart review *(38)* and a prospective study of patients who were well for 2 mo after antidepressant augmentation of mood stabilizer therapy (Altshuler, in preparation)—the outcomes for patients who continued antidepressant therapy vs those who did not were compared. In both studies, antidepressant continuation was associated with a lower risk for depressive relapse over 1 yr (30–40% vs 65–70% with antidepressant discontinuation). Strikingly, the lower relapse rate in those who continued on antidepressants was achieved without an increased risk for switching to mania.

These data appear to confirm the general proposition that if the illness is stable, a conservative approach should be taken and pharmacological regimens should not be revised. In the case of continued mood instability, however, a more aggressive approach may be necessary, using a revised pharmacological intervention.

Our personal algorithm involves considering antidepressant augmentation of a mood stabilizer in patients with non-rapid-cycling depressive episodes. When depression emerges within the context of rapid or continuous cycling, we recommend the use of a second or perhaps a third mood-stabilizing agent before adding a unimodal antidepressant. In this fashion the primary problem of the combination of mood instability and cycling would be addressed before an antidepressant is used, and hopefully the combination of several mood stabilizers will be sufficient and prevent the necessity for unimodal antidepressant therapy or prevent a switch to mania if one is used. In cases of rapid or continuous cycling, we strongly endorse the use of lamotrigine or lithium augmentation, if these agents are not already part of the therapeutic regimen.

4. MOOD STABILIZERS IN THE TREATMENT OF BIPOLAR DEPRESSION

Lithium, carbamazepine, and valproate all demonstrate some efficacy in the acute treatment of bipolar depression, but this effect is less well documented and apparently less impressive than their efficacy in rapid-onset mania.

However, long-term prophylaxis against depression with each of these agents may be closer to that of their ability to prevent manic relapses.

4.1. Lithium

A substantial number of studies in the literature—including the off-on-off studies of Goodwin, Bunney, and associates and other groups, as well as a num-

ber of placebo-controlled, parallel-group studies—suggests that lithium has both acute (immediate) and prophylactic antidepressant efficacy in its own right; however, the antidepressant effects of lithium remain controversial. The weight of evidence suggests that lithium is more effective in patients with bipolar vs unipolar depression *(39)*.

In seven controlled studies, lithium was judged effective as short-term therapy for bipolar depression in 79% of 164 patients *(39)*. Additionally, lithium was equal in efficacy to a TCA in four of five studies, but had a slower onset of action— approx 3 to 4 weeks before the first changes in the depressive syndrome were seen *(39)*.

Lithium has been widely used for prophylaxis of recurrent unipolar illness in Europe; in patients with BD, it appears to prevent recurrence of depressive as well as manic episodes *(40,41)*. In 10 controlled studies, lithium was reported effective for the prophylaxis of depression and mania in 63% of 739 patients *(39)*. Newer studies show that prophylaxis against depression was better in patients with BD II than BD I *(42)*. Lithium has been associated with an eight-fold lower rate of hospitalization and a seven-fold lower suicide rate *(43–45)*. Lithium may even be linked with a low suicide rate when it is poorly effective for mood *(35)*. Unfortunately, long-term studies indicate a good outcome in less than 40% of patients on lithium *(46)*. Additionally, in newer studies, lithium has demonstrated better prophylaxis against mania or hypomania than against depression; furthermore, its efficacy in patients with rapid cycling was only about 30% *(47,48)*.

Less controversially, lithium can augment the antidepressant effects of almost any unimodal antidepressant used to treat unipolar depression *(39,49)*. Improvements rates of 50 to 65% are typically reported when lithium is used as an adjunct to an antidepressant, randomized, parallel placebo groups, with showing lesser degrees of antidepressant efficacy.

Unfortunately, few studies have specifically examined lithium augmentation of antidepressant response in patients with BD. Traditionally, lithium is already in the regimen; therefore, the antidepressant is added to lithium rather than the reverse, as in patients with unipolar depression.

Clinical predictors of lower rates of response to lithium during short-term therapy and pharmacoprophylaxis of BD in general (if not in depression per se) include presentations with dysphoric mania; rapid cycling; comorbid anxiety disorder; comorbid substance abuse and personality disorder; negative family history of unipolar or bipolar illness in first degree relatives; continuous cycling patterns; more episodes prior to instituting lithium prophylaxis; and the pattern of depression (D)-mania (M) and then a well interval (I) (the D–M–I pattern), rather than the converse pattern of M–D–I.

In the German collaborative studies of Greil and associates, lithium worked best in patients with classical BD I presentations without psychotic elements and without substance abuse comorbidity *(50)*. In contrast, carbamazepine appeared more effective in patients with BD II disorder, schizoaffective illness, and comorbid substance abuse. It is important to note that these are only relative correlates of responsivity; with many exceptions, certainly lithium may be efficacious in particular patients, despite negative predictors (and vice versa).

4.2. Carbamazepine

The acute effects of carbamazepine as an acute treatment for bipolar depression have been less well studied than for menia. Its overall efficacy in patients with depression was 44% of 108 patients in six controlled studies *(39,51)*. Its acute antidepressant response appears to take several times longer than its antimanic effects *(52)*. In 14 controlled studies, the efficacy of carbamzepine for the prophylaxis of depression and mania was reported to be 63% of 191 patients *(39,51)* and its efficacy in rapid cycling was approx 50% better than for lithium (30%) *(47)*. Two long-term studies found carbamazepine equal to lithium *(53,54)*, but lithium has been found more effective in patients with "classic" BD *(50)*.

In a series using an off–on–off design, 17 of 54 patients with refractory affective disorders had at least a moderate response to the drug.

Those with more severe cases of depression and increased acuity were among those who responded best. The possibility of a placebo response was mitigated by the observation that a second course of carbamazepine therapy in a subgroup of 10 initially responsive patients, after depression returned while they were not taking an acute drug, resulted in a antidepressant response similar to that seen during the first course of carbamazepine therapy. Thus, in at least a subgroup of initially responsive patients, the efficacy of carbamazepine as an acute treatment for bipolar depression was unequivocally confirmed. Furthermore, their response during the second carbamazepine exposure indicates that their initial response to carbamazepine was not a placebo response.

A key clinical issue has been determining which patients will respond to carbamazepine vs other mood stabilizers. Despite its structural similarity to TCAs, carbamazepine exerts numerous opposing biochemical effects. For example, unlike most traditional antidepressants—which reduce the number of β-adrenergic receptors in the frontal cortex—long-term carbamazepine therapy increases the number of receptors. Instead of upregulating glucocortoid receptors and decreasing cortisol secretion, like many antidepressants, long-term carbamazepine administration increases cortisol, as indicated by an increased rate of secretion of free cortisol in 24-h urine samples in patients and normal volunteers. Based on these and other mechanistic differences between carbamazepine and traditional antidepressant modalities, the carbamazepine-responsive subgroup may be

neurochemically different from patients who respond to more traditional antidepressant modalities.

Consistent with this suggestion, Ketter and associates found that carbamazepine exerted antidepressant effects in a subgroup of patients who demonstrated atypical patterns of frontal lobe and paralimbic hypermetabolism on a PET scan, rather than the more classic pattern of frontal hypometabolism associated with the depressive syndrome. The degree of hypermetabolism in the left insular cortex was correlated with the degree of response to carbamazepine; the opposite relationship was observed for nimodipine. For this dihydropyridine L-type calcium blocker with some antidepressant efficacy, the degree of left insular hypometabolism was associated with the degree of response. In general, relative hypometabolism at baseline appears to be a marker of response to a variety of other antidepressant modalities, including lamotrigine, while baseline limbic hyperactivity appears to be correlated with a positive response to repeated low-frequency transcranial magnetic stimulation (rTMS) in patients with sleep deprivation.

Several studies have suggested that carbamazepine is effective in individuals with alcohol withdrawal syndromes, both in preclinical laboratory studies and in clinical populations. Carbamazepine is used for this indication in a number of Scandinavian countries, and improvement in alcohol-related dysphoria has been observed during short-term maintenance therapy. Several studies suggest that carbamazepine is effective in patients with depression who have a history of alcoholism (in contrast, this appears to be a relative correlate of lithium nonresponse).

In a German collaborative study, Greil and colleagues *(50)* assessed differential correlates of prophylactic response to carbamazepine vs lithium in a randomized study discussed earlier. They found that lithium was more effective in patients with classical BD I who did not have mood-incongruent delusions or any comorbidities. In contrast, carbamazepine showed a tendency to be more effective than lithium in patients with Bipolar II and Bipolar NOS presentations, recurrent mood incongruent delusions, and comorbid substance abuse. Patients with schizoaffective depressive presentations appeared to be particularly responsive to carbamazepine in long-term prophylaxis.

4.3. Valproate (VPA, Divalproex Sodium, or Depakote™)

Valproate is approved by the FDA for the treatment of acute-onset mania. Several studies suggest that valproate has antidepressant properties, although more systematic studies remain to be performed and the potential clinical and biological predictors of response examined. Earlier reviews of its overall efficacy in patients with depression revealed a 32 % response rate in 170 patients in seven uncontrolled studies *(39,51)*, including an 8-wk open study in which a 66% response rate was determined in 33 patients with unipolar depression *(55)*. In a recent 12-wk open

trial, Ketter and colleagues found valproate to be highly effective as monotherapy for patients with BD II *(56)*. In 11 earlier uncontrolled studies ($N = 496$), the overall efficacy of valproate for prophylaxis of depression and mania was 64 % *(51)*. The efficacy of valproate and lithium in rapid cyclers is approximately the same *(47)*.

Less data are available from controlled studies of the efficacy of valproate in patients with depression. In a recent double-blind, randomized, placebo-controlled study, Sachs and colleagues found that valproate was not significantly superior to placebo on most measures, although on weeks 3, 4, and 6, this difference was significant *(58)*. In a recent double-blind study of long-term (1 yr) prophylaxis, valproate demonstrated a superior ability to prevent depressive episodes than lithium or placebo, but failed on the primary measure of efficacy of "time remaining in the study without a manic episode" *(57)*. Surprisingly, the efficacy of lithium was actually inferior to that of placebo on one measure: "time to intervene for depression." Given the low rate of efficacy of lithium compared with placebo in preventing both manic and depressive relapses in this study, however, these findings remain controversial.

In open trials of adjunctive therapy and monotherapy studies in patients with rapid cycling BD, a distinctly different picture emerged, one that is more consistent with conventional wisdom about the psychotrophic profile for valproate *(59–61)*. In a study of more than 100 treatment-resistant patients with rapid-cycling BD, Calabrese and colleagues found excellent efficacy for valproate in patients experiencing a manic and mixed state, but substantially worse efficacy during the depressive phase of the illness. Covariables of valproate efficacy in that study included a patient history of a stable (nonaccelerating) course of illness, less severe mania, lack of psychosis or personality disorder, and less severe depression; additionally, the more severe the mania over the course of illness, the better the antidepressant outcome.

In a series of patients studied at the NIMH, we have observed differential responsivity among the anticonvulsants, with some patients responding well to carbamazepine and not valproate or phenytoin, and other patients revealing the opposite pattern by failing to respond to carbamazepine (even with adjunctive lithium) and showing a complete response to valproate. Thus, response to the anticonvulsant therapy in bipolar illness cannot be considered a class effect, which makes it increasingly important to identify potential clinical and biological predictors of such differential responsivity.

4.4. Lamotrigine

Unlike the three most widely used mood stabilizers—lithium, carbamazepine, and valproate, which all appear to show a better antimanic than antidepressant efficacy—lamotrigine is effective short-term as antidepressant monotherapy in patients with BD depression. A randomized, double-blind, placebo-controlled

trial in patients with BD I depression, by Calabrese and associates *(15)* found that the efficacy of both lamotrigine 50 mg/d and 200 mg/d dosages to be significantly superior to that of placebo ($p < 0.05$), based on Montgomery–Asberg Depression Rating Scale MADRS score while 50 mg/d had a trend for superior efficacy vs placebo ($p = 0.058$).

Interestingly, such a statistical difference was not seen using the Hamilton Depression rating scale (HAM-D), which many investigators have found less sensitive to antidepressant effects in bipolar illness. Lamotrigine has not been found to be efficacious in the treatment of patients with acute-onset mania, but the need for slow dose titration rate may compromise the ability to see such an effect.

In a 6-wk, placebo-controlled study of lamotrigine vs gabapentin (which was followed by two 6-wk crossover studies designed to expose each patient to all three treatment arms) in 31 highly treatment-refractory patients, most of whom had BD *(62)*, Frye and associates found superior overall and antidepressant efficacy for lamotrigine compared with both placebo and gabapentin. In both the Calabrese et al. *(63)* and Frye et al. *(62)* studies studies, the switch rate to mania observed with lamotrigine did not exceed that of placebo (*see also* ref. *15*).

The prophylactic antidepressant effects for lamotrigine were also seen in two recent 76-wk, double-blind, randomized, placebo-controlled studies of lamotrigine vs lithium. Interestingly, lithium had a superior prophylactic effect in patients with mania in this study compared with lamotrigine and placebo. In contrast, lamotrigine was more effective than lithium or placebo on the primary outcome measure of "time-to-intervention for a depressive episode." Taken together with the findings of a substantial number of open trials *(64,31,65)* and recent randomized, placebo-controlled studies, evidence is clearly mounting in support of lamotrigine for prophylaxis and short-term therapy in patients with BD depression. Such a view is mirrored by the revised American Psychiatric Association (APA) guidelines for the treatment of bipolar depression, which place lamotrigine in a first- or second-line position among treatment approaches to bipolar depression. Lamotrigine also appears to benefit affective lability, demonstrating good responses in patients with rapid-cycling BD *(66–68)* and showing benefits for patients with borderline personality disorder *(69)*.

Lamotrigine carries the risk for inducing rash and severe and potentially life-threatening dermatologic reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). When lamotrigine was titrated rapidly in early studies in seizure patients, the incidence of SJS/TEN was approx 1 in 1000 *(70)*. With more conservative dosing strategies and a much slower dose escalation *(71)*, the incidence is now reported to be 2 in 10,000 patients in adults and 4 per 10,000 children.

Calabrese and colleagues recently reported the findings of a retrospective analysis of lamotrigine rash in 12 multicenter mood disorder studies *(72)*. In the

1198 patients who received lamotrigine and the 1056 patients who received placebo, the rash rates were 8.3% and 6.4%, respectively; no cases of SJS was observed with lamotrigine. In open-label settings, 1955 patients taking lamotrigine exhibited a rash rate of 13.1%, including two cases of serious rash and one (mild) case of SJS apparently not requiring hospitalization. TEN was not observed in any of these settings.

Other risk factors for rash, SJS, and TEN include a history of drug allergy (which increases the risk for rash two- to threefold); a history of allergy to an anticonvulsant specifically increases the risk for rash three- to fourfold *(73)*. The risk for rash increases threefold in children *(74)*. For 57 cases of SJS ($N = 43$) and toxic epidermal necrolysis ($N = 14$), the median time to onset was 17 d and the median dosages were 50 and 87.5 mg/d, respectively. In 74% of SJS cases and 64% of TEN cases, valproate had been used concomitantly. The SJS group was younger than the TEN group (21 vs 31 yr), and the risk for SJS/TEN in children was fivefold higher than in adults *(74)*. Cyclosporin, immunoglobulin G, and plasmaphoresis have been used to treat SJS/TEN associated with lamotrigine therapy.

Valproate essentially doubles the blood level of lamotrigine, resulting in the need to reduce the lamotrigine dose by half and titrate at a slower rate when using valproate/lamotrigine combination therapy compared with that used in patients treated with lamotrigine alone.

The conventional rate of upward titration is 25 mg/d during the first 2 wk and 50 mg/during the next 2 wk, with subsequent increases not exceeding 25 mg/wk. When the patient is taking valproate, the lamotrigine dose should be reduce by half. By contrast, carbamazepine induces the metabolism of lamotrigine and reduces lamotrigine levels approximately by half; this results in the need for a more rapid rate of titration to achieve the same blood level of lamotrigine as is seen in monotherapy.

In contrast to several other anticonvulsants, such as carbamazepine and valproate, lamotrigine has the advantage of not having a sedative effect. Some patients find it slightly excitatory or even capable of inducing some degree of insomnia. The latter effect may be helpful for some patients with BD who are experiencing reverse vegetative symptoms, including hypersomnia, rather than the more classic symptom of insomnia which often accompanies unipolar depression. Lamotrigine also is weight neutral and does not appear to cause sexual dysfunction, an effect that is often associated with 5-HT selective antidepressants.

Recent reports have suggested differential predictors of a positive response to lamotrigine vs gabapentin *(75)* or lithium *(76)*. A response to lamotrigine has been associated with male gender, fewer hospitalizations, and fewer medication trials, while a response to gabapentin has been associated with younger age and lower baseline body weight *(75)*. Lamotrigine appeared more effective in patients

with a personal and family history of anxiety and substance abuse disorders; lithium appeared more effective in patients with a family history of affective illness, including unipolar depression in a first-degree relative *(76)*.

4.5. Gabapentin

The picture that is evolving for the role of gabapentin in the treatment of patients with bipolar depression is much less clear than it is for lamotrigine. In a placebo-controlled short-term trial of gabapentin to augment neuroleptic therapy in patients with mania, Pande and associates found a lack of efficacy for gabapentin compared with placebo *(77)*. Similarly, in the study by Frye and colleagues *(62)*, lamotrigine demonstrated superior efficacy for depression and overall illness in highly treatment-refractory patients compared with gabapentin and placebo, which had approximately the same effect.

These controlled data stand in sharp contrast to those produced by large open trials and case-series literature, which indicated the usefulness of gabapentin as augmentation therapy in patients with an inadequate responsive to a range of current pharmacotherapies *(78–81)*. One possible interpretation of this discordance is that gabapentin may have a number of therapeutic properties that are of particular use in patients with bipolar illness that are not primarily antimanic or mood stabilizing. Considerable evidence from controlled studies indicates that gabapentin is effective in patients with anxiety disorders, including social phobia, as well as in patients with somatic complaints (which are a common in patients with BD) or headache or a variety of other pain syndromes. Gabapentin has also been reported helpful as adjunctive therapy in patients with obsessive-compulsive disorder, restless leg syndrome, insomnia, and alcohol withdrawal—all of which are often comorbid with bipolar illness.

Thus, more definitive evidence is required before it can be determined whether gabapentin has primary antidepressant effects in patients with BD depression or is merely a useful adjunct that targets a variety of comorbidities of BD depression. In the studies of Frye and Obrocea *(81a)*, patients who had the best responses to gabapentin were relatively younger and had a relatively shorter duration of illness and relatively lower weight at baseline. Since the role of GABA in the central nervous system changes from excitatory early in development to inhibitory, perhaps an examination of its potential efficacy in younger individuals is indicated.

4.6. Topiramate

Topiramate studies have had discrepant results in the clinical literature on BD . A large series of open trials suggested that topiramate may be useful as an adjunct in the treatment of mania and cycling *(82,83)*. However, the findings of a recent series of three randomized, double-blind, placebo-controlled studies suggest that topiramate is not effective as an acute treatment for mania when

administered as monotherapy. In contrast, lithium—the comparator drug in these studies—did show the expected positive efficacy profile compared with placebo.

The role topiramate in bipolar depression is even less clear. During an open-label study in 56 bipolar outpatients, McElroy and associates *(82)* found that the response to adjunctive topiramate was much lower in patients with acute-onset depression (27%) than in those with mania and cycling (i.e., 50–60%). However, in a single-blind, randomized study of topiramate compared with bupropion as add-on therapy for breakthough bipolar depression, a response rate of approx 60% was seen for both drugs *(84)*, suggesting the need to further explore the potential antidepressant effects of topiramate. A role for adjunctive topiramate therapy for prophylaxis in patients with depression and mania is suggested by a 6-mo study in 34 bipolar patients, in which investigators found that 55% of depressed patients and 59% of manic patients were considered responders *(85)*.

Several open trials have produced results suggesting that topiramate may play a role in PTSD. Its efficacy may be a result of the unique mechanism of action for topiramate that involves blocking AMPA-kainate glutamate receptors, which are involved in the maintenance of long-term memory (as determined by studies in the hippocampal slice model of long-term potentiation).

The findings of a placebo-controlled study have also suggested utility for topiramate in alcohol abuse.

PTSD and alcohol abuse are not uncommon in patients with bipolar illness; thus, topiramate could play a therapeutic role independent of its intrinsic antimanic and antidepressant effects. Topiramate can also inhibit carbonic anhydrase; in an open trial of carbonic anhydrase inhibitor acetazolamide, investigators found improvement in 7 of 16 treatment-refractory patients with BD, with all responders having depressed or rapid cycling *(86)*.

4.7. Other Anticonvulsants

Oxcarbazepine is the keto-congener of carbamazepine. In controlled studies of oxcarbazepine in patients with mania and epilepsy, it demonstrated clinical effectiveness similar to that of carbamazepine (*see* ref. *51*). The findings of two recent small studies—a prospective study in patients with mania *(87)* and a retrospective study in treatment-refractory patients, most of whom had BD depression*(88)*, suggested mild to moderate mood-stabilizing benefits with oxcarbazepine. The literature on epilepsy indicates that oxcarbazepine, as compared with carbamazepine, had fewer adverse effects *(89,90)*, with the exception of more frequent hyponatremia induction *(91,92)*. Oxcarbazepine is probably less capable of inducing auto- and heteroinduction of the cytochrome P450 enzyme system *(89,93)*; this can result in large increases in neuroleptic plasma levels and extrapyramidal symptoms when patients are switched from carbamazepine to oxcarbazepine *(94)*.

The potential antidepressant effects of levetiracetam and zonisamide have not yet been adequately delineated. Levetiracetam is noteworthy for its unique profile of action, given that it is not effective on patients with maximum electroconvulsive seizures (MES) or pentylenetetrazole (PTZ) therapy, but is effective in both the development and completion of amygdala kindling. It appears to act, in part, by blocking inhibitory modulators (i.e., zinc and β-carboline) of the γ-amino butyric acid (GABA) A-benzodiazepine-chloride-ionophore, thus enhancing the efficacy of GABA indirectly. It also has a stereospecific binding site in the brain. Interestingly, levetiracetam had recently been reported to have additive or potentiating effects in an animal model of mania when used in combination with valproate.

Zonisamide is not only a sodium-channel blocker, but also has complex effects on the metabolism of DA and 5-HT, raising the question that these actions may contribute to its efficacy in affective disorders, although this remains to be demonstrated. The results of one small open trial demonsrated the antimanic effects of zonisamide *(95)*.

The efficacy of the GABAergic agents valproate and gabapentin (both agents also block sodium channels) in patients with BDs apparently does not extend to the GABAergic agents tiagabine and vigabatrin, which appear to be poor choices for mood disorders. The results of open trials have not indicated efficacy for tiagabine in patients with mania or depression. Grunze and coworkers found that tiagabine was not an effective antimanic agent, as none of their first eight patients showed good response *(96)*. Similarly, Suppes and coworkers *(97)* reported clinically relevant effects in only 3 of 17 treatment-refractory patients with BD who had been exposed to adjunctive tiagabine. In a study conducted by Schaffer and colleagues *(98)*, 8 of 22 bipolar outpatients benefited from adjunctive tiagabine therapy, but 14 patients could not tolerate it. At least one patient in each of the above studies had a seizure during while taking tiagabine; none of these individuals had a history of seizure disorders. Vigabatrin also is not promising, possibly owing to its reported ability to induce depression and affective psychosis *(99–101)*.

5. ATYPICAL ANTIPSYCHOTIC AGENTS

All of the conventional antipsychotic agents (older term: neuroleptics) have antimanic and antipsychotic properties. This principal now seems to extend to the atypical antipsychotic agents, as well. However, the lack of adequate acute antidepressant properties in conventional antipsychotic agents is problematic. It remain to be determined whether the antidepressant therapeutic spectrum will be better achieved with the atypicals; however, the initial data are supportive of this possibility *(110,112,114)*.

From a mechanistic perspective, considerable theoretical reasons exist for assuming that the atypicals will have a better antidepressant profile. As a group,

the atypicals affect a relatively wide range of receptors that are thought to be involved in antidepressant mechanisms, e.g., the 5-HT_2 receptors and DA receptor subtypes, on which atypical agents may have more selective effects.

Clozapine is paradigmatic of this shift. Studies of *c-fos* induction indicate that clozapine is much more active in the mesolimbic and mesocortical regions of the brain compared with the more exclusively striatal mechanisms of the typical antipsychotic agents, such as haloperidol. Additionally, the atypicals are less likely to have extrapyramidal adverse effects and long-term risk for tardive dyskinesia; this redistribution of activity may be relevant to antidepressant properties, as well. Whether this is a true difference or just related to the absence of unpleasant adverse effects—such as asthenia and akathisia, which plagued the typicals—remains to be determined.

5.1. Efficacy and Tolerability of Atypical Antipsychotic Agents in Bipolar Depression

As noted in the introduction, recent data indicate that the clinical response to conventional and novel mood stabilizers and adjunctive therapy is not as consistent or robust as had been expected. For example, in the prospective follow-up study in the Stanley Foundation Bipolar Network (SFBN), which was discussed earlier, approximately two-thirds of the patients remained substantially affected by their illness, with one-quarter remaining symptomatic most of the year (Post et al., in press). This occurred despite being treated with an average of 4.1 medications during the year and considerable use of conventional and atypical antipsychotic and anticonvulsant agents.

Earlier epidemiological studies indicated a high incidence of conventional antipsychotic agent use in patients with BD, with an associated 20 to 40% risk of tardive dyskinesia. With the availability of six atypical antipsychotic agents—beginning with clozapine in 1990, risperidone in 1994, olanzapine in 1996, quetiapine in 1997, ziprasidone in 2001, and aripiprazole in 2002—the crucial question has switched from that concerning their antimanic activity to their antidepressive efficacy and tolerability.

5.2. Clozapine, Risperidone, Olanzapine, Quetiapine, Ziprasidone, and Aripiprazole

The findings from a series of open trials have suggested that clozapine is more effective in bipolar vs schizoaffective/schizophrenic illness *(102,103)*, and that it is particularly effective in treatment-refractory individuals experiencing rapid cycling and patients with dysphoric components of mania. Its antidepressant efficacy is less well delineated. Its usefulness as short-term therapy and prophylaxis in patients with depression has been suggested by the results of several open

trials *(104,105)*. However, Barbini and associates *(106)* found that although 19 bipolar and schizoaffective patients receiving add-on clozapine had less mania and psychosis after 12 mo of treatment, no difference in depression was identified for these patients vs 19 other bipolar and schizoaffective patients who did not receive add-on clozapine therapy.

Vieta and associates *(107)* studied 299 patients with BD I and 183 with bipolar-type schizoaffective disorder treated with risperidone (mean dose: 4.0mg/d) for 6 mo. While the minority of patients presented with psychotic depressive episodes, the mean HAM-D score declined significantly ($p < 0.0001$) from 12.8 ± 7.9 at baseline to 4.1 ± 4.8 at 6 mo, suggesting antidepressant effects in this study. In a controlled study of 62 schizoaffective patients (33 with a bipolar subtype and 29 with a depression subtype), Janicak and coworkers *(108)* found that risperidone decreased HAM-D scores more than haloperidol. Additional suggestions of risperidone utility in depression comes from its efficacy as an adjunct to prophylaxis of depression and mania *(109)*, and from risperidone augmentation of SSRIs *(110)*.

Similarly, the antidepressant effects of olanzapine are suggested by the results of a chart review in which researchers observed improvement with olanzapine in 67% of 15 patients with psychotic depression *(111)*, and in a chart review by Ghaemi and colleagues *(112)*, who observed a 60% improvement rate in patients with depressive symptoms and improvement vs haloperidol in patients with schizoaffective BD *(113)*. A recent double-blind study of olanzapine observed some efficacy for olanzapine in bipolar depression compared with placebo, with much more dramatic antidepressant effects when administered in combination with the SSRI fluoxetine *(114)*; similar results were observed in patients with unipolar depression *(115)*. A randomized, 1-yr study showed that olanzapine has superior prophylactic antimanic effects to lithium and equal antidepressant effects *(116)*.

Mullen and associates *(117)* compared quetiapine vs risperidone in an open randomized study in patients with diverse psychotic disorders. They found equivalent efficacy on PANSS scores, but quetiapine showed a greater reduction in the HAM-D score (5.4 ± 0.38, $N = 491$) than risperidone (–4.0–0.59, $N = 150$, $p < 0.028$). Tolerability was equivalent based on dropout rates, whereas quetiapine resulted in greater incidence of somnolence, dry mouth, and dizziness than risperidone, and risperidone resulted in a greater incidence of extrapyramidal adverse effects (mean dose: 3.17 mg for quetiapine; 4.7 mg for risperidone). In a nonrandomized, open trial of adjunctive quetiapine, risperidone, and clozapine therapy in patients at the SFBN, presented by Keck and associates at the APA in 2001 *(117a)*, preliminary analysis revealed improved depression ratings on the Inventory of Depressive Symptoms (IDS) for quetiapine *(117a)*.

Improvement with quetiapine therapy was detectable within the first mo of treatment and maintained through the second to fourth month. In contrast, no

significant decrements in IDS ratings were observed with adjunctive risperidone or clozapine therapy when assessed in the same fashion.

The potential antidepressant effects of the two latest atypicals, ziprasidone and aripiprazole, remain to be assessed systematically, but have the advantage of being weight neutral.

Ziprasidone blocks 5-HT_2 and D2 receptors like other atypical antipsychotic agents, and also demonstrates some 5-HT and NE reuptake inhibition and 5-HT_1 receptor agonist activity. Its pharmacological profile suggests that it may also have some antidepressant activity. Aripiprazole is a partial dopaminergic agonist with intermediate intrinsic activity at the D1, D2, D3 receptors; it is also a partial agonist at the 5-HT_{1A} receptor and blocks 5-HT_2 receptors. It is a mechanistically promising agent—perhaps Carlsson's "dopamine buffer." In a large controlled study in patients with schizophrenia and schizoaffective disorder, investigators found aripiprazole to be equal to haloperidol based on Positive and Negative Syndrome Scale(PANSS) and the Clinical Global Impression scale scores, but better tolerated *(118)*.

Thus, in contrast to the typical antipsychotics—which, according to the findings of several studies, may result in an increase in depression severity and the number of depressive episodes during long-term maintenance therapy—observations during therapy using atypical agents indicate that they are more promising in the treatment of bipolar depressive phases of the illness; this is in accord with their different mechanisms of action and generally better tolerated side-effects profiles. Given the incidence of extrapyramidal side effects with conventional antipsychotic agents and the associated risk of tardive dyskinesia, the atypicals appear to be indicated for bipolar illness in general and BD depression in particular in preference to the first-generation antipsychotic agents. Although the potential mood-stabilizing properties of several atypicals appear highly promising, controlled trials of short-term efficacy and the ability to prevent depressive recurrences in long-term prophylaxis remain to be demonstrated.

6. SEQUENTIAL TREATMENT APPROACHES

6.1. Acute Treatment of Depressive Episodes

Given the very substantial residual depressive morbidity following intensive treatment for BD, how should this problem be addressed, given the wide range of treatment options available? Again, we begin this section with the caveat that most of the following recommendations are not based on a database obtained through systematic, controlled, clinical trials. As such, they should be considered highly provisional and readily changed as warranted by new data. We focused mainly on the issue of breakthrough depression occurring during ongoing treatment with one or more mood stabilizers used during the initial episode of BD

depression; this breakthrough is generally more straightforward, typically involving the concurrent administration of an antidepressant and mood stabilizer.

As noted previously, in the face of an isolated incidence of breakthrough BD depressive episodes during mood-stabilizer therapy, the addition of unimodal antidepressant to the mood stabilizer regimen would seem to be indicated. If a patient has a history of manic and depressive recurrences, particularly if they have rapid or fast cycling, lamotrigine or an alternate mood stabilizer might be considered for adjunctive therapy instead of an antidepressant. This approach seems to limit the risk for switching that accompanies unimodal antidepressant therapy and to target primarily episode recurrence rather than the current acute-onset depression.

If depression persisted or recurred in spite of the use of two mood stabilizers, the addition of a unimodal antidepressant might be considered. If this antidepressant is not effective in relieving chronic depression, another antidepressant—one with an alternative mechanism of action—may be indicated. If an SSRI was used, the clinician might consider bupropion or venlafaxine.

If the depression persists, a variety of augmentation strategies could be considered, including folate (1 mg/d for women; 2 mg/d for men), ascorbate (3000 mg/d), and T_3 (25.0 to 37.5μg/d). Each of these approaches appears to be a low-risk option, with each agent having a modicum of data to support its potential in unipolar disease, if not bipolar illness. If lamotrigine were not already in the therapeutic regimen, it would be useful to consider it as an option for adjunctive therapy.

Similarly, revisions of the basic mood-stabilizer regimen and the antidepressant regimen may be in order as well. Substantial evidence indicates that individual patients may respond to lithium, valproate or carbamazepine, even if they have failed to respond to the other two agents. Denicoff and coworkers found a much better response rate for the combination of lithium and carbamazepine in patients with rapid cycling compared with a year of either as monotherapy (adjunctive antidepressants and antipsychotic agents were allowed as needed) *(53)*.

Obviously, if the depression included psychotic symptoms, earlier use of atypical antipsychotic agents would be indicated. Use of atypicals after one or more revisions of mood-stabilizer and antidepressant modalities would also appear particularly worthwhile, given the new preliminary evidence of their antidepressant effects, especially when used in combination with antidepressant modalities. Insomnic vs hypersomnic depressive presentations would differentially suggest the initial use of sedating vs activating atypicals, respectively, whose side-effect profiles are most in accord with these differences.

As one gets into complex combination therapy by necessity (by virtue of the fact that the patient has not responded adequately to simpler regimens), it becomes increasingly important to titrate each additional agent against the side effects incurred, because a primary concern is the tolerability of the entire drug regimen.

6.2. Focus on Long-Term Prevention

If an effective antidepressive response from short-term therapy is achieved without adverse effects, the same regimen should be continued long term for prophylaxis. This recommendation is based on the observation of a moderate relapse rate, even when patients who responded to short-term antidepressant therapy continue their regimen; an even higher rate of relapse into depression has been observed when patients who were maintained well for 2 mo discontinue their antidepressant drugs. Evidence is weaker for the need to continue other adjunctive elements long term; in light of the generally high relapse rates into depression, however, it is suggested that full doses be maintained. One caveat would be that in the face of at least a moderate increase in the incidence of adverse effects, clinicians should attempt to reduce the dose of agent most likely to be responsible for those effects to achieve better tolerability and avoid jeopardizing a sustained antidepressant response.

Another reason for continuing short-term therapy as long-term prophylaxis is that when a good response is achieved during the first year or two of therapy, there is still a moderate risk for an eventual loss of efficacy by means of a phenomenon resembling tolerance. Development tolerance that results in treatment resistance has been observed to some extent with essentially all of the mood stabilizers. One of the factors thought to be relevant to the development of tolerance is the use of minimally effective doses, so at dose reduction or drug-regimen simplification (in the absence of the need to do this to prevent adverse effects) may put the patient at increased risk for breakthrough episodes.

6.3. Supraphysiologic Thyroid Hormone Augmentation

The use of supraphysiologic or hypermetabolic doses of levothyroxine (T_4) is another augmentation strategy for bipolar illness *(119,120)*. Following slow increases in the dose of T_4 into the range of 300 to 500 μg/d (which usually produces a free thyroxine index 150% of normal), a substantial response rate (≥50%) has been observed, with relatively good tolerability. The most frequent adverse effects indicate a mild hyperthyroidism, e.g., tachycardia, sweating at night, and increased tremulousness. Interestingly, a lower serum free T_4 level, even in the normal range, has been associated with greater mood instability in patients with BD being maintained with lithium *(121)*.

Bauer and colleagues have found that this approach is not only helpful in patients with treatment-refractory rapid cycling, but also in those with persistent treatment-refractory depression. It would appear useful to attempt this approach (in the absence of medical contraindications) prior to considering even more aggressive and invasive approaches, such as maintenance electroconvulsive therapy (ECT) or a vagal nerve stimulator (VNS) implant.

6.4. Omega-3 Fatty Acids (OFAs)

The status of augmentation therapy using OFAs is somewhat ambiguous, based on the results of three positive small trials. They failed to show efficacy over placebo in the largest trial, recently completed by Keck and colleagues. Stoll and associates *(122)* originally reported success in bipolar depression with 9.6 g/d of a preparation containing the mixture of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Peet and Horrobin recently reported antidepressant effects for 2 g/d of EPA in patients with unipolar depression, as did Nemits and associates *(123)*. In the negative trial, Keck and colleagues used 6 g of EPA vs placebo in a 4-mo, randomized, double-blind, controlled trial in patients experiencing a refractory depressive episode or cycling. Failure to see superior effects vs placebo may be associated with a variety of factors, one of which is based on the findings by Horrobin and colleagues *(124)* of an inverted U-shaped dose–response curve for EPA on arachidonic acid levels in schizophrenia (arachidonic acid is thought to be important for its antidepressant and mood-stabilizing effects). They observed that lower doses of EPA increased arachidonic acid levels as expected, but the highest dose actually caused arachidonic acid levels to decrease compared to baseline. These changes corresponded with better antipsychotic effects at 2 g than at the higher doses of EPA.

Another alternative explanation was offered by Hibbeln and associates, also from their experience with EPA in the treatment of schizophrenia. In their study, they found no overall positive effect of EPA compared with placebo. However, for those patients who received low doses of EPA and demonstrated the expected increase in cell membrane DHA levels, a significant improvement in schizophrenia was seen. However, in patients in whom a decrease in membrane DHA levels was seen, symptoms worsened compared with placebo. Thus, other doses and preparations of this drug in specific patients subgroups must be studied before the negative findings from the 6 g of EPA study can be generalized to the OFA augmentation strategy in all patients with treatment-refractory depression.

6.5. Inositol

An interesting pilot study suggested that inositol is a useful adjunctive treatment for BD depression *(125)*. In a randomized, placebo-controlled trial of inositol 12 g/d or D-glucose added to stable mood-stabilizer regimens ($N = 24$), 67% of inositol-treated patients improved vs 33% of placebo patients, based on MADRS scores; no difference in GCI scores were detected.

6.6. Other Therapies: ECT, rTMS, VNS, and Total Sleep Deprivation (TSD)

ECT has been used effectively in patients with BD depression *(126)*. There is some evidence that patients with BD respond more rapidly than patients with uni-

polar depression *(126)*. A number of investigative groups have noted some success with prophylactic ECT, which has shown generally good tolerability in patients with treatment-refractory unipolar or bipolar depression, although large case series have not yet been reported to our knowledge. One group suggested using prophylactic ECT with the atypical antipsychotic clozapine, because this agent lowers the seizure threshold and does not interfere with the induction or duration of the ECT seizures, as is feared with some mood-stabilizing anticonvulsants. Moreover, there is the theoretical possibility that prophylactic ECT would exert protective anticonvulsant effects against the risk for clozapine-induced seizures; thus, patients for whom high-dose clozapine therapy was prescribed would not also need an anticonvulsant. This possibility is based on the original observations that ECT was an effective anticonvulsant modality in patients with epilepsy prior to the advent of more widespread use of pharmacological anticonvulsant compounds.

Meta-analyses have suggested a significant effect of moderate- to high-frequency (5–20 Hz) repeated transcranial magnetic stimulation (rTMS) over stimulation of the left prefrontal cortex in the treatment of unipolar or bipolar depression compared with sham stimulation. The overall effect sizes are moderate; however, a number of studies have not shown positive results, and the field has not yet agreed on optimal treatment parameters. Although rTMS is available as a potential treatment option in some countries, it is not currently available outside of highly specific treatment protocols in the United States.

Vagal nerve stimulation (VNS) is available in many European countries and Canada, but not in the United States. Initial open trials suggested that approx 50% of patients with highly treatment-refractory depression respond to this unique type of augmentation treatment, which has gained FDA approval in the United States for refractory epileptic seizures. The procedure used in patients with either an affective illness or epilepsy appears to be well tolerated, and apparently triggers a quick response in affectively ill patients. Although most treatments show some loss of efficacy over time, the effects of the VNS appear to increase in magnitude and in number of responders over the initial months of treatment. This suggests that a placebo effect is unlikely.

However, a recent comparison had equivocal results for active VNS vs sham stimulation.

Furthermore, the ultimate availability of VNS for patients with treatment-refractory unipolar and bipolar depression in the United States is currently uncertain. Several groups have begun to explore the use of VNS in bipolar patients with more cyclic presentations; assessment of this modality for this subgroup of patients is eagerly awaited.

The majority of patients apparently would choose a course of rTMS or even VNS implantation (if VNS implants were available) over the option of prophylactic ECT for a variety of reasons, including expense, inconvenience, inad-

equate documentation of long-term efficacy in controlled trials, requirement for anesthesia, the need to induce a seizure, and, for many, the major concern of short-term or more sustained periods of retrograde memory loss with ECT.

Total sleep deprivation (TSD) regimens (typically three cycles) have been found to improve bipolar depression, albeit temporarily, until the patient can sleep again. TSD is apparently more effective in patients with bipolar than unipolar depression *(127)*. Treatment to enhance and extend the improvement afforded by TSD include lithium, light therapy, and pindolol *(128,129)*.

6.7. Psychosocial Considerations

BD patients benefit from psychosocial treatments, and controlled trials that support the efficacy of such approaches, especially for targeted educational and cognitive behavioral therapy interventions *(130,131)*.

6.8. Rationale for Early Detection and Intervention

Perhaps our strongest recommendation is for the clinician to attempt to intervene pharmacologically with primary and adjunctive agents, and introduce psychotherapeutic and educational techniques, as early in the development of bipolar illness as possible. Many studies have indicated that the average length of time between the initial detection of symptoms of an affective disorder and the initiation of treatment in patients with BD is, incredibly, approx 10 yr. During this time, repeated episodes of depression and/or mania may not only interfere with patient functioning and cause a substantial morbidity and psychosocial loss, but it could also worsen the subsequent course of illness and its responsivity.

The findings of Kessing and colleagues *(132)* support one of the fundamental postulates of the sensitization hypothesis, which suggests that neurobiological vulnerabilities accrue with each successive episode. Kraepelin was the first to report a tendency over the first several episodes for the interval of wellness between successive episodes to decrease (i.e., cyclic acceleration) and for stressors to be less important in the precipitation of episodes of illness *(133)*.

Using the Danish case registry, Kessing and colleagues found that the best predictor for the rate and latency to relapse into a depressive episode was the number of prior episodes of depression requiring hospitalizations. Although these data can be interpreted in other ways, they strongly suggest the importance of intervening early and preventing episodes in the hopes that this would reduce the risk of recurrence.

A variety of other untoward consequences may occur as a result of the repeated experiences of untreated depressive components of bipolar illness. Women with bipolar illness are at substantially greater risk compared with the general population for engaging in alcohol use and abuse (a more than sixfold increased risk). A covariable of alcohol abuse was the number of prior episodes of depression. Vul-

nerability to other forms of substance abuse appears to increase with the time in adolescence and young adulthood when a patient experiences an inadequately-treated affective disorder. Other risks include a serious suicide attempt, which also appears to be associated with an increased number of prior depressive episodes.

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5 Treatment of Depression in Psychotic Disorders

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Contents

1. INTRODUCTION

Depression is common among patients with schizophrenia and is associated with a wide range of poor outcomes, including relapse and suicide. Although some dysphoria may be an adverse effect from conventional antipsychotic agents and some depressive reactions may follow resolution of a psychotic episode, most depression appears to be a chronic, comorbid condition commonly present throughout the course of the illness. Pharmacologic treatment of depression in patients with schizophrenia is not well studied. Identification of contributing factors—including substance abuse and neuroleptic toxicity—before augmentation strategies are employed is important.

In this chapter, the epidemiology and clinical characteristics of depression in schizophrenia are briefly reviewed, including the differential diagnosis of dysphoria. The older literature describing augmentation of conventional antipsychotic agents is also reviewed, along with studies of electroconvulsive therapy (ECT). Evidence suggesting that the newer atypical antipsychotic agents possess antidepressant efficacy is presented. Unfortunately, very limited data are available regarding augmentation of atypical antipsychotic agents when depressive symptoms persist, although the addition of antidepressants is common in clinical

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practice. For this reason, potential pharmacokinetic interactions between atypical antipsychotic agents and selective serotonin reuptake inhibitors are outlined.

2. SCHIZOPHRENIA

2.1. Prevalence and Course of Depression in Schizophrenia

Depression is common in schizophrenia and may represent a core symptom cluster of the illness. Factor analyses of individual items of the Positive and Negative Syndrome Scale (PANSS) in large samples of patients with schizophrenia have identified a symptom cluster representing depression and anxiety that remains consistent even after treatment with an atypical antipsychotic *(1,2)*. Rates of depressive episodes have varied from 20 to 80% among schizophrenia patient samples, reflecting in part differing definitions of depression and assessment methods *(3,4)*. In most studies, researchers have identified dysphoric mood only or threshold scores on depression rating scales, rather than establishing a diagnosis of major depression. Siris *(5)* calculated a modal depression rate of 25% derived from more than three dozen published studies in patients with schizophrenia. Although subsyndromal depressive symptoms are consistently found in the majority of patients, the prevalence of full major depression is quite variable among studies *(6,7)*.

The schizophrenia prodrome is frequently associated with depression, which often becomes the initial target of treatment until psychotic symptoms emerge and the diagnosis of schizophrenia is established *(7)*. Clinically significant depressive symptoms have been reported in as many as 75% of first-episode patients *(8)*. Wassink and colleagues *(7)* found a 30% prevalence of major depression in patients with schizophrenia who had been ill fewer than 5 yr; more than half of the nine symptoms identified by the third edition of the *Diagnostic and Statistical Manual of Mental Disorders—Revised* (*DSM-III-R*) as constituting major depression were present in the majority of patients. Depression is similarly common among older patients with schizophrenia. Jin and colleagues *(9)* reported that 66% of elderly outpatients with schizophrenia scored in the moderate to severe range on the Hamilton Depression (HAM-D) Rating Scale. Hogarty and colleagues *(10)* found that most "distressed" patients with schizophrenia experience chronic depression, often accompanied by anxiety, rather than discrete, time-limited episodes of depression.

Whereas certain features of depression—such as anergia, psychomotor retardation, and anhedonia—overlap with the negative symptoms of schizophrenia, the two syndromes can usually be distinguished based on the presence or absence of dysphoric mood *(11)*. The Calgary Rating Scale for Depression was developed specifically to distinguish depressive symptoms from the deficit syndrome by

identifying depressive symptoms that do not overlap with negative symptoms *(12)*. In several studies, severity of depression correlated with severity of psychotic symptoms rather than negative symptoms, despite the partial phenomenological overlap with negative symptoms *(6,13,14)*.

2.2. Functional Consequences of Depression in Schizophrenia

The presence of depression at the onset of schizophrenia has been associated with a favorable outcome in some studies *(15)*. However, comorbid depressive symptoms generally are associated with increased risk for suicide and relapse, as well as worse quality of life. In a survey of older outpatients with schizophrenia, depressive symptoms were significantly associated with worse everyday functioning *(9)*.

In a large prospective clinical trial, improvement of mood with risperidone or olanzapine significantly correlated with improved quality-of-life scores *(16)*. Improved interpersonal relationships was the factor most strongly correlated with a reduction in depression *(16)*. Furthermore, worsening of depressive symptoms also significantly predicted relapse over a 4-wk period *(17)*. Several other studies have also linked depressive symptoms to relapse in patients with schizophrenia *(18,19)*. Additionally, comorbid depression has been identified as a significant risk factor contributing to the high incidence of suicide in patients with schizophrenia *(18,20,21)*.

2.3. Differential Diagnosis

The first step in treating depression in a patient with schizophrenia should involve a careful diagnostic assessment *(3)*. Depressive symptoms may reflect conditions other than comorbid endogenous depression. Negative symptoms—including anhedonia, social isolation, constricted affect, and apathy—may mimic depression, although, as discussed previously, the absence of depressed mood usually distinguishes negative symptoms, or the deficit syndrome, from depression. Antipsychotic agents, in particular the conventional agents, can produce side effects that may also be mistaken for depression. The mask-like facies, psychomotor retardation, and dysphoria of neuroleptic-induced parkinsonism may resemble depression, but can be distinguished on the basis of tremor, increased muscle tone, and impaired gait. Conventional agents may also produce dysphoria as an isolated effect that presents with a sense of physical discomfort and anxiety; neuroleptic-induced dysphoria may be accompanied by akinesia or agitation, but is not accompanied by neurovegetative symptoms of depression *(22,23)*. In theory, dose reduction or the addition of an anticholinergic agent should improve neuroleptic-induced dysphoria, although Hogarty and colleagues *(10)* found no improvement in dysphoria with increasing doses of anticholinergic medication and only modest improvements 6 wk after fluphenazine dose reduc-

tion. Switching a patient to an atypical antipsychotic agent represents a more compelling strategy for eliminating neuroleptic-induced dysphoria *(24)*.

Substance abuse may also contribute to dysphoric mood in patients with schizophrenia. Almost half of patients with schizophrenia surveyed in the Epidemiologic Catchment Area Study *(25)* reported abusing drugs, with alcohol and stimulants the most frequently abused substances. Self-reporting of substance abuse is notoriously unreliable among patients with schizophrenia *(26)*, making an assessment of the contribution of alcohol and stimulants to dysphoric mood quite difficult. In studies of patients with schizophrenia who use cocaine, investigators have consistently reported elevated levels of depression and anxiety associated with cocaine use; dramatic increases in hospitalization rates during periods of cocaine ingestion have also been observed *(27,28)*. Other drugs that may produce depression include alcohol, antihypertensives, steroids, and interferon-α.

After other medical etiologies of dysphoria have been ruled out, the clinician should assess whether the patient has affective symptoms complicating schizophrenia vs a primary affective disorder with psychotic features, such as bipolar disorder or psychotic depression. The distinction between schizoaffective disorder-depressed type and schizophrenia with superimposed depression is of unclear clinical or theoretical significance. Dysphoria experienced by individuals with schizophrenia may in some cases reflect demoralization, especially if it occurs early during the course of the illness while patients first come to terms with the devastating effects of schizophrenia on their lives. However, most recent studies of "post-psychotic depression" have indicated that depression usually is present at the earliest stages of the illness and becomes more prominent as the florid psychotic symptoms resolve with treatment *(29,30)*. Psycho-educational interventions and supportive counseling for patients and family members are crucial to assist this coping process, but depressed mood in most cases should not be viewed solely as an appropriate psychological reaction to losses associated with the illness.

2.5. Treatment

2.5.1. Augmentation of Conventional Antipsychotic Agents

In 1989, Kramer and colleagues *(31)* published the results of a 4-wk, placebo-controlled trial of desipramine and amitriptyline in 58 acutely decompensated patients with schizophrenia who continued to demonstrate depression after 5 wk of haloperidol monotherapy. The tricyclic antidepressants (TCAs) did not enhance resolution of depressive symptoms compared with placebo and appeared to retard the response of psychotic symptoms. This rigorous study was a major factor in subsequent recommendations that antidepressants not be prescribed for acutely psychotic depressed patients with schizophrenia *(32)*. In contrast, inves-

tigators studying patients whose psychosis had been fully stabilized with conventional antipsychotic agents tended to find more positive results. Singh and colleagues *(33)* added trazodone 150 to 300 mg/d to phenothiazines in a 6-wk placebo-controlled trial involving 60 patients with chronic schizophrenia with "marked depressive symptoms." Trazodone was associated with significant reduction in HAM-D scores compared with placebo, without worsening of psychosis. In a series of studies culminating in a placebo-controlled trial, Siris and colleagues *(34)* similarly demonstrated that imipramine 200 mg/d significantly improved depressive symptoms when added to depot fluphenazine for 6 wk in 33 patients with schizophrenia accompanied by major or minor depression but not with active psychosis. All patients were treated with benztropine to minimize the risk for neuroleptic-induced akinesia. Imipramine was not associated with worsening of psychosis, but did improve measures of negative symptoms *(35)*. Siris and colleagues *(36)* subsequently demonstrated that maintenance therapy with imipramine can prevent relapse of depression in patients who responded to an initial course of treatment. Hogarty and colleagues *(10)* randomly assigned 57 persistently depressed or anxious patients with schizophrenia to augmentation of low-dose fluphenazine decanoate with either desipramine, lithium carbonate, or placebo for 12 wk. At 6 wk, the effect of desipramine augmentation did not differ from that of placebo; however, at the end of the study, a significant reduction in depression, anxiety, and psychosis was observed in the desipramine group compared with placebo. Response to desipramine was most evident among female patients and did not correlate with serum desipramine blood levels. There was no evidence of psychotic exacerbation or relapse in patients treated with desipramine. Similarly, 900 to 1200 mg/d of lithium was associated with significant improvement in anxiety and depression compared with placebo at week 12. Unlike desipramine, the lithium-treated group exhibited an increase in ratings of akinesia and akathisia.

Results from other placebo-controlled trials of antidepressants added to conventional antipsychotic agents in schizophrenia have been less positive. Prusoff and colleagues *(37)* randomized 40 patients with schizophrenia with elevated depression scores to 100 to 200 mg/d of amitriptyline or placebo added to perphenazine for 1 to 6 mo. HAM-D scores were significantly reduced in the amitriptyline group; however, ratings of thought disorder and agitation showed significant worsening with amitriptyline compared with placebo and the dropout rate was 47% at 4 mo. Waehrens and Gerlach *(38)* found no effect with 50 to 200 mg/d of maprotiline added to conventional agents in 20 patients with schizophrenia during a 6-wk, placebo-controlled, crossover trial. Patients had been stabilized for at least 2 mo with neuroleptic therapy and were selected for study on the basis of elevated anergia ratings on the Brief Psychiatric Rating Scale rather than meeting formal criteria for depression. Finally, no effect was found by Johnson

(39) when nortriptyline (75 to 150 mg/d) was added for 5 wk to low-dose fluphenazine or flupenthixol decanoate in 50 patients with schizophrenia and elevated scores on the Beck Depression Inventory. Blood levels of nortriptyline were not obtained; in light of the reported "therapeutic window" for nortriptyline and the possible elevation of TCA blood levels by phenothiazines, it is possible that patients in this study did not receive optimal nortriptyline dosing *(40)*.

Surprisingly, only two placebo-controlled trials of augmentation with a selective serotonin reuptake inhibitor (SSRI) in depressed patients with schizophrenia have been reported. Mullholland and colleagues *(41)*, in a preliminary report, identified a trend toward improvement in depressive symptoms compared with placebo with sertraline (50 mg/d) added to conventional and atypical antipsychotic agents for 6 wk in 26 patients with schizophrenia. Addington and colleagues *(42)* conducted a 6-wk, multicenter, placebo-controlled trial of sertraline in 48 patients with chronic schizophrenia who met the criteria for major depression. In this trial, 28 patients were receiving atypical antipsychotic agents; the remainder were treated with conventional agents. All patients were first treated with an anticholinergic for 1 wk to exclude neuroleptic-induced akinesia, then were randomized to placebo or sertraline at a dose of 50 mg/d for 4 wk. Sertraline could be increased to 100 mg/d during the final 2 wk of the trial. Less than 5% of patients dropped out from either treatment group. Significant improvement in depression was recorded for both the placebo and sertraline groups, with no evidence of superiority with sertraline. The response rates, defined by a 50% or greater improvement in the Calgary Depression Scale for Schizophrenia, were 48% with placebo and 43% with sertraline. Levels of psychosis did not differ between treatment groups. In the only other controlled study of an SSRI, Kirli and Caliskan *(43)* randomized 40 depressed patients with schizophrenia to sertraline and imipramine, and found no significant difference between the treatment groups.

2.5.2. ECT

A body of literature consisting largely of uncontrolled studies supports the use of ECT in patients with treatment-refractory schizophrenia *(44,45)*. In general, this treatment has been found most effective when administered early in the course of the illness; the presence of affective symptoms has predicted a positive outcome in some studies, but not all. ECT has not been studied in patients with schizophrenia and comorbid major depression, but has shown efficacy for depressive and anxiety symptoms in samples of patients with treatment-resistant schizophrenia and those experiencing their first episode *(44,46)*. The effect on depressive symptoms has been of a smaller magnitude than the effect on positive symptoms, although this could reflect the absence of major depression and possibly some confusion regarding the distinction of negative and depressive symptoms on the rating scales employed.

2.5.3. Atypical Antipsychotic Agents

In the landmark Clozapine Collaborative Study, Kane and colleagues *(47)* demonstrated a significant reduction in a broad range of symptoms with clozapine compared with chlorpromazine in patients with treatment-refractory schizophrenia. Depression and anxiety were among the symptom clusters that displayed a preferential response to clozapine. In subsequent trials with other atypical antipsychotic agents, investigators have found superior efficacy against depressive symptoms, best demonstrated with olanzapine, risperidone, and ziprasidone *(2,24,48,49)*. Although the atypical agents appear to possess greater antidepressant efficacy than the conventional agents, it is unclear whether significant differences in antidepressant efficacy exist among atypicals. The findings of comparative studies of risperidone vs olanzapine have been inconsistent *(17,50,51)*. A meta-analysis of the North American trials of risperidone found that risperidone (6 mg/d) produced a larger antidepressant effect compared with haloperidol 20 mg daily, with a between-treatment group-effect size of 0.30, which was larger than effect sizes for other symptom domains *(2)*. However, risperidone monotherapy was less effective than the combination of haloperidol and amitriptyline during a 6-wk trial involving 123 patients with psychosis and depression. The superior efficacy of haloperidol and amitriptyline was most apparent in patients with psychotic depression; no significant difference was found between the two treatments in depressed patients with schizophrenia and patients with schizoaffective disorder-depressed type. Of note, olanzapine was found to enhance antidepressant efficacy when added to fluoxetine in patients with treatment resistant unipolar depression, but produced only modest antidepressant effects when administered as monotherapy *(52)*.

The combination of antidepressants and antipsychotic agents for depression in patients with schizophrenia, while quite appropriate from a theoretical standpoint, has not been well studied for safety or efficacy. Studies combining conventional agents with TCAs and SSRIs have been generally well tolerated, although the goal of most of these studies has been the amelioration of negative symptoms *(53)*. Additive side effects represent a potential problem, particularly anticholinergic side effects arising from the combination of a highly anticholinergic TCA and a low-potency neuroleptic or clozapine. Other potential additive side effects from drug combinations include sedation and dizziness. Clinicians must also be aware of potential pharmacokinetic interactions between antidepressants and antipsychotics. Some phenothiazines are reported to elevate blood levels of TCAs, which may result in serum concentrations that are high enough to produce serious toxicity *(40,54)*. Most conventional antipsychotic agents are metabolized primarily by the hepatic cytochrome (CYP) 2D6; metabolism of these drugs may be significantly inhibited by certain SSRIs. For example, a dose

of 20 mg/d of fluoxetine increased haloperidol serum concentrations by 20% and fluphenazine serum concentrations by 65% in one placebo-controlled augmentation trial for negative symptoms *(55)*. However, measures of extrapyramidal symptoms did not change significantly. Of greater concern is the inhibition of clozapine metabolism by fluvoxamine and nefazadone on the basis of CYP3A4 inhibition. In one well-controlled trial, fluvoxamine co-administration raised serum clozapine levels more than threefold *(56)*. In contrast, sertraline produced no effect on clozapine in one study, and paroxetine produced only a small effect *(57)*. Buchanan and colleagues *(58)* found that fluoxetine up to 40 mg/d was well tolerated when added to clozapine in a placebo-controlled parallel group trial in 33 patients with treatment-resistant schizophrenia, although depressive symptoms did not improve. Pharmacokinetic studies have found only modest interactions between fluoxetine and olanzapine *(59)*.

3. CONCLUSION

Depressed affect is common in schizophrenia and is often chronic. The presence of depression predicts a worse outcome, as indicated by quality-of-life measures, relapse, heightened risk of suicide, and other signs. The conventional antipsychotic agents may produce or exacerbate dysphoria in patients with schizophrenia, whereas some atypical antipsychotic agents appear to possess substantial antidepressant activity. The clinician should first carefully evaluate a depressed patient for medical etiologies, including substance abuse and neuroleptic-induced dysphoria. Distinguishing comorbid depression from negative symptoms and from primary affective psychoses is also crucial. Switching dysphoric patients from conventional neuroleptics to atypical agents is probably the most sensible first step. Augmentation of atypical antipsychotic agents with antidepressants has not been adequately studied—there is no compelling evidence for efficacy in either acutely depressed patients with schizophrenia or in chronically dysphoric patients. High rates of placebo response have been reported in several studies, suggesting that major depressive episodes may resolve spontaneously, whereas chronic dysphoria is less likely to resolve. Combination of antidepressants with antipsychotic agents should be guided by an understanding of potential pharmacokinetic interactions—the combination that is potentially most dangerous is the addition of fluvoxamine to clozapine. Although not well studied, psychosocial interventions should also be made available to dysphoric patients and their families.

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6 Substance Abuse and Depression

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CONTENTS

1. INTRODUCTION

Depression, complicated by substance abuse, is a common clinical problem and is often associated with poor clinical outcomes. Clinicians need to understand the relationship between these two conditions and must adjust their treatment plans to address both disorders simultaneously. It is critical that the clinician not confuse a substance-induced mood disorder with an independent depressive disorder. Unfortunately, the relationship between substance abuse and depression is not well understood and relatively few well-controlled studies have been conducted to help guide the treatment of these patients.

The nature of the relationship between substance abuse and psychopathology has long been an area of controversy. Meyer identified six paradigms to explain

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this relationship, including the possibility that psychiatric disorders are a consequence of substance abuse or that they are a risk factor for substance abuse *(1)*. There is a high familial incidence of both alcoholism and depression, suggesting a common genetic vulnerability for both conditions. Genetic research suggests that alcoholism and depression are two common, but independent conditions that sometimes run in the same families *(2,3)*. Analysis of the Mid-Atlantic Twin Registry showed that individuals with major depression were at increased risk for alcohol abuse or dependence. This study indicated that environmental and genetic factors influence both disorders. While these factors overlap, they are not identical. The authors concluded that these findings do not support a model in which alcoholism causes major depression, or major depression causes alcoholism *(4)*. To date, no single gene has been identified that links these conditions.

This chapter reviews the epidemiology of major depressive disorder (MDD) complicated by substance abuse and describes common clinical presentations. The differential diagnosis of these conditions is also addressed. Evidence is reviewed on the efficacy of antidepressant medications in this comorbid population. The potential anticraving effect of some of the selective serotonin reuptake inhibitors (SSRIs) is also considered. Finally, recommendations are made for comprehensive treatment plans that address both the pharmacotherapy of the depressive disorder and management of the substance use disorder.

2. PREVALENCE AND COMORBIDITY

Since the 1980s, a number of studies have shown a high rate of co-occurrence—or "comorbidity"—of depression and other affective disorders with substance-related disorders. In studies of psychiatric patients, the range of comorbid alcoholism has been from 10 to 30% *(5,6)*. In two studies, structured interviews were used to estimate the incidence of these disorders in large samples of the general population. They supply the highest quality information available about the rates of psychiatric disorders in the general population *(7)*.

In the Epidemiological Catchment Area (ECA) study, investigators found increased rates of depression in alcoholic individuals. The rate for men was 5%, whereas for women the rate was almost three times the national rate (19 vs 7%) *(8)*. Analysis of these data indicated that individuals who had depression or other affective disorders had increased rates of substance-related disorders and that the reverse relationship was true as well. Selections from these data, listed in Table 1 show the rates of these disorders in the general population, as well as the increased rate of additional psychiatric diagnoses in individuals already identified as having psychiatric problems.

The analyses showed increased rates of co-occurring affective disorders in people with substance-related problems. Individuals with alcohol- or drug-related

Table 1. Lifetime Prevalence and Comorbidity of Substance-Related and Affective Disorders

	Sample Population				
	General population	*Alcohol dependent or abusing*	*Drug dependent or abusing*	*Unipolar Major depressive*	*Dysthymic*
Diagnosis					
Any nonsubstance-related psychiatric disorder	22.5%	36.6% RR: 2.3	53.1% RR: 4.5		
Any affective disorder	8.3%	13.4% RR: 1.9	26.4% RR: 4.7		
Unipolar major depression	4.9%				
Dysthymia	3.3%				
Alcohol dependent or abusing	13.5%	N/A	47.3% RR: 7.1	16.5% RR: 1.3	20.9% RR: 1.7
Drug dependent or abusing	6.1%	21.5% RR: 7.1	N/A	18% RR: 3.8	18.9% RR: 3.9

RR, relative risk or odds ration; N/A, not applicable. (Adapted from ref. *8.*)

disorders were, respectively, 1.9 and 4.7 times more likely to have a history of affective disorder than the general population. Individuals with depression or dysthymia were found to have an increased incidence of alcohol-related problems (16.5–21.9 vs 13.5%) and drug problems (18.0–18.9 vs 6.1%). Interestingly, individuals with alcohol- or drug-related problems were much more likely to have other substance-related disorders, with more than seven times the risk of an additional substance-related diagnosis. The authors summarized their impressions of the impact of their findings with the following statement: "These data provide clear and persuasive evidence that mental disorders must be addressed as a central part of substance abuse prevention efforts in this country" *(8)*.

In the National Comorbidity Survey (NCS), a representative sample of more than 8000 people was interviewed. The investigators found that major depression and alcohol dependence were the most commonly identified psychiatric diagnoses, with lifetime incidence rates of 17 and 14.1%, respectively; alcohol abuse without dependence had a lifetime incidence rate of 9.4%. Dependence on other drugs was found in 7.5% of this population. Just over half of the population surveyed had no history of psychiatric disorder, and another one-fifth had a diagnosis of only one disorder. The study also identified a high degree of comorbidity, with 13% reporting two diagnoses and 14% reporting three or more diagnoses. This concentration of many different psychiatric disorders in a small segment of the population suggests that comorbid depression and substance abuse are the norm in some of the most seriously impaired psychiatric patients in the United States *(9)*. Analysis of the NCS data also focused on the temporal sequences of diagnoses. This data set indicated that anxiety disorders and, to a lesser degree, depression had a tendency to precede the development of alcohol dependence *(10)*.

Other studies have described high rates of depression in various populations with substance-related problems. Gold surveyed 6355 substance abuse patients and found a lifetime incidence of major depression of 43.7% *(11)*. Miller found a 28% prevalence for major depression in alcohol and drug users treated in a variety of clinical settings *(12)*. Hasin and Grant recently reported a four-fold increased risk for major depression in a community sample of individuals with a history of alcohol dependence, despite the fact that a majority of them had not used alcohol for more than 2 yr *(13)*. In a review of a community sample of individuals with alcohol dependence, Kirchner noted that comorbid depression was more likely to occur in women and that women were more likely to have comorbid drug-use disorders *(14)*. Elderly patients with depression are three to four times more likely to have an alcohol use disorder than elderly persons without depression. Devanand reported a prevalence of 15 to 30% for comorbid alcoholism in patients with late-life major depression *(15)*.

In a sample of drug-dependent individuals in treatment, Compton found a 24% lifetime prevalence for major depression. This sample was not specific for any

one drug of abuse *(16)*. Specific details on the comorbidity of depression in opiate and cocaine abusers will be covered later in this chapter.

Minimal information is available about the relationship between other drugs of abuse and depression. Methylenedioxymethamphetamine (MDMA; ecstasy) has been shown to deplete serotonin (5-HT) levels in animal models. Two recent studies have shown increased levels of depressive symptoms in ecstasy users *(17,18)*. Increased rates of depression and suicidal ideation have also been found in individuals with methamphetamine dependence *(19)*.

One often overlooked issue is the co-occurrence of depression and nicotine dependence, which has been demonstrated in adolescents in a number of studies *(20,21)*. It is also thought that depression and substance-related disorders influence the progression of nicotine dependence in teenagers *(22)*. Although these are important topics, the treatment of these disorders in adolescents and the treatment of comorbid depression and nicotine dependence in general fall outside the scope of this chapter.

Several studies have reported an association between marijuana use and the later development of major depression *(23–26)*. Data from the NCS suggested a "moderate" to "modest" association *(25)*. Research done in 44 schools in Australia showed that regular marijuana use by girls predicted later depression. Daily users were at the highest risk, with a fivefold increase in the odds of reporting depression later in life *(26)*. In none of these studies was there evidence that depressive symptoms in teenagers predicted later heavy marijuana use.

Considering these high rates of co-occurrence of depression and substance-related disorders, clinicians must become skilled in the evaluation and management of these complex, dually diagnosed patients. Findings to date on the sequence of onset of these disorders have been inconsistent. With alcohol, cocaine, and opiates, depressive symptoms typically precede the development of substance-abuse problems; with marijuana, the reverse seems to be true. To treat these patients effectively, clinicians need to carefully separate the symptoms of substance abuse from those of depression, and determine which symptoms reflect an independent psychiatric disorder and which symptoms are the result of alcohol or drug use or abuse.

3. FUNCTIONAL CONSEQUENCES OF COMORBID DEPRESSION AND SUBSTANCE ABUSE

Recognizing the high rate of co-occurrence of depression and substance-related disorders, researchers have studied the effects that the presence of one of these disorders has on the clinical course of the other disorder. A number of studies showed that the treatment of alcoholism in the presence of any comorbid psychiatric disorder was associated with a poorer prognosis *(27–31)*. One pro-

spective treatment outcome study compared patients with alcoholism alone with alcoholism co-occurring with psychiatric disorders. At the 1-yr follow-up, the patients with alcoholism plus a psychiatric comorbidity had a more stressful course but not necessarily a worse outcome *(32)*. Among women, even moderate social drinking (up to three drinks per week) is associated with increased Beck Depression Index (BDI) and Beck Anxiety Index scores compared with women who abstained from drinking *(33)*.

Mueller and colleagues followed a group of patients who entered treatment for depression; all subjects met full research diagnostic criteria for MDD. Over the course of 10 yr, patients with active alcoholism were significantly less likely to recover from depression than either patients with alcoholism in remission or people with no history of alcohol-related problems *(34)*. During a 5-yr study, Hasin and colleagues demonstrated that the resolution of alcohol-related problems both increased the chance of recovering from depression and decreased the chance of the depression recurring *(35)*.

Studies have shown that 15 to 25% of successful suicides involve alcohol *(36,37)*. Although depression and substance abuse each are associated with an increased risk of suicide, the risk is increased even more when both types of disorders are present *(38–40)*.

Recent studies have also evaluated the effect of depression on outcomes for the treatment of substance-related disorders. In a group of male veterans followed for 12 mo after alcohol detoxification, those with depressive symptoms at 3 mo were significantly more likely to relapse during the study period. Furthermore, the risk of relapse increased with the severity of the depressive symptoms *(41)*.

In another study, individuals with depression and various types of substance dependence were followed for 18 mo after inpatient treatment. Patients with a history of major depression that occurred before the onset of substance dependence were less likely to achieve remission; this difference remained even after patients with active depression were factored out of the analysis. Patients with depression that occurred after the development of substance dependence and persisted during periods of sobriety were at three times the risk for relapse to substance dependence after periods of stable remission. Even patients meeting the criteria for major depression that would be categorized as "substance-induced," with depressive symptoms that resolved within 2 to 4 wk of detoxification, were less likely to achieve stable remission of substance dependence *(42)*.

These poor-outcome cases may be related to impaired coping skills. Kahler reviewed a group of depressed alcohol-dependent patients (BDI ≥ 15) and compared the coping skills of individuals with an independent MDD with those of individuals who never met the criteria for an independent depressive disorder. He noted greater cognitive vulnerabilities and defective coping skills in those with

an independent MDD, suggesting that they were at higher risk for recurrent depression *(43)*.

Overall, this evidence suggests that the prognosis is worse for patients with depression and substance-related disorders than for individuals with a single disorder. In addition, successful treatment of one disorder may in part depend on adequate treatment of the co-occurring disorder. Alcoholism with all types of depression (independent MDD, substance-induced depressive disorder, and dysthymia) indicated an increased risk for relapse, but those with independent MDD probably experienced the most malignant course of illness.

4. CLINICAL EVALUATION AND DIFFERENTIAL DIAGNOSIS

4.1. The Importance of an Adequate History

Appropriate diagnosis is dependent upon an accurate history. It is critical to determine the initial, presenting condition. Which symptoms developed first: the depression or the alcohol/drug use? An accurate history of the sequence of symptoms is necessary to separate the presentation of an underlying depressive illness from symptoms induced by specific substance abuse. Unfortunately, it is difficult for some patients to provide an adequate history. Neurological impairment may limit or distort the patient's recall. Denial, repression, or both may also confound the evaluation process. Ideally, the patient's history should be confirmed with relatives or significant others. It is critical to determine if depressive symptoms were present prior to any substance use and during any drug-free periods, and if there is a family history of depressive disorders.

4.2. MDD vs Substance-Induced Mood Disorder

No specific symptoms can be used reliably to distinguish an independent depressive disorder from a substance-induced mood disorder. *DSM-IV* identifies a substance-induced mood disorder as a mood disturbance that develops during or within a month of substance intoxication or withdrawal, and substance use is thought to be etiologically related to the mood disturbance *(44)*. An accurate history, coupled with clinical observations following 2 to 4 wk of sobriety, can help clarify whether the depressive symptoms represent an independent illness or occur secondary to alcohol or drug use. A history of depression prior to the development of a substance use disorder or during periods of extended sobriety, along with a history of depression in biological family members, increases the likelihood that a patient with substance abuse and depression has an independent affective disorder *(45)*.

4.3. Evaluation for Suicide Risk

All substance abuse patients need to be assessed for depression and suicidal risk at the time of admission for treatment. Close observation and suicide precau-

tions should be initiated when indicated. Intoxicated patients or those in acute withdrawal are at particular risk for acting on suicidal ideas. Such depressive symptoms may be the result of an alcohol-induced mood disorder and do not necessarily indicate the presence of an independent depressive disorder nor the need for ongoing pharmacotherapy for depression.

4.4. Dysthymia

Substance abuse patients may also suffer from chronic forms of dysthymia. Prolonged hypophoric states have been described in alcoholism following detoxification *(46)*. Khantzian *(47)* proposed that chronic problems with affect regulation, including underlying depressive disorders, lead some individuals to self-medicate with alcohol or other drugs. Based on this theory, successful addiction treatment requires the treatment of both the addiction and the underlying psychiatric disorder.

4.5. Depression After Prolonged Sobriety

Alcoholics often describe episodes of depression occurring after extended periods of sobriety. Behar reported a 15% incidence of "disabling" depression after a mean period of 36 mo sobriety *(48)*. If there is a history of prior depressive episodes independent of drinking, it can be presumed to be the recurrence of a major depression and managed as such. If there is no prior history of depression, this may represent part of the psychological process of recovery from addiction. These patients should initially be referred for psychotherapy to help them mourn the real losses in their lives: family, health, self-respect, career, time, opportunities, etc. Clinicians should be particularly alert to identify such depressive syndromes in women who abuse alcohol. Some patients become very discouraged when they realize that sobriety does not resolve all of life's problems. Reliance on the disease model of alcoholism leads some recovering alcoholics to expect that sobriety will eliminate most of their problems. The realization that sobriety is not a panacea can be profoundly discouraging for many alcoholics. If significant symptoms of depression persist for more than 1 mo, we recommend antidepressant pharmacotherapy for these patients.

5. CLINICAL PRESENTATIONS

5.1. Alcohol Dependence

5.1.1. Depression and Acute Intoxication

As many as 70% of alcoholics are clinically depressed at the time of admission for detoxification. These patients often score in the severely depressed range on

the BDI *(49)*. Symptoms may include suicidal ideation or behavior, which is often the primary reason for hospitalization. Such patients are at serious risk for suicide and will require observation on a secure unit. Typically this presentation is a symptom of an alcohol-induced depressive disorder; these patients usually improve rapidly following detoxification. Within 2 wk, the patients generally score in the mildly depressed range on the BDI. At that point, the number of clinically depressed patients has dropped to 6 to 7% among male alcoholics and 11 to 13% among women alcoholics. This pattern suggests that the majority of depressive syndromes seen in acutely intoxicated individuals are transient and do not reflect an independent psychiatric disorder *(50)*.

Beyond necessary supervision during periods of suicidal ideation, the primary treatment needed is alcohol detoxification. There is no evidence or rationale to justify the use of antidepressant medication in this subgroup. The primary long-term management for this condition is to help the patient maintain sobriety. Those patients who remain depressed beyond this period or develop a depression during extended periods of sobriety most likely have an independent MDD and require therapy for this comorbid condition.

5.1.2. Alcohol Dependence and Depression

There is no consistent agreement on the relationship between depression and alcoholism. Jaffe and Ciraulo described at least 10 possible causes of depressive symptoms in alcoholics, ranging from the direct pharmacologic effect of alcohol on the brain to alcohol withdrawal and major affective disorders *(46)*. Depending on the diagnostic criteria used and the point at which the diagnosis is established, the reported incidence of depression in alcoholics ranges from 8 to 70% *(50–52)*. It is difficult to compare these studies owing to a lack of consensus on diagnostic approaches and the failure to separate substance-induced disorders from independent depressive disorders. Abraham screened 375 psychiatric outpatients with depression for comorbid substance-use disorders to determine the age of onset and the sequence of symptoms *(53)*. In this outpatient clinic population, he determined that alcohol dependence followed the onset of depression on average by 4.7 yr. Similarly, cocaine dependence followed the first major depressive episode by 6.8 yr. In a study of inpatients admitted for alcoholism treatment, Hesselbrock documented a lifetime and current prevalence of major depression of 32% in men and 52% in women. Only 3% of men and women reported bipolar affective disorder. In 41% of the men and 65% of the women, major depression preceded the development of alcohol abuse, alcohol dependence, or both *(54)*. In one study, investigators suggested that depressed alcoholics who present with physical/neurologic complaints and little or no irritation or agitation are more likely to remain depressed after 30 d of therapy for substance abuse *(55)*.

Table 2. Alcoholic Hypophoria Following Detoxification

Group	*Mean Hypophoria Scores*
Inpatient alcoholics	
Abstinent 1 wk	38.4
Abstinent 2 wk	35.8
Abstinent 4 to 6 wk	35.9
Alcoholics Anonymous group	27.3
Nonalcoholic medical patients	20.5

Adapted from ref. *46*.

The Hypophoria Scale shares many items with the Addiction Research Center Inventory – Morphine Benzedrine Group scale *(137)* colloquially referred to as the "euphoria" scale. Alcoholics show increases in scores on this scale after the administration of either alprazolam or diazepam whereas control subjects do not *(138)*. These findings suggest that alcohol dependent patients self-medicate with GABA agonists like benzodiazepines because of a desire to enhance mood. The finding that subjects without a personal or family history of alcoholism do not experience an enhanced mood after a benzodiazepine suggests that this is a pharmacodynamic unique to alcoholics and children of alcoholics.

5.1.3. Alcoholic Hypophoria

Substance abusers who do not meet the criteria for major depression may still present with clinically significant symptoms. Jaffe and Ciraulo *(46)* studied male alcoholic veterans hospitalized for detoxification and observed low-level symptoms of dysphoria and low self-esteem which they labeled "Alcoholic Hypophoria." Using the Present Affect Rating Scale developed by Kay, the hypophoria scale showed persistent elevations in negative mood following detoxification (*see* Table 2) *(56)*. As compared with Zung Self-Rating Depression Scale scores, which dropped quickly following detoxification, BDI scores did not normalize, and the hypophoria scale scores remained elevated for many weeks. Alcoholics who had been sober for 6 mo and participated in an Alcoholics Anonymous program continued to demonstrate elevated hypophoria scores compared with non-alcoholic, hospitalized medical patients. These patients' complaints can easily be missed, because they did not meet all the criteria for a diagnosis of a major depression. Tricyclic antidepressants (TCAs) were not effective in treating these low-level depressive symptoms *(46)*. Benzodiazepines may relieve symptoms of hypophoria in abstinent alcoholics (Fig 1; *46a*).

Table 3. Five Common Patient Profiles

PRIMARY AFFECTIVE DISORDER and SECONDARY ALCOHOLISM

1. 2–5% of all alcoholics (2% of males; 13% of females)
2. Depressive symptoms clearly antedate the alcoholism
3. Depression continues after detoxification; symptoms are likely to be severe
4. Requires treatment for BOTH depression and alcoholism; suggest use of an antidepressant medication in therapeutic doses

PRIMARY ALCOHOLISM and SECONDARY ALCOHOLIC HYPOPHORIA

1. Occurs in 30–50% of all alcoholics
2. Symptoms similar to primary depression, but less severe
3. Symptoms are only present during drinking bouts and gradually diminish after detoxification.
4. Requires no specific treatment for depression.
5. May have greater tendency to use other drugs (marijuana and LSD, compared to alcoholics with no symptoms of depression).
6. Look for symptoms of persistent HYPOPHORIA in this group *(46)*.

PRIMARY ALCOHOLISM and PRIMARY AFFECTIVE DISORDER

1. Occurs in 3–7% of all alcoholics
2. Depressive symptoms are severe and do not moderate with sobriety
3. Symptoms may be present during and between episodes of drinking
4. Requires treatment for both depression and alcoholism

BIPOLAR AFFECTIVE DISEASE and SECONDARY ALCOHOLISM

1. Drinking usually begins AFTER the onset of manic-depressive cycles
2. These patients rarely drink while depressed or in normal phases
3. Drinking is evident mainly in manic phase
4. Primary treatment is a mood stabilizer; these patients may not require specific treatment for alcoholism *(96)*.

SUBSYNDROMAL MANIC DEPRESSIVE ILLNESS and ALCOHOLISM

1. Patients often present with personality maladjustments (borderline, antisocial, alcohol and drug abuse, emotional lability)
2. May complain of "RACING THOUGHTS"
3. Complaints of depression are rare, or may not be obvious
4. These patients benefit from a mood stabilizer
5. Alcoholism treatment is also REQUIRED *(139)*

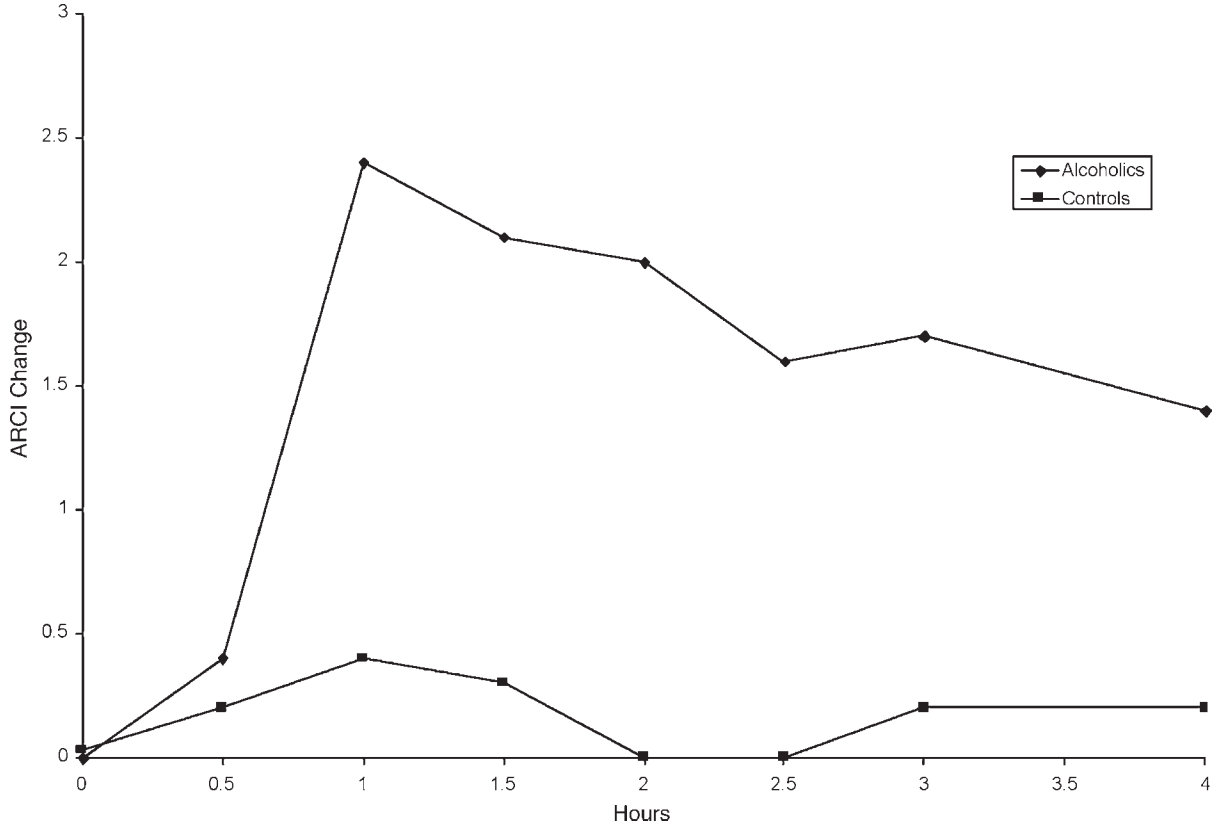

Fig. 1. The upper line of the graph indicates that abstinent alcoholics experienced greater euphoria (ARCI change) after a single dose of alprazolam compared with control subjects (lower line of graph). (Redrawn from data from ref. *46a*).

6. PHARMACOTHERAPY OF DEPRESSION IN THE ALCOHOLIC

6.1. Clinical Pharmacology of Antidepressants in Alcoholism

Consideration of antidepressant interactions in patients with substance abuse is complicated not only by the use of prescribed medications, but also by the many illicit and prescription drugs that such individuals may consume. With respect to TCAs, both pharmacokinetic and pharmacodynamic interactions may occur. Pharmacodynamic interactions are the most common and most important clinically. In general, concurrent ingestion of ethanol and cyclic antidepressants leads to impaired psychomotor function and sedation; the combination is particularly dangerous in overdose *(57,58)*. Interestingly, bupropion may antagonize the sedative effects of ethanol without affecting the perception of inebriation. Acute ingestion of ethanol and SSRIs or mixed-action agents, such as venlafaxine, appear less likely to interfere with laboratory measures of psychomotor performance *(59)*, although some patients will report that the subjective effects of alcohol-containing beverages change when they are taking SSRIs. This is consistent with the modest decreases in alcohol consumption observed in studies of heavy drinkers taking fluoxetine, zimelidine, or citalopram *(59,60)*. This action does not appear to generalize to alcoholics, since the SSRIs have not been proven effective in alcoholism treatment (as discussed later). Pharmacokinetic interactions with antidepressants differ little among drug classes. Acute ethanol impairs the metabolizing capacity in the liver and gut, resulting in high plasma concentrations of the antidepressant. With long-term ethanol use, the hepatic enzyme capacity is usually enhanced, and all antidepressants that are metabolized by liver enzymes will have increased clearance and lower steady-state levels. Unbound fractions of imipramine, desipramine, and their hydroxymetabolites are decreased in chronic alcoholics, with corresponding increases in α_1-acid glycoproteins *(61,62)*.

6.2. Initiating Pharmacotherapy

Placebo-controlled trials of medication in depressed alcoholics have demonstrated significant improvement in comorbid depression *(63)*. A diagnostic evaluation should be repeated after 2 wk sobriety in patients who continue to present symptoms of depression. If the depression has cleared or significantly diminished by that time, antidepressant treatment is not required and alcoholism can be assumed to be the primary problem. If there is no improvement in depressive symptoms by week 2, it is likely that the patient has a comorbid depression and it is appropriate to initiate specific pharmacotherapy. In patients with a history of depressive symptoms prior to the development of alcohol dependence, depression during extended periods of sobriety, or a strong family history of depression,

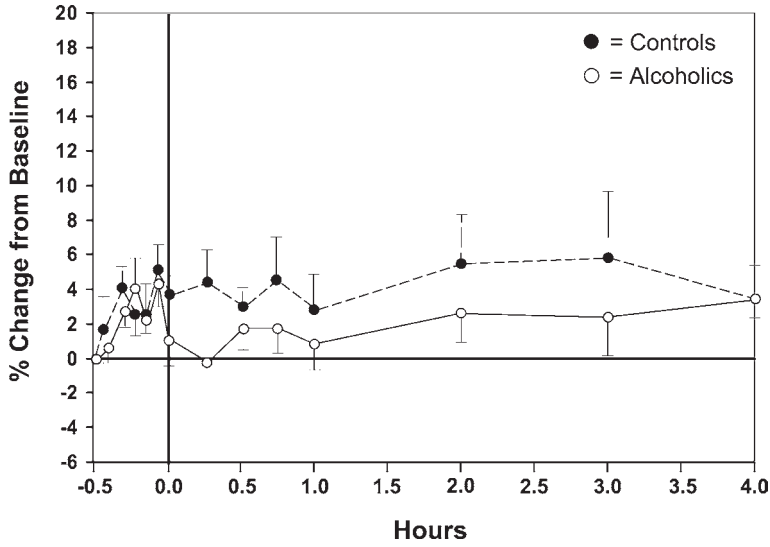

Fig. 2. Mean (± SEM) percent change from baseline in QTc interval vs time during and following an intravenous infusion of 2-hydroxyimipramine in alcoholic and control subjects. (Redrawn from data from ref. *62.)*

there is a strong assumption that they have an independent depressive disorder. There is no reason to delay pharmacotherapy once these patients have completed detoxification. In any case, symptoms of major depression that persist longer than 2 wk after detoxification should always be treated.

6.2.1. TCAs

Relatively few controlled studies of the efficacy of TCAs have been conducted in depressed alcoholics. Alcoholics given 150 mg imipramine had significantly lower plasma levels compared with nonalcoholic depressed patients, and their BDI scores were worse compared with controls, who had been given no medication. Lower plasma levels of desipramine and imipramine lasting at least 5 wk have been documented in recently detoxified alcoholics. These TCAs are metabolized primarily by the hepatic microsomal drug oxidizing system, which is induced in chronic alcoholics without cirrhosis *(64)*. Desipramine clearance is less affected, suggesting that this is the preferred TCA for use in recently detoxified depressed alcoholics *(61,65)*. Induction of this enzyme will dissipate over time if the patient remains sober. The clinician needs to monitor plasma TCA levels and adjust doses correspondingly to ensure that plasma levels remain within the appropriate therapeutic range. Additionally, recently detoxified alcoholics appear to be more sensitive to the cardiac effects of imipramine, desipramine, and their hydroxymetabolites (*see* Figs 2, 3, and 4) *(62)*. The me-

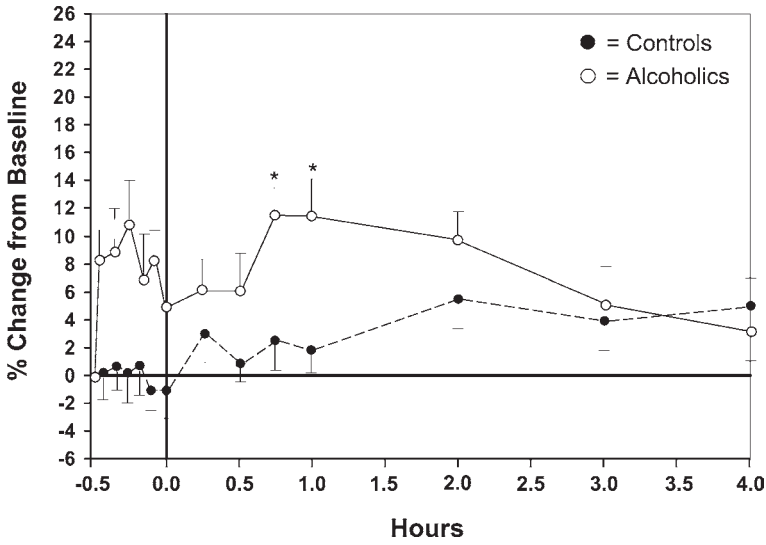

Fig. 3. Mean (± SEM) percentage change from baseline in P-R interval vs time both during and following an intravenous infusion of 2-hydroxyimipramine in alcoholic and control subjects (star indicates $p < .05$). (Redrawn from data from ref. *62.)*

tabolism of TCAs is also inhibited in patients with cirrhosis. Lower doses may therefore be adequate in such cases, although plasma levels should always be monitored.

One double-blind, placebo-controlled trial of desipramine in depressed alcoholics showed that medicated participants were significantly less depressed than controls. After 6 mo of therapy, no significant difference in the rate of sobriety between the two groups was observed, though the desipramine treated participants appeared to have longer periods of sobriety *(66)*. Plasma levels were monitored in this study. This is similar to our experience with MAOIs inhibitors in alcoholics with atypical depression. Symptoms of depression often respond well, but there is no evidence that relapse rates are diminished in the medication-treated group; furthermore, the risk of food and drug interactions with MAOIs rarely justify their use by in-patients with substance-use disorders (Ciraulo, unpublished data, 2003).

An uncontrolled, open-label study of imipramine in depressed alcoholics showed improvement in mood and drinking patterns in 45% of the patients. The addition of disulfiram to the protocol produced improvement in an additional 13% of the subjects. At the completion of this trial, the patients were randomized to either imipramine or placebo for an additional 6 mo. During this trial extension period, 31% of the patients taking imipramine relapsed compared with a 70% relapse rate for those taking placebo *(67)*. A double-blind, placebo-controlled

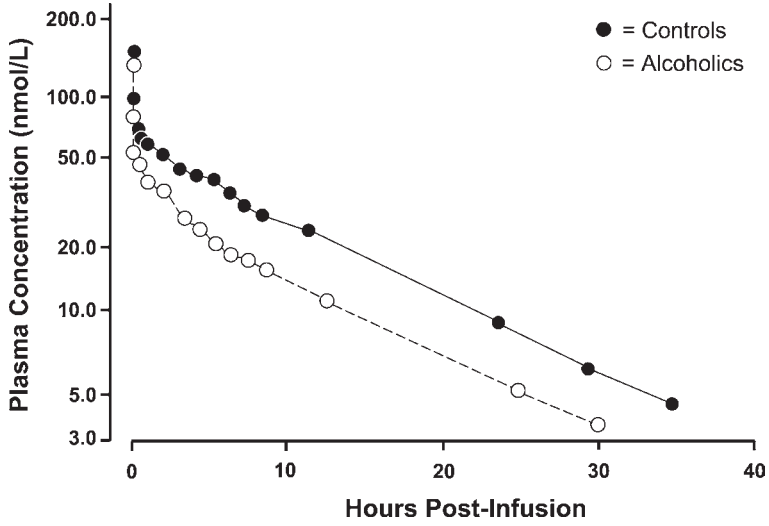

Fig. 4. Mean 2-hydroxyimipramine plasma concentration vs time data for alcoholic and control subjects following an intravenous infusion of 2-hydroxyimipramine 10 mg. (Redrawn from data from ref. *62*.)

trial of imipramine showed efficacy in treating depression in alcoholics, but no improvement in drinking patterns *(68)*. In another double-blind, placebo-controlled trial of desipramine, patients showed improvement in both depression and a reduction in the rate of relapse to drinking *(69)*.

In summary, these studies demonstrate that the TCAs are effective in treating depression in substance-abuse patients. Unfortunately, the TCAs have no predictable effect on the rate of relapse to substance use. It is therefore critical that these patients participate in a comprehensive substance-abuse treatment program. Although there has been an anecdotal report of the abuse of amitriptyline when used to treat depressed alcoholics *(70)*, we do not think this drug class carries a significant risk for abuse. However, it has been associated with a greater risk for lethality of overdose, especially when combined with alcohol or other drugs.

6.2.2. SSRIs

Animal studies have shown that 5-HT systems regulate drug-taking and other consumatory behavior. SSRIs have been shown to reduce drug-seeking behavior in animals. Research has also shown lower 5-HIAA in the cerebrospinal fluid of alcoholics, suggesting an abnormality in 5-HT metabolism. These findings suggest that the SSRIs may both reduce alcohol craving and treat affective symptoms in depressed alcoholics *(71,72)*. The side-effect profile for the SSRIs makes them more acceptable to substance abuse alcoholic patients compared with TCAs

and suggests improved compliance with treatment. There have been no reports of accelerated metabolism or altered pharmacokinetics of SSRIs in alcoholics, and there is less risk of overdose and life-threatening side effects with this class of drugs *(73)*.

There have been relatively few studies on the use of the SSRIs to treat depression in alcoholics. In one 4-wk trial comparing tianeptine (a 5-HT enhancer) with amitriptyline in depressed alcoholics, investigators found tianeptine to be slightly more effective; unfortunately they had not used placebo controls *(74)*. Cornelius and colleagues *(75)* conducted an open trial of fluoxetine in 12 severely depressed suicidal patients who met *DSM-III-R* criteria for both MDD and for alcohol dependence. After 8 wk, all subjects showed improvement in measures of depression and alcohol consumption after discharge. These results were not duplicated in a large randomized, placebo-controlled trial of fluoxetine in 101 alcoholics. Kranzler reported that mood improved in study participants with mild depressive symptoms, but there was no difference between drug and placebo on drinking patterns *(76)*.

In a second study of fluoxetine, Cornelius reported both reduced drinking and improved mood during a double-blind, placebo-controlled trial in 51 severely depressed alcoholics *(77)*. A subset of 17 patients in this trial abused both alcohol and cocaine. Within that group, no improvement was seen in either depression or alcohol or cocaine use *(78)*. In a 1-yr follow-up on the 31 patients who responded to fluoxetine in the original 1997 trial, the responders showed fewer depressive symptoms and less drinking than the placebo group *(79)*.

A single small, open-label trial of fluoxetine was carried out in adolescents with comorbid major depression and an alcohol-use disorder. Investigators observed significant decreases in both depressive symptoms and drinking *(80)*. Riggs reported a similar reduction in depressive symptoms in an open trial of fluoxetine in abstinent adolescent delinquents with major depression and comorbid substance use disorders *(81)*.

Roy reported the successful treatment of depressive symptoms with sertraline in a double-blind, placebo-controlled trial in 36 depressed, recently abstinent alcoholics *(82)*. However, Pettinati did not find a benefit for sertraline in a double-blind, placebo-controlled trial in 100 alcohol-dependent subjects. Drinking was reduced in those patients with no history of depression. However, for patients who met *DSM-III-R* criteria for past or current depressive disorder, sertraline was no better than placebo in reducing drinking *(83)*. These results suggest the need to subtype alcoholics on the basis of the presence or the absence of a history of MDD.

Citalopram has been studied for its anticraving effect in alcoholics, but not in a depressed alcoholic population. This SSRI reduced alcohol craving and drinking in nondepressed alcoholics in two double-blind, placebo-controlled trials *(84,85)*, but was effective in only less severe drinkers in a third study *(86)*. In a

related study of citalopram as an anticraving drug in nondepressed mild to moderate alcoholics, Naranjo reported a 44% reduction in the number of drinks per day in men vs a 27% decrease in women, suggesting that gender may be a significant variable in the response of alcoholics to pharmacotherapy *(87)*.

Insomnia is frequently reported by depressed alcoholic patients treated with SSRIs. Supplemental trazodone 25 to 75 mg hs works well to alleviate this complaint *(88)*. The effect of trazodone 150 to 200 mg on sleep quality was compared with placebo in a small number of inpatient alcoholics *(89)*. Sleep efficiency was significantly increased in the trazodone group, primarily because of differences in the number of awakenings, wake time after sleep onset, and non-rapid eye movement sleep compared with placebo. Baseline-endpoint differences in the trazodone group included these measures as well as the apnea index and number of stage shifts. Much recent research has focused on the association of persistent sleep disturbances and relapse in alcoholism, fueling the search for nonaddictive sleep-promoting agents. Other antidepressants and some anticonvulsants (e.g., gabapentin) have been used clinically and are currently being studied. Sexual dysfunction is also a commonly reported side effect with the SSRIs. In our male patients, this has responded well to treatment with sildenafil.

The SSRIs appear to have significant efficacy in treating depression in abstinent substance-abuse patients, irrespective of any effect on drinking behavior or drug use. Results are less clear in depressed individuals who actively abuse drugs or alcohol. The data regarding a specific SSRI anticraving effect are inconsistent. The recent work of Pettinati *(83,90,91)*, Johnson *(92)*, and Pettinati and Naranjo *(92a)* suggests that there may be subtypes of alcoholics that obtain a specific anticraving effect from various medications. Specifically, Types A/B, early/late onset, or specific genetic polymorphisms may influence SSRI response. Additional research is needed to clarify these findings. When this phenomenon is better understood, it may be possible to clarify the inconsistent results seen in some of the SSRI trials.

6.2.3. Nefazodone

Nefazodone has been noted to be effective for alcoholics with depression and anxiety and also to be helpful in normalizing sleep patterns *(93)*. Roy-Byrne treated 64 alcohol-dependent subjects with comorbid MDD using nefazodone in a 12-wk, double-blind, placebo-controlled trial. The medication group showed a significant decrease in depression scores but did not show any advantage over the placebo (psychoeducation) group in terms of drinking outcome. Both groups showed a similar decrease in alcohol consumption *(94)*. However, because of the risk for hepatoxicity that is associated with nefazodone, this drug must now be considered a second-line agent and must be used with caution in this population.

We have been unable to locate any reported trials of bupropion, mirtazapine, or venlafaxine in the treatment of depression in substance-abusing patients.

6.2.4. Mood-Stabilizing Antidepressants

Among patients with bipolar disorder (BD), 60% have a history of addiction to alcohol, drugs, or both *(95)*. No adequately controlled studies of lithium or other mood-stabilizing anticonvulsants have been conducted in these patients. Most studies have had high dropout rates. Nonetheless, our clinical experience supports the value of lithium or selected anticonvulsant drug therapy for patients with BD. Once there is satisfactory control of mood fluctuations, alcoholic problems are generally amenable to substance-abuse treatment *(96)*. Brady reported the findings of an open-label trial of valproate in nine patients with comorbid BD and substance abuse. She believes that valproate is of particular value for BD II patients *(97)*. In another open-label trial of valproate in 20 inpatients with comorbid mood disorder and substance abuse, Albanese reported valproate to be both efficacious and safe, alone and in combination with other psychiatric drugs *(98)*. Hertzman reported the findings from a retrospective chart review of patients treated with valproate for comorbid substance abuse and mood disorders. He noted diminished substance use in response to treatment *(99)*. In another retrospective chart review of 204 patientswith BD I who were treated with anticonvulsant mood stabilizers or lithium, Goldberg reported that patients with BD and a history of substance abuse had a better response to anticonvulsant mood stabilizers than to lithium *(100)*. Despite the lack of well-controlled studies, these reports all suggest that lithium and the anticonvulsant mood stabilizers can be effective treating this population. The most convincing evidence for efficacy of anticonvulsants is the recent report of Johnson and associates *(101)*, who found that topiramate reduced ethanol consumption in individuals who abuse or are dependent on alcohol. These investigators proposed that a combination of enhanced γ-amino butyric acid (GABA) activity and decreased glutamatergic activity are the likely mechanisms of action. Although not approved by the FDA for alcohol dependence at this time, we have found the effects dramatic in some patients and that effective doses may be as low as 50 mg (much lower than the doses used by Johnson and colleagues). Cognitive impairment, especially difficulty word finding, may be associated with topiramate, especially at higher doses; therefore, we recommend trials of 25 to 50 mg/d for at least 2 wk prior to increasing the dose. Monitoring of cognitive function is also recommended.

6.3. Cocaine

Depression and other affective disorders have long been recognized as complications of both intoxication and withdrawal from cocaine *(102–104)*. In co-

caine users entering treatment, rates of depression as high as 47% have been identified *(105)* although a recent study has suggested that the high rate of concurrent alcohol and cocaine abuse probably complicates the analysis of cocaine-associated symptoms *(106)*.

Gawin *(102)* reported a 30% incidence of major depression and a 15% incidence of bipolar or cyclothymic disorder in chronic cocaine abusers. Depression is also common during withdrawal (crash) following a cocaine binge. Users may complain of suicidal ideation, insomnia, loss of energy, anhedonia, and loss of interest in sex. Once cocaine use has stopped, symptoms of severe depression will usually clear within 48 h. However, anhedonia may continue for months during early sobriety. Chronic cocaine use will deplete central dopamine and norepinephrine (NE). The depletion of catecholamines is thought to explain the symptoms of depression and anhedonia that typically persist for the first 3 mo of sobriety. TCAs have been suggested as treatment for the anhedonia that follows cocaine use and for drug craving owing to their ability to potentiate NE neurotransmission. Desipramine has been reported to facilitate abstinence in early recovery *(107)*, but Weiss also noted that it can trigger relapse when taken by patients who are already abstinent *(108)*. Ziedonis reported improvement in depressive symptoms and reduced cocaine use in a randomized, double-blind trial of despiramine in depressed, cocaine-abusing, methadone-maintenance patients *(109)*. In a placebo-controlled, randomized trial of imipramine as a treatment for cocaine abuse, Nunes noted minimal effect on cocaine use, except in those individual with comorbid depression *(110)*.

There have been two trials of fluoxetine in cocaine-dependent patients who were comorbid for MDD. Neither trial demonstrated a drug-related improvement in depressive symptoms or a significant reduction in cocaine use. In the previously described trial of fluoxetine in 17 depressed cocaine and alcohol-abusing patients, Cornelius noted an increase in BDI scores and worse clinical outcomes as compared with depressed alcoholics given fluoxetine *(78)*. Schmitz reported a 12-wk, placebo-controlled, double-blind study of 68 patients whose depressive symptoms decreased over time, unrelated to medication. Fluoxetine had no significant effect on their cocaine use *(111)*.

McDowell reported a successful trial of venlafaxine in a small study of depressed cocaine abusers, all of whom had been in a larger double-blind trial of desipramine and had failed to respond to desipramine or were unable to tolerate its side effects. There were significant improvements in mood in 11 of 13 patients, and all patients who completed the trial reported a greater than 75% reduction in cocaine intake *(112)*. McDowell's report on the positive effect of venlafaxine is promising, however, in nondepressed cocaine-dependent individuals, the Medication Development Research Units of the National Institute on

Drug Abuse and the Department of Veterans Affairs (NIDA/DVA) did not find efficacy for venlafaxine.

The NIDA/DVA conducted a series of clinical trials searching for a "signal" of drug efficacy in cocaine dependence *(112a)*. Several antidepressants were included in these short-term trials, including paroxetine, venlafaxine, and sertraline. By most standards, these studies would be considered negative, i.e., the drugs had no effect on cocaine use, although a slight signal was seen for sertraline in one study. In a study that included only depressed cocaine-dependent patients, nefazodone was superior to placebo in reducing cocaine use, as assessed by quantitative urinary benzoylecgognine (BE) levels *(112b)*. There is also some evidence that mood-stabilizing anticonvulsants, e.g., tiagabine or topiramate, may be effective in cocaine dependence; however, larger clinical trials of these drugs will be required to confirm this finding. In separate studies, early data on selegeline were encouraging, but larger studies do not appear to support its efficacy in cocaine dependence. Lithium has been found to be effective only in those cocaine users with clear evidence of BD *(113)*.

As Meyer noted in 1992 in his review of pharmacotherapies for cocaine dependence, most well-designed double-blind studies failed to document the efficacy of desipramine in the long-term treatment of cocaine abuse and did not support the optimistic results seen in early open trials *(114)*. More recent trials of TCAs in depressed cocaine abusers have shown improvement in depressive symptoms, but this does not consistently correlate with a decrease in cocaine use. Trials of SSRIs in this population have not demonstrated a beneficial effect on either the depression or the cocaine use. In a review of 18 trials of antidepressants for the treatment of cocaine dependence, Lima found no evidence to support the clinical use of antidepressants in the treatment of cocaine dependence *(115)*. However, depressed cocaine addicts demonstrated decreased drug use when measured by urine BE but not by self-report *(112b)*. It should be pointed out that studies using quantitative urine BE as an outcome measure sometimes find positive results, whereas studies using self report do not *(116)*.

6.3.1. Opiates

In patients addicted to opiates, symptoms of depression and anxiety are usually overshadowed by withdrawal symptoms and by the patient's character-related features. Once these patients have been detoxified or stabilized on methadone maintenance, they should be carefully evaluated for evidence of comorbid psychopathology. The lifetime incidence of any affective disease in this population is 74% *(117)*. Brooner and colleagues conducted diagnostic interviews with 716 opiate-dependent patients who had been admitted to and stabilized on methadone maintenance therapy. Almost half of these patients had

had another non-substance-related psychiatric disorder during their lifetimes, with more than one-third meeting criteria for two or more other diagnoses. They found a 15.8% lifetime incidence of major depression, which is almost three times the rate found in the general population in the ECA study. They also found a strong correlation between the severity of the substance abuse disorder and the degree of psychiatric comorbidity in these patients *(118)*. Major depression is particularly common in women seeking treatment for opiate dependence and typically precedes the development of opiate dependence. These patients should also be carefully evaluated for posttraumatic stress disorder and early childhood trauma.

Woody studied a group of depressed methadone maintenance patients and compared standard drug counseling to either supportive-expressive or cognitive behavioral therapy and showed measurable improvements with psychotherapy *(119)*. Woody also reported that doxepin was more effective than placebo in reducing depressive symptoms in a double-blind study of 35 depressed methadone-maintenance patients *(120)*. Titievsky reported similar results with doxepin in a study of 46 depressed methadone-maintenance patients *(121)*.

Other trials using other TCAs in this population were not promising. In a trial of 46 depressed methadone-maintenance patients, Kleber found that imipramine was no more effective than placebo for treating depression. He noted that both the placebo and imipramine groups showed similar levels of improvement. Kleber suspected this was caused by the intensive nonpharmacologic treatment provided to both groups by the methadone maintenance clinic *(122)*. However, in a more recent large, double-blind, placebo-controlled trial of methadone-maintenance patients with evidence of a primary MDD, Nunes reported a 57% positive response rate to imipramine in 84 patients who had been judged to have received "adequate" treatment compared with a 7% response rate in the placebo group *(123)*. These results may be explained by improved TCA dosing techniques. Since methadone has been reported to induce higher serum desipramine levels, it is now clear that TCA levels must be monitored when prescribed to patients taking methadone *(124)*.

SSRIs are attractive options for treating depression in methadone-maintenance patients because of their low toxicity and minimal abuse potential. Unfortunately, there is minimal research to support this practice. Fluoxetine has not been found to be effective in treating depressed opiate addicts in methadone maintenance. In a double-blind, placebo-controlled trial, depressive symptoms decreased over the 12-wk trial. However, there was no medication effect, even in those subjects with the most severe depression *(125)*. Dean reported similar results in 49 depressed methadone maintenance patients randomized to either fluoxetine or placebo for 12 wk. Depression and functioning improved in both groups, but no medication effect was observed *(126)*. Hamilton described a 12-

wk, placebo-controlled trial of sertraline in this population, but did not report any outcome data. He did note that sertraline may produce a modest increase in serum methadone levels during the first 6 wk of therapy *(127)*. We have not been able to locate reports describing the use of paroxetine, citalopram, or any of the newer antidepressants in this population. To date, only doxepin and imipramine have been demonstrated to be effective for treating depressed opiate addicts. However, we have had positive clinical experience using other agents, especially citalopram, in this patient group.

The presence of severe comorbid psychopathology clearly determines the outcome of opiate addiction treatment *(29,128)*. Patients with minimal psychopathology do well with standard drug abuse counseling. Patients with severe psychopathology usually get worse in a therapeutic community. They generally do better on methadone maintenance, but require skilled psychotherapists, long-term treatment *(129)*, and access to skilled psychopharmacologic therapy. Traditional psychotherapy does not help individuals with antisocial personality disorders; they will do better in a therapeutic community. Unfortunately, this form of treatment is expensive and of limited availability in many areas. Addiction treatment increases the likelihood of addicts remaining abstinent, but major depression and life crisis increase the risk for relapse *(130)*.

6.3.2. Depression and Opiate Detoxification

Depression has a significant impact on the success of detoxification from methadone maintenance. The development of depressive symptoms in patients in maintenance who are undergoing slow detoxification was associated with failure to successfully complete detoxification treatment *(131)*. These finding demonstrate the importance of careful screening for depression before and during methadone detoxification. If depressed, detoxification patients should be treated with an antidepressant to maximize their potential for successful treatment outcome. Methadone itself has been thought to have some primary antidepressant effects and to be beneficial in treating comorbid depression *(122)*. Once such patients are detoxified from methadone, it may be impossible for them to avoid relapse unless they are aggressively treated for depression.

7. TREATMENT FAILURES

The following is a list of suggestions for managing treatment failures.

1. Check plasma drug levels in alcoholics and other drug abusers who have not responded to TCAs. If plasma levels are below the therapeutic range, increase the dose. If the depression does not improve despite adequate serum levels, consider switching to a different TCA or to an SSRI. If that fails, try one of the newer antidepressants; if there is no response, try lithium.

2. Patients who fail to respond to antidepressant therapy may be drinking or using drugs again. No treatment is likely to succeed if the patient does not maintain sobriety. Depressed patients whose symptoms are secondary to a non-affective psychiatric condition (e.g., alcoholism, drug use, or an anxiety disorder) are much more likely to fail to respond to antidepressant therapy and to develop chronic symptoms *(132)*.
3. If there are repeated alcohol- or drug-abuse relapses, consider enforced treatment with disulfiram, mandatory twelve step groups, and random breathalyzer tests or drug screens, in addition to treatment with antidepressants *(133)*.
4. In alcoholics who continue to drink, consider adding an anticraving medication. Naltrexone may be helpful in patients with less severe alcoholism if they struggle with significant carving *(134,135)*. Ondansetron has also been reported to reduce drinking in early onset alcoholics *(92)*.

8. CONCLUSION

Depression is one of the most common problems seen in substance-abuse patients. Dysphoria and more serious forms of depression may persist for months or years after detoxification. Unfortunately, difficulty in the management of such "dual-diagnosis" problems has discouraged many clinicians from working with these patients. Matching these patients to appropriate types of psychiatric treatment has clearly improved treatment outcome. This requires that all substance abuse patients be carefully screened for other psychiatric disorders and that psychiatric treatment be provided, when needed, as a part of the routine treatment for addictive disorders *(136)*.

Clinicians need to distinguish carefully between substance-induced mood disorders and independent depressive disorders, and must become expert in the evaluation and management of these patients. When symptoms of depression have not cleared following detoxification, it is important to initiate antidepressant therapy, including both psychotherapy and pharmacotherapy. Major depression in substance-abuse patients will usually respond to standard antidepressant pharmacotherapy, as long as the patient is able to achieve sobriety. Except in alcoholics with bipolar affective disease, it is not clear that treating dysphoria or depression will alter drinking habits. In most patients, antidepressant pharmacotherapy alone is unlikely to reduce the use of alcohol or other drugs. Research has shown that matching such patients to both addiction treatment and appropriate psychiatric treatment will improve the outcome for both conditions. Based on available data, fluoxetine and desipramine are the current drugs of choice. However, clinical experience suggests that these patients respond to most of the standard antidepressants, as long as medications are prescribed in adequate doses and the treatment is integrated into a comprehensive substance abuse treatment program.

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7 Depressive Disorders in the Context of HIV/AIDS

Prevalence and Treatment

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CONTENTS

1. INTRODUCTION

As of June 2001, an estimated 466,023 persons were living with HIV/AIDS in the United States alone and an estimated 40 million people worldwide *(1)*. It has become increasingly clear that people living with HIV/AIDS confront many challenges in their daily lives (e.g., following a complex medication regimen and facing premature death), some of which are unique to HIV (e.g., coping with stigma and changes in sexuality) *(2–6)*.

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Although it might seem intuitive that challenges associated with HIV/AIDS would enhance vulnerability to depression for this population, a review of the literature suggests a more complex picture of the relationship between HIV/AIDS and depressive symptoms. As evidence of this, researchers have reported such widely differing rates of depressive disorders among populations of people living with HIV/AIDS that it is difficult to make any meaningful interpretation of this information. These variations in prevalence rates have been attributed to the different methodologies and assessment instruments utilized, as well as the variety of communities and subpopulations studied and the time periods in which the research was conducted. A review of this data is presented here.

2. PREVALENCE

Rates of major depressive disorder (MDD) among the general population have been estimated to be 2.2% *(7)*. Most published research indicates rates of depressive symptoms in HIV-positive populations to be significantly higher than this (e.g., 8–12%). However, the inclusion of matched HIV-negative comparison groups suggests that the relationship between HIV/AIDS and depressive symptoms may be mediated by other factors. Whereas a few researchers have observed increased rates of depressive symptoms for HIV-positive participants compared with matched controls *(13–16)*, the results of most studies in this area indicate similar rates of depressive symptoms for both HIV-positive and HIV-negative groups, suggesting that increased rates of depressive symptoms are more likely to be due to life situation and other factors, rather than HIV/AIDS per se *(17–21)*. For instance, in a study investigating rates of depression among women with and without HIV, researchers found that 57.7% of HIV-positive participants scored at or above 16 (the cutoff suggestive of clinical depression) on the Center for Epidemiological Studies-Depression Scale (CES-D) vs 55% of participants without HIV *(22)*. Results of this study further indicated that lower educational achievement, lower income, lack of social support, substance abuse, and a history of trauma exposure were associated with elevated CES-D scores. The authors suggest that these factors were likely present prior to the HIV diagnosis and speculate that depressive symptoms may be reasonably attributed to these variables, rather than to HIV/AIDS itself. Similar results have been found with samples of intravenous drug users *(23–25)* and gay/bisexual men *(26–28)*, two populations in which elevated rates of depression have been noted (e.g., *29,30*).

To better understand these findings, meta-analytic techniques have been employed to assist in determining whether a modest difference in prevalence might exist that had not been detected by the small sample sizes used in single studies *(31)*. Researchers aggregated data from 10 studies published between 1988 and 1998. Criteria for study inclusion were the use of an HIV-negative

comparison group, use of diagnostic interviews (rather than paper-and-pencil screening instruments), report of current rates of MDD and/or dysthymia, and recruitment of participants not exclusively through the mental health system.

The results of these analyses suggested that participants with HIV/AIDS were 1.99 times more likely to be diagnosed with MDD than their HIV-negative counterparts. Across studies, 9.4% of participants with HIV/AIDS were diagnosed with MDD, as compared with 5.2% of HIV-negative participants. This translated to an average weighted effect size of 0.69, characterized as a moderate to large difference. Similar results were not found for dysthymia, indicating that people with HIV/AIDS are not more likely to meet criteria for this disorder, as compared with HIV-negative comparison participants.

These results, along with the results of other studies, suggest that prevalence rates of depression are somewhat higher among people living with HIV/AIDS, as compared with people without HIV. However, the mixed findings across studies are important to note. Researchers are also beginning to better understand some of the factors that may mediate the relationship between HIV/AIDS and depression. A summary of this research is presented here.

2.1. Subpopulation Differences

One factor that appears to be associated with differential prevalence rates is the subpopulation sampled. For example, researchers investigating depressive symptoms among disenfranchised women of color are likely to find much higher rates of depression than those studying educated, middle-class gay/bisexual men. Subpopulation differences such as this highlight the need for researchers to include HIV-negative matched comparison groups in their sampling.

The method of recruitment for study inclusion may also be important. For instance, several authors reported using newspaper advertising, posting flyers and brochures at local service organizations, or both. Participants who take the initiative to contact research staff after seeing posted information are likely to be qualitatively different from those who agree to participate after being approached in a clinic waiting room while waiting to see a medical provider. It is reasonable to speculate that participants recruited through the former methods might have more energy, feel less hopeless and anhedonic, and, hence, less depressed.

2.2. Cohort Effects

Also emerging is an interesting cohort effect for rates of depression among HIV-infected populations found after the introduction of antiretroviral therapies (Highly Active Antiretroviral Therapy [HAART]).

Research conducted before the availability of HAART was more likely to indicate significantly higher rates of depression compared with studies conducted after this time *(32–35)*. In a recent study, researchers assessed participants

over a 9-mo period and investigated the association between changes in viral load and depressive symptoms, finding that a decrease in viral load was associated with a "clinically meaningful" decrease in depression *(36)*. Although not all participants in this study were being treated with antiretroviral medications, the use of such medications often results in a comparable decrease in viral load; thus, this information provides insight regarding the observations that might be observed in individuals taking HAART.

The reasons for this cohort effect, noted in this and other studies, are unclear at this time, although many investigators have speculated that the widespread optimism that accompanied the introduction of HAART may have fueled increased hopefulness about living with HIV/AIDS and decreased rates of depression *(33,37,38)*. Other theories include the decreased incidence of opportunistic infections and improved quality of life accompanying HAART*(32,37)*, as well as a direct effect of antiretroviral medications, although the mechanisms for this have not been identified *(37)*. Finally, it is important to consider an important epidemiological change in HIV infection that has occurred over the history of the epidemic. Research conducted in the early years of the epidemic primarily assessed samples of gay/bisexual men, a population for which rates of depression have also historically been noted *(29)*. More recent studies, however, have been more likely to use samples of people infected via heterosexual transmission, where rates of depression may not be inherently as high. Therefore, it has been suggested that shifts in rates of depression may be attributable to this shift in populations *(33,37)*.

3. FACTORS ASSOCIATED WITH DEPRESSIVE SYMPTOMS

A number of researchers have attempted to identify situational and other factors associated with depressive symptoms for people living with HIV/AIDS. As with research attempting to clarify prevalence rates, this body of work has yielded mixed results. Only a small handful of these factors have been consistently linked with symptoms of depression.

The presence and/or severity of physical symptoms (HIV/AIDS-related or not) appears to be most consistently associated with depressive symptoms in this population *(38–44)*. Fairly consistent associations have also been found for functional limitations *(10,45–47)*, perceived lack of social support *(9,18,26,43,45,48)*, lack of employment and/or income *(8,9,22,25,46,49)*, and history of trauma exposure *(12,22,49)*.

Other factors have been found to be more inconsistently associated with depressive symptoms among people with HIV/AIDS, in particular CD4 cell count and viral load, which have been found by some researchers to be related to depressive symptoms *(9,21,35,36,50)* but not by others *(14,15,35,38,46,51)*.

Similarly, some researchers have noted an association between depressive symptoms and substance abuse (both current and/or recent use as well as lifetime history of substance abuse or dependence), whereas others have found no such association *(22,39,46,49,52)*. There is evidence to suggest that intravenous drug use in particular may be more consistently and strongly associated with depression *(9,13,22,53,54)*.

Of note, there are also now some consistent data suggesting the lack of an association between depressive symptoms and other factors in this population. For instance, many researchers have noted no association between depressive symptoms and gender *(40,46,50,55–58)*, a finding which is compelling given increased rates of depression for women, as compared with men, found in the general population *(59)*.

3.1. Methodology and Assessment Instruments

Variations in prevalence rates may also reasonably be attributed to methodological differences across studies, including differences in the methods and instruments used to assess depressive symptoms. The majority of published studies in this area are based on data obtained from brief screening instruments, primarily the CES-D, Beck Depression Inventory (BDI), Profile of Mood States (POMS), Hamilton Rating Scale for Depression (HAM-D), and the Depression Subscale of the Hospital Anxiety and Depression Scale. These inventories are advantageous for many reasons, including ease of administration, the brief time period needed to complete them, and low cost. However, because these instruments were developed for use as brief screens, they are appropriately oversensitive in identifying people who *may be* experiencing symptoms of depression. Therefore, endorsement of symptoms on these instruments should not necessarily be interpreted as indicating the presence of depression in the absence of more thorough information, such as can be obtained by clinical interview.

A criticism of the use of these instruments for people with HIV/AIDS specifically is the difficulty in interpreting the endorsement of somatic/vegetative symptoms. Items reflecting fatigue, lack of energy, appetite, or sleeping changes—commonly endorsed by people with depressive disorders—may also be direct manifestations of HIV/AIDS or of medications used to treat HIV/AIDS. Therefore, the etiology of these symptoms is difficult to understand without further clarification. To address this problem, researchers have offered several recommendations, such as omitting the somatic/vegetative items altogether or conducting follow-up clinical interviews to more closely examine the etiology of these symptoms.

Kalichman and colleagues *(60)* conducted a study designed to compare the efficacy of the BDI and CES-D in assessing depressive symptoms for people

with HIV/AIDS. They also compared the shortened versions of these scales, with the somatic/vegetative items removed, against the full-scale versions. The authors noted that 31% of participants met criteria for moderate depression on the full-scale versions of both measures, compared with only 21% when the somatic/vegetative items were removed. Furthermore, although absolute prevalence rates were identical, the authors observed very poor correspondence between the BDI and CES-D, with only 50% of participants categorized in the same way (i.e., depressed or not depressed) on both measures. The degree to which one scale could be recommended over the other could not be determined on the basis of this study, owing to the lack of a more thorough diagnostic interview to corroborate a true diagnosis of depression. However, the authors cautioned that the use of multiple measurements of depression is always important for greater confidence in diagnosis, and that the greater specificity in measurement to be gained by removing somatic/vegetative items must be weighed against the loss of sensitivity in detecting depression *(60)*.

An alternative to screening instruments is the use of structured interviews, such as the Structured Clinical Interview for *DSM-IIIR/IV* (SCID), the Diagnostic Interview Schedule, and the Composite International Diagnostic Interview. The primary advantage of structured interviews such as these is the availability of more detailed information about participants' experience of symptoms, and thus greater confidence in making differential diagnoses. Although identifying the etiology of specific symptoms (e.g., identifying whether fatigue is a direct effect of HIV, side effects of medications, or endogenous depressive disorder) often remains difficult, establishing the temporal onset of symptoms through the use of clinical interviews can aid greatly in diagnosis. However, despite their utility, these interviews can be costly in terms of training interviewers, the amount of time needed for assessments, and time needed for scoring and interpretation.

Although no data yet exist to demonstrate differences in prevalence rates obtained by use of screeners vs structured interviews, it is clear that the use of one or the other, as well as the decision to include somatic symptoms in consideration of diagnosis, can greatly affect the rates of depressive disorder detected in a sample under investigation. As evidence to this, researchers of one study of HIV-positive participants conducted "standard psychiatric interviews" with all participants who endorsed enough symptoms on the BDI to meet the standard cutoff *(14)* suggestive of depression *(55)*. They observed that of the 83 participants scoring at or above this cutoff, only 33 (39.8%) met criteria for a clinical disorder (including, although not limited to MDD) based on information obtained during the follow-up diagnostic interview. Therefore, it seems reasonable to speculate that prevalence rates based on studies utilizing diagnostic screeners are likely to be significantly higher than those based on studies utilizing structured clinical interviews. It should be noted, however, that a cutoff score of 14 on the BDI is suggestive of mild to moderate depression and

that a higher, more conservative cutoff score might be more closely associated with rates of identified depression obtained by clinical interview.

4. IMPORTANCE OF TREATMENT

Regardless of exact prevalence rates, it is imperative that clinicians recognize and treat depressive symptoms experienced by people living with HIV/AIDS. Investigators have reported a strong association between depressive symptoms and decreased quality of life among people living with HIV/AIDS *(9,47,49,61)*. Additionally, although the data is unclear at present, depressive symptoms among people with HIV/AIDS have also been associated with decreased CD4 counts and increased viral load by some investigators. These changes in health parameters may contribute to observations of decreased longevity and increased mortality rates *(49,62)*, although not all researchers have found evidence of an association between depression and survival rates *(e.g., 63)*.

Severity of depression may also be an important predictor of longevity among people living with HIV/AIDS. In one study *(41)*, researchers assessed women over a 7-yr period, characterizing them as having either limited or no depressive symptoms, intermittent symptoms, or chronic symptoms, based on CES-D scores. By the end of the study period, 8% of the women with limited or no depressive symptoms had died, compared with 16% of the intermittent group and 23% of the chronic group. The authors statistically controlled for factors that may have mediated this association, including baseline CD4 count and viral load, presence of HIV-related symptoms, use of HAART, age, and employment, and still found that those women with chronic symptoms of depression were twice as likely to have died than those with limited/no symptoms. This association was more pronounced for participants with lower CD4 counts, as indicated by the finding that for women with baseline CD4 counts of 200 cells/mm^3 or less, 54% of those with chronic depressive symptoms and 48% with intermittent symptoms died, compared with 21% of those with limited or no symptoms.

There is also compelling evidence to suggest that depressive symptoms can impact adherence *(46,47,64,65)*. Although this finding is based only on correlational data and the specific mechanisms of this association are unknown, the ways in which specific depressive symptoms (e.g., lack of energy, fatigue, hopelessness) may contribute to decreased rates of adherence to healthcare behaviors is perhaps easy to understand. It is also reasonable to speculate that the association between depressive symptoms and decreased adherence might contribute to effects of depression on longevity and health. Finally, there is evidence to indicate that depressive symptoms are associated with high-risk sexual and drug-use behaviors *(22,66)*; suggesting that failure to address and treat depression can contribute to more rapid declines in health and increased spread of HIV.

5. TREATMENT OF DEPRESSIVE SYMPTOMS

As with depression in any other population, treatment for people with HIV/AIDS primarily consists of psychotropic medications, psychotherapy, or a combination thereof. These are discussed in turn.

5.1. Psychotropic Medications

Before discussing the psychopharmacological treatment of depression in HIV/AIDS, it is important to briefly discuss the pharmacological treatment of HIV/AIDS more broadly. In recent years, a regimen of three or more antiretroviral medications has become the medical standard of HIV care. These regimens, referred to as HAART, typically consist of a protease inhibitor (PI) or a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI), as well as two nucleoside-analogue reverse transcriptase inhibitors. These combinations are found to be significantly more effective than treatment with a single medication, as several steps in the HIV life cycle are targeted *(67).* Some have speculated that HAART treatment in and of itself may actually reduce depressive symptoms. Researchers conducting a 2-yr longitudinal study in Australia found an overall decrease in depressive symptoms with a temporal relationship to changes in HAART *(33)*. Similarly, the results of a 3-mo pilot study in the United States involving 70 patients showed that PI naïve patients started on HAART regimens had significant improvement in symptoms of depression after 1 mo of treatment *(32)*. These findings require duplication in larger controlled studies, but indicate that HAART may be important for psychological, as well as physical, health. One aspect of HAART complicating treatment is that a greater number of medications increases the potential for drug–drug interactions. A further difficulty is that antiretroviral medications have side effects that often produce psychiatric symptoms. For example, fatigue, anxiety, depression, and confusion are all common side effects of HAART medications, which can certainly complicate diagnosis and treatment of patients on these regimens *(68)*.

5.2. Hepatic Cytochromes P450

Drug–drug interactions occur primarily as a result of competition for the catalytic enzyme system responsible for the metabolism of drugs in the liver. This system, referred to as the cytochrome P450 (CYP) isoenzyme system, prepares substances for elimination via oxidation and reduction mechanisms. There are five cytochrome isotypes of importance to the metabolism of psychotropic and antiretroviral medications: CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Two of these are especially important, because together they metabolize approx 75% of all medications: CYP3A, accounting for 50% of drug metabolism, and CYP2D6, accounting for 25% *(68)*.

Medications interact with the enzyme activity of the CYP system in three ways: competition with other enzyme substrates, direct inhibition, and induction. Thus, the blood level of enzyme substrates can increase if the activity of a particular enzyme is reduced, either by competition or inhibition. This could potentially lead to toxicity or increased side effects. Conversely, blood levels of substrates can decrease if enzymatic activity is induced, leading to decreased medication efficacy *(68)*.

Reports in the medical literature of adverse events and side effects of psychotropic medications for people living with HIV/AIDS can be useful in the selection of treatments. However, important limitations in these studies should be noted. For example, studies were generally conducted using relatively asymptomatic patients, were often restricted to adult men, and were conducted before use of combination antiretroviral therapy. Another limitation of these studies is that liver disease, particularly hepatitis C, is becoming an increasingly common comorbid condition *(67)*. The concomitant baseline liver impairment associated with hepatitis C creates a more complicated presentation in which to determine appropriate antiretroviral treatment regimens.

5.3. Antiretroviral Medications

Among antiretroviral medications, protease inhibitors impact the cytochrome P450 enzyme system to the greatest extent, in vitro and clinically. Many PIs are powerful inhibitors of the isoenzyme system. Ritonavir has the strongest in vitro inhibition and decreases the activity of isoenzymes 3A, 2D6, 2C19, and 2C9 *(66)*. As most psychiatric medications are metabolized through these pathways, ritonavir may profoundly affect the efficacy of psychotropic medications that are concurrently prescribed. For example, desipramine levels have been shown to increase 145% in vitro when coadministered with ritonavir *(67)*. Indinavir causes intermediate inhibition, decreasing isoenzymes 2D6 and 3A. The weakest inhibition is produced by saquinavir and nelfinavir, which affect 3A and 2C9 *(68)*. However, significant clinical effect can still occur, as prolonged sedation caused by concomitant administration of saquinavir and midazolam has been found *(67)*.

5.4. Tricyclic Antidepressants (TCAs)

TCAs are metabolized primarily by the 2D6 pathway. Thus, increased blood levels of TCAs can occur if prescribed concurrently with ritonavir or other PIs. Unlike the selective serotonin reuptake inhibitors (SSRIs), TCAs have a narrower range of safety in blood levels. It can be critical to monitor side effects, including delayed cardiac conduction, orthostasis, urinary hesitancy, and dry mouth. Monitoring of blood levels as well as electrocardiogram results is strongly recommended *(69)*.

5.5 SSRIs

SSRIs are generally better tolerated than the TCAs. SSRIs are also metabolized mainly through the 2D6 pathway. Some are also inhibitors of this pathway, but to a lesser extent than ritonavir. Thus, when coadministered with ritonavir, SSRI blood levels may increase. SSRIs are well tolerated across a broad range of blood levels, however, so adverse reactions from this inhibition appears to be minimal. Nonetheless, clinicians may prescribe SSRIs at lower doses if coadministered with PIs and might choose to closely monitor for adverse effects, such as serotonin syndrome *(68)*. Citalopram is an exception to this general rule, as no adverse events have been reported between this medication and PIs. Citalopram has minimal inhibition on the cytochrome system and therefore may be particularly useful in patients taking multiple medications *(67)*. Schwartz and McDaniel *(70)* presented the results of a double-blind comparison study of fluoxetine and desipramine in the treatment of depressed women with HIV/AIDS. Although the small sample size limits the statistical power, the results indicated that participants experienced a decrease in depressive symptoms *(70)*. Another randomized, placebo-controlled trial compared paroxetine with imipramine. Both medications were found to be significantly more effective than placebo, although there were significantly more dropouts owing to side effects for those taking imipramine, compared with those in the other medication conditions. However, the small sample size and high attrition rate observed in this study warrants replication *(71)*.

5.6. Other Antidepressants

Nefazodone is a potent inhibitor of CYP3A. PIs react with nefazodone to produce synergistic inhibition of this pathway. Potentially dangerous interactions exist with the antihistamine astemizole, the gastric motility agent cisapride, and the antipsychotic pimozide. All of these agents may cause increased rates of cardiac arrhythmias. Other important interactions produced by inhibition of CYP3A involve benzodiazepines resulting in respiratory depression, clozapine leading to seizures, ergot alkaloids producing systemic vasoconstriction, and sildenafil with potential for priapism *(68)*. Elliott and colleagues *(69)* reported an open trial of nefazodone in 15 depressed HIV-infected patients. Of these, 73% were classified as full responders. Only one dropped out in response to a drug interaction with ritonovir causing headache, confusion, dizziness, and anxiety *(69)*. Venlafaxine has been reported to decrease the concentration of indinavir. Because a decrease in the concentration of PIs can affect efficacy and lead to viral resistance, it has been recommended that venlafaxine be avoided in individuals for whom indinavir is prescribed *(67)*. Buproprion was initially thought to be metabolized through the 2D6 isoenzyme pathway. As ritonavir strongly inhibits

this pathway and buproprion presents a dose-dependent risk for seizures, buproprion is commonly listed as contraindicated for patients taking PIs *(68)*. However, recent studies show that buproprion is metabolized through the 2B6 isoenzyme and is no longer considered contraindicated with ritonavir *(67)*. Mirtazapine has no reported adverse events with HIV medications. It may be especially useful for patients with insomnia and anorexia, as it tends to be sedating and promotes increased appetite *(67)*.

5.7. Psychostimulants and Other Somatic Treatments

Other agents, including dextroamphetamine and testosterone, have been tested in placebo-controlled trials for treatment of depression. Both have produced improvement with minimal side effects *(72)*. Ferrando and colleagues *(73)* reported findings of a placebo-controlled trial of dextroamphetamine in 23 men with HIV/AIDS. In this study, 73% of study completers assigned to dextroamphetamine responded to treatment (based on HAM-D, BSI, and Beck Hopelessness Scale scales), compared with only 27% taking placebo *(73)*. The use of electroconvulsive therapy (ECT) with people living with HIV/AIDS has not yet been thoroughly evaluated. However, a published article presented information about four depressed patients with HIV/AIDS who had been treatment refractory to pharmacotherapy and were found to benefit significantly from ECT *(66)*.

5.8. Alternative Therapies

Limited data exist on the efficacy of alternative agents for the treatment of depression in HIV. However, there is one published report of the use of St. John's wort, which induces the 3A isoenzyme. The authors of this study reported that use of St. John's wort dramatically reduced the level of indinavir. Of note, the FDA has also issued a public health advisory that use of St. John's wort with PIs and NNRTIs is not recommended *(67)*.

In summary, depression is a common comorbid illness in HIV infection, but is also highly responsive to psychotropic medication. In considering the use of antidepressant treatment, HAART regimens, the potential for drug–drug interactions, and CYP450 isoenzyme pathways should all be considered and can be helpful in selecting appropriate medications in order to minimize adverse effects and maximize therapeutic benefit.

6. PSYCHOTHERAPY

In contrast to research on the efficacy of psychotropic medications for people living with HIV, research on the efficacy of psychotherapy for depressive symptoms in this population is somewhat sparse at this time. Thus far, a review of the literature suggests that people with HIV/AIDS respond to treatment in much the

same way as people without HIV/AIDS. However, some important differences have been noted and are described later in this chapter.

Only a very small number of studies investigating the effectiveness of cognitive-behavioral interventions (CBT) in treating depressive symptoms in people with HIV have been published. Of note, researchers in the majority of these studies excluded participants who met criteria for a current or past psychiatric disorder, including MDD, and none of these studies restricted participation to people meeting criteria for a depressive disorder. Thus, the degree to which these results are helpful in providing insight for the efficacy of CBT for people who do meet criteria for a depressive disorder is unknown at this time.

Researchers in one study described their participants as experiencing "significant psychosocial distress," although not all participants were found to meet criteria for a depressive disorder, based on interviews using the SCID (39% met criteria for MDD and 36% met criteria for an adjustment disorder) *(74)*. Participants were referred to a consultation-liaison psychiatry department and given the opportunity to participate in a 16-wk CBT group, including components of progressive muscle relaxation, problem-solving skills training, modification of cognition, and education about HIV and mental health. Although there was no control group against which to compare results, the authors report a significant decrease over time on BDI scores [$F(3,114) = 17.837$; $p = 0.000$], changing from a mean baseline score of 20.1 (8.7 to 13.2) 7.2 at the end of the intervention. This decrease was maintained at follow-up 3 mo later, with a mean BDI score of 13.6 (7.3). Although these results appear to be clinically as well as statistically significant, the absence of a control or comparison group does not allow for ruling out history effects.

Lutgendorf and colleagues *(75)* report the results of a CBT stress management intervention, which included didactics, stress management, group discussion, and 45 min of formal relaxation exercises. The intervention was conducted in a group format over a 10-wk period. The authors report a significant group-×-time effect, with BDI scores for intervention participants decreasing from a mean baseline score of 10.38 to a score after intervention of 7, whereas scores were unchanged for control participants. While statistically significant, the clinical meaningfulness of this relatively small change is unclear. It should also be noted that the initial mean baseline score was within the "nondepressed" range, although the authors note that scores were most likely to decrease for those initially presenting with more symptomatology.

Inouye and colleagues *(76)* provided a similar CBT intervention, providing 14 sessions over 7 wk. The authors report treatment effects for overall mood, anger, and confusion, and a decrease in depressive symptoms for all participants from before to after intervention (all based on POMS scores). However, a decrease in depressive symptoms was also noted for participants in the control condition, and

no significant differences were noted by condition. This is perhaps not surprising, given that other studies also had participants who did not exhibit elevated depression scores prior to the intervention.

The effect of CBT has also been investigated in a sample of incarcerated women *(77)*. This study had the advantage of a much larger sample size 87 intervention participants and 52 waiting-list control participants). Striking intervention effects on BDI scores were observed for participants receiving the intervention, which decreased from a mean of 39.5 before the intervention to 17.6 after the intervention. The authors attributed this decrease to the history of marginalization these women had experienced, stating that their participation in this study was, in many cases, the first time they had had consistent therapeutic assistance. Two considerable methodological problems were noted, however, both resulting from constraints of the jail system. First, they were unable to ask women to provide their HIV status. Although some women voluntarily disclosed their status, not all did; thus, the number of participants who carried an HIV diagnosis was unclear, as was the degree to which this could be described as a study of women with HIV. Second, researchers were unable to randomly assign participants to intervention conditions, further complicating their ability to interpret these results.

Although not described as CBT, Pomeroy and colleagues *(78)* provided a 10-wk "psychoeducational intervention," including components of education, emotional support, activity scheduling, and coping skills. The authors report a significant intervention effect, with BDI scores for intervention participants decreasing from 25.63 (moderate to severe range) before the intervention to 17.13 (mild to moderate range) after the intervention. In contrast, scores for control participants remained virtually unchanged. Although these results indicate that this treatment package effectively reduced symptoms of depression, it should be noted that participants were not randomly assigned. Instead, the first 10 eligible participants were assigned to the intervention and the next 6 were assigned to the control condition. The small sample size should also be noted.

Finally, the results of one published study on the efficacy of behavioral interventions (guided imagery and relaxation) on depressive symptoms indicate that these techniques were not beneficial for participants with depressive symptoms, based on CES-D scores *(79)*.

Researchers have also begun to compare the efficacy of different approaches to psychotherapeutic treatment of depressive symptoms for people living with HIV/AIDS. In one study, 20 gay men with either MDD or adjustment disorder were randomly assigned to receive either structured group therapy with fluoxetine or group therapy alone *(80)*. After 6 wk of treatment, improvements on HAM-D scores were observed for both groups, with no differential effects, suggesting that fluoxetine was not associated with enhanced symptom reduction over and above that which was associated with group therapy.

Markowitz and colleagues (81) reported the results of a study designed to compare CBT, interpersonal therapy (IPT), supportive therapy (ST), and supportive therapy with imipramine (SWI), a TCA. Investigators randomized 101 participants who were HIV-positive, scored 15 or above on the HAM-D, and were judged on the basis of clinical interview to be depressed (although only 53% met criteria for current MDD) to one of the four treatment conditions. Each intervention lasted 16 wk. A significant decrease in both BDI and HAM-D scores was noted for all groups, but more striking improvements were observed for the IPT and SWI groups. CBT, in contrast, did not result in gains that were significantly better than those of ST alone, suggesting that for this sample of participants, (there was) "... no advantage for CBT beyond so-called 'nonspecific' psychotherapy effects" (i.e., ST).

The authors of the same study also examined data on the differential effects of treatment on depression remission—operationally defined by a HAM-D-17 score of 6 or below. Statistically significant differences across groups were not found, although there was a trend that mimicked the statistically significant results obtained for general symptom reduction, with 50% of the SWI participants achieving remission and 46% of the IPT participants, followed by 30% of the CBT participants and 21% of participants receiving SP. Similar results were found when the data on study completers alone were analyzed. The authors speculated that IPT may have been a better fit for these patients, given the high prevalence of negative life events they had experienced. The authors stated that "CBT ... addresses patients' exaggeration of hopeless thoughts, a relatively disadvantageous stance in treating patients with objectively negative life events. Even with optimistic cognitive restructuring and refocusing, CBT may fit HIV patients' situations less well." The efficacy of an IPT approach to depressive symptoms in people with HIV is promising and in need of future study.

The results of this same study also provided information suggesting differential effects by ethnicity. Specifically, the authors found that scores on both the BDI and HAM-D increased among African-American participants receiving CBT, whereas they decreased among African Americans receiving all other forms of therapy (i.e., IPT, ST, and SWI). Mean BDI and HAM-D scores decreased among all participants of all other ethnic groups who received CBT (82). The authors caution that the sample size was small, especially after it was broken down into ethnic groups, and that they had not hypothesized this difference a priori. Although the therapists for the CBT group were Caucasian, no cross-ethnic difficulties were noted. Similarly, no differences on the Working Alliance Inventory—designed to measure participants' perceptions of rapport with treatment providers—were found. The authors speculated that CBT may be a worse fit for African Americans with HIV/AIDS, and given the disproportionate rate of infection in this group, future research in this area is warranted.

6.1. Combination Treatment

Researchers have also begun to investigate the efficacy of combining antidepressant medication and psychotherapy. For instance, Avants and colleagues *(83)* provided 12 wk of twice-weekly group therapy for HIV-positive cocaine- and opioid-dependent participants. The psychotherapy component included case management and cognitive remediation strategies, with an emphasis on health promotion and risk reduction. Participants were also prescribed opiate or cocaine anticraving medication (buprenorphine) along with an antidepressant (bupropion). Comparison group participants received only standard methadone treatment. Although the sample size was quite small ($n = 6$) and participants were not randomly assigned to conditions, the authors reported a significant time-x-condition interaction, whereby the BDI scores for intervention participants improved (mean: 19.8 [SD = 13.2] before treatment and 8.0 ([SD = 5.7] after treatment), whereas scores for comparison participants worsened (13.9[SD = 9.5] before treatment and [SD = 12.0] after treatment) [$F(1, 12) = 9.57$; $p < 0.009$].

Lee and colleagues *(84)* presented similar results after providing 5 mo of CBT group therapy for depressed HIV-positive gay men. A subset of participants also received antidepressant medication. Postintervention data indicated a significant decrease in BDI and HAM-D scores. Specifically, the authors reported a decrease in HAM-D scores by more than 50% for one-third of participants and for two-thirds of participants on the BDI. However, the authors did not include a control or comparison group, making it difficult to attribute these differences to the intervention with a high degree of confidence. Given this—as well as the lack of control of medication use and the fact that participants who did take antidepressant medications initiated them at different time points throughout the intervention—interpretation of these results is limited.

Zisook and colleagues *(85)* attempted to investigate the effect of a supportive and educational group therapy intervention in combination with either fluoxetine (an SSRI) or placebo, and reported a significant decrease in depressive symptoms for participants receiving fluoxetine. They further reported increased gains for participants with more severe baseline depression scores (≥24 on the HAM-D), as well as a lack of significant improvement for those with baseline depression in the mild range. The authors also observed that fluoxetine was very well tolerated by this sample and that participants experienced very few difficulties with side effects, indicating that this is likely to be a good selection for treatment.

Finally, Savard and colleagues *(86)* employed a time-series design to investigate the effect of fluoxetine and cognitive therapy on participants when provided either in combination or sequentially (with fluoxetine given 8 wk prior to the initiation of psychotherapy). All participants met SCID criteria for MDD. Although the sample size was quite small ($N = 6$), improvements in depressed

mood were observed for four of the six participants, increased activity levels for three of the participants, and increased interest in activities for five of the participants. What is perhaps the most significant contribution of this study, however, is that the study design allowed researchers to examine both the combination and timing of treatment that might be most efficacious. Researchers observed that participants who received fluoxetine first and were given time to adjust to the medication before initiating psychotherapy exhibited a more significant decline in depressive symptoms compared with those who initiated both treatments simultaneously. The data also suggested that combination treatment (fluoxetine and cognitive therapy) was more efficacious than fluoxetine alone. Again, the small sample size necessitates that these results be interpreted with caution.

Several comments can be made about this body of research as a whole. First, although the number of these studies is small, their results suggest that psychotherapeutic treatments can be efficacious in reducing symptoms of depression and appear quite promising. However, it is clear that replications, with larger samples, inclusion of control or comparison groups, and inclusion of participants who are, at baseline, exhibiting clinically significant depressive symptoms, is critical for us to begin to better understand the utility of these interventions. The fact that many of these interventions are provided as treatment "packages" also makes it difficult to dismantle the effective aspects of these interventions. It is also noteworthy that the vast majority of these studies included only adult men; thus the efficacy of these interventions in women and children or adolescents is much less well understood.

Based on this and other research, investigators are beginning to offer specific suggestions regarding components that should be incorporated into interventions for people with HIV/AIDS who are exhibiting depressive symptoms. Given that many patients present for care with a lack of knowledge about the disease process, the importance of care, and methods for maintaining their health, education about these topics can be quite important for improving motivation and empowering them to take control of their care and well-being.

It is also clear that treatment of any kind should be sensitive to ethnicity and culture, taking into account the cultural traditions and beliefs that may impact the participants' ability to benefit from intervention and/or apply the skills and information to their "real lives." For instance, authors of one study observed that religious beliefs and practices were associated with increased symptoms of depression in Puerto Rican participants, whereas it was associated with decreased depressive symptomatology in African-American and Caucasian participants. The authors speculated that this might be attributed to Puerto Rican religious beliefs of shame and punishment for sin. Puerto Rican women in particular may be especially vulnerable to feelings of shame related to sexual transmission.

Therefore, interventions emphasizing activities such as HIV status disclosure to the patients' social support network may be countereffective *(87)*.

Finally, it is clear that interventions with people living with HIV/AIDS must be of a supportive nature, acknowledging and normalizing the difficulties inherent in living with this disease. Treatment should also be flexible and tailored to each individual person to every extent possible. Encouragement and support for adhering to antiretroviral medications, following through on other healthcare activities, communicating with treatment providers, and avoiding high-risk behaviors is also crucial. Use of psychotropic medications should be accompanied by a careful consideration of possible drug–drug interactions and alternative substances, as well as consideration of each patient's ability to tolerate side effects and manage their regimens.

Despite the potential efficacy of treatment, it is clear that many people experiencing depressive symptomatology are not accessing care. Many reasons for this have been offered, including the patient's failure to recognize his or her own symptoms as those of depression, failure to report such symptoms to providers, lack of resources necessary for accessing care (e.g., childcare, transportation, insurance), and inaccessibility of mental health treatment, particularly in rural areas *(9,52,53,87–89)*. Evidence also suggests that providers may perceive depressive symptoms to comprise a "normal" reaction to HIV and may not believe that it warrants treatment *(53)*. The short duration of medical consults and lack of training in assessing psychological symptoms may also contribute to this problem.

However, it is clear that screening for these symptoms can be quite important, because it is effective in identifying patients who may be experiencing depression and can be easily incorporated into routine health care visits. Health care providers should be strongly encouraged to not consider depression in relation to HIV as "normal" and to encourage their patients to access treatment as appropriate. There are also data to suggest that patients who do not respond to HAART as hoped may be in particular need of support and encouragement. One group of researchers have found that failure to respond to these regimens is associated with more negative beliefs about the effectiveness of treatment and health care *(36)*.

In summary, although most people living with HIV/AIDS do not meet diagnostic criteria for a depressive disorder, depression and depressive symptoms appear to be commonly experienced by this population. Although some evidence indicates that depression is associated with decreased longevity and increased mortality rates, the strength of this association—as well as potential mediators—remains unclear. It is clear, however, that depressive symptoms impact quality of life, influence compliance with medical regimens, and increase the practice of risk behaviors that can compromise health and contribute to further transmission

of HIV. Depressive symptoms have been shown to be highly amenable to treatment, responding to both psychotropic medications and psychotherapy, and leading to improved quality of life, making this a critical component of care.

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8 Diagnosis and Treatment of Depression During Pregnancy and Lactation

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CONTENTS

1. INTRODUCTION

The biological, psychological, and social changes that occur during pregnancy make many women susceptible to developing depressive symptoms and experiencing dysregulation of mood *(1)*. Although pregnancy has commonly been considered a time of emotional well-being, recent data indicate that 10% of women of

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childbearing age experience clinically significant depressive symptoms, and those with a history of major depression are at a greater risk for recurrent episodes, particularly if antidepressant medication is discontinued *(2–4)*. With a substantial number of women with depression seeking treatment prior to conception, throughout their pregnancies, and during the postpartum period, clinicians treating women of childbearing age are faced with the significant challenge of balancing maternal health and fetal safety. Although the emergence of depressive symptoms among women of childbearing age is relatively common, there is little information available to use to educate patients and families and insufficient reports to guide the actions of treating physicians *(4,5)*. The Committee on Research on Psychiatric Treatments of the American Psychiatric Association recognized the need for more clinical studies and characterized the treatment of depression during pregnancy as a priority for further investigation *(6)*. The information that has accumulated from initial studies and clinical experience provides the groundwork for the development of a system of clinical guidance designed to assist physicians with the pharmacotherapy of depression during pregnancy and in the postpartum period.

2. PREVALENCE AND COURSE OF DEPRESSION DURING PREGNANCY

A study conducted by the World Health Organization and the Harvard School of Public Health found unipolar depression to be the leading cause of medical disability throughout the world; among women aged 15 to 44, unipolar depression was found to be the leading cause of medical impairment *(7)*. Additional evidence from the National Comorbidity Survey and the Epidemiological Catchment Area Study indicates that the lifetime prevalence of unipolar depression was between 1.7 and 2.7 times greater for women than for men, with average age of onset during childbearing years *(8–10)*. Depending on patient demographics and differences in methodology, studies have generated results indicating that between 10 and 20% of women are at risk for developing symptoms of depression during their lifetime *(11,12)*. Reproductive events such as conception, miscarriage, and stillbirths have been shown to precipitate numerous psychiatric disorders, including major depression *(13)*. The risk for major depressive disorder (MDD) during pregnancy increases with prior history of depression, maternal youth, maternal isolation, insufficient social support, marital discord, and ambivalence about the pregnancy *(5,14–16)*.

It has also been demonstrated that between 3 and 8% of women experience severe dysphoric symptoms during the premenstrual phase of the menstrual cycle and meet research diagnostic criteria for premenstrual dysphoric disorder (PMDD), which has been identified as a major risk factor for depression during pregnancy and during the postpartum period *(17)*. The recurrent physical and

emotional symptoms occurring during the late luteal phase of the menstrual cycle often predict the occurrence of mild to moderate depressive symptoms during gestation and postpartum. Women diagnosed with PMDD who also have a history of MDD face a 30 to 70% likelihood of experiencing symptoms of MDD during pregnancy and are thought to be at an increased risk for a subsequent major depression during the postnatal period *(17)*. Following 12% of all pregnancies, women experience symptoms meeting the research diagnostic criteria for depression during the postpartum period, indicating that continuation of treatment may be required after delivery.

A 2001 study monitoring the prevalence of psychiatric disorders in a random gynecological population of more than 1000 women found that 10.1% of patients met diagnostic criteria for major depression and 12.4% experienced symptoms of minor depression *(13)*. Despite the high prevalence of depression in this population, only 21.4% of the individuals who received a diagnosis of a mood or anxiety disorder were treated for that disorder. The frequency of individual symptoms of both major and minor depression, which were also recorded during this study, indicated that 61% of those diagnosed with depression reported experiencing a depressed mood; 83% reported diminished interest in their usual activities; and 90% reported feeling fatigued or having limited energy. Reports indicate that 30% of the women with depression described a decreased or increased appetite, 60% experienced insomnia or hypersomnia, and 47% reported feelings of worthlessness or inappropriate guilt.

3. RISK FACTORS FOR DEVELOPING MDD AMONG WOMEN

It is believed that the interaction of exogenous factors (negative life events), reproduction-related hormonal changes, genetic factors, prior history of depressive episodes, and overall temperament mediate depression in women. Exogenous factors thought to increase the risk for depression may include death of close friends and family members, parental divorce and marital discord, severe illness or injury, robbery or assault, and loss of a job *(18,19)*. Pregnancy-related stress factors such as poor social support networks and isolation may also increase the risk for depression *(14)*. Hormonal changes, specifically, an increase in oxytocin, may lead to an increased need for acceptance and intimacy in women and may increase their depressive vulnerability to negative life events *(20)*. This risk is significantly increased when such women must develop new or multiple interpersonal attachments while experiencing these hormonal fluctuations *(20)*.

Other physiological changes that occur during pregnancy, labor, and the postpartum period—including pregnancy-related fluctuations in estrogen and progesterone levels and changes in hypothalamic–pituitary axis activity—may increase the likelihood of a woman developing depressive symptoms by affecting the

sensitivity of various neurotransmitter systems *(21)*. During the postpartum period, depression may be associated with the withdrawal of steroidal hormones, which occurs following delivery. Bloch and colleagues demonstrated that the induction of depression can occur through the experimental withdrawal of gonadal steroids in vulnerable individuals *(22)*.

With increasing evidence of the role of hormones in depressive symptoms during pregnancy and the postpartum period, researchers have become interested in monitoring the efficacy of hormone replacement therapy (HRT) in the treatment of depression. Data generated through a study of 55 women diagnosed with bipolar disorder (BD) indicate that HRT can be effective in alleviating the symptoms of depression that occur during the postpartum period *(23)*. Since women with BD face a greater risk for the recurrence of depressive symptoms during subsequent pregnancies, as well as worsening of symptoms during the perimenopausal period, HRT may be particularly valuable *(23)*. However, recent studies suggest that some types of HRT may be associated with a higher risk for cardiovascular disease (CVD) and certain types of cancer *(24–27)*.

4. DIAGNOSIS OF DEPRESSION DURING PREGNANCY AND THE POSTPARTUM PERIOD

Individuals experiencing severe depressive symptoms often neglect themselves by exhibiting poor eating and sleeping habits and engaging in high-risk activities such as smoking or drinking; they are also more likely to have suicidal ideation than nondepressed individuals. The consequences of this neglect are potentially devastating to fetal development and require early recognition and intervention. Numerous studies of recovery outcomes among patients diagnosed with depression indicate that the longer a patient remains untreated, the lower the probability that the patient will adequately respond to selected treatment options. It has also been shown that with each subsequent depressive episode, the likelihood of a recurrent episode increases dramatically. Whether a woman is consulting a physician for symptoms of depression experienced during pregnancy or seeking preconception information on acceptable plans to continue antidepressant medication during gestation, it is necessary for physicians and patients to actively discuss all available treatment options and to perform a comprehensive risk–benefit analysis.

In women without a history of major depression, symptoms of the illness that become apparent during pregnancy, such as sleep and appetite disturbances and low energy, are often mistaken for common neurobiological effects of pregnancy. Physicians must recognize that depressive symptoms could be the result of numerous physical illnesses, for example, endocrine disorders, infectious diseases, nutritional deficiencies, neurological disorders, CVD, and various types of cancer. Medical disorders that are commonly associated with pregnancy (e.g.,

anemia, gestational diabetes, and thyroid dysfunction) may also precipitate depressive symptoms and complicate the diagnosis further. It is important for physicians to perform a comprehensive medical examination to detect medical conditions that may be associated with depressive symptoms.

Features that are often used to assist physicians in confirming a diagnosis of MDD are feelings of guilt or hopelessness, anhedonia, or suicidal thoughts, although the risk of suicidal behavior during pregnancy is relatively low. Patients presenting depressive symptoms must also undergo a detailed medical history to rule out drug-induced depression. A variety of drugs may induce symptoms of depression, including most drugs of abuse, antihypertensive drugs, gastrointestinal (GI) drugs, corticosteroids, and oral contraceptives. In addition to excluding these possible sources for depressive symptoms, physicians should determine whether other psychiatric disorders are present and which type of depression exists (e.g., unipolar, bipolar, or depression with psychotic features).

5. MATERNAL DEPRESSIVE SYMPTOMS AND CHILD DEVELOPMENT

Pregnant women seeking treatment for depressive symptoms and their physicians must find a balance between maternal well-being and fetal safety. Current research suggests that untreated depressive symptoms in mothers are correlated with adverse effects on the developing fetus. Assessing the impact of maternal depressive symptoms on fetal development and neonatal well-being is difficult, but data suggest that an association exists between depressive symptoms and preterm birth, lower birth weights, reduced head circumference, and lower Apgar scores *(28)*. It has been shown that maternal depressive symptoms, especially those that manifest during the prenatal period, are a risk factor for the well-being of the child and a healthy childhood development *(1)*. It has also been demonstrated that the timing and frequency of depressive episodes also influence child development *(1)*. In a recent longitudinal study, prenatal, postnatal, and current maternal depressive symptoms were shown to be associated with low levels of psychosocial adaptability and high levels of emotional and behavioral problems among school-age children *(1)*. Specifically, concurrent maternal depressive symptoms were associated with reduced social competence and low social adaptive functioning in the child, maternal postnatal depressive symptoms were associated with low social competence in the child *(1)*, and prenatal maternal depressive symptoms were associated with an increased tendency for the child to externalize problems as well as with a higher total problem level *(1)*.

Inadequate measures to preserve health and poor adherence to recommended prenatal care plans are also commonly associated with major depression in pregnant women. Consequently, women with a decreased appetite fail to meet expected

levels of weight gain during pregnancy, resulting in the risk for a negative neonatal outcome. Data have also suggested that women diagnosed with MDD are more likely to engage in high-risk behaviors, such as smoking, drinking, and the use of illicit drugs—all of which increase the risk for a poor pregnancy outcome.

There is some evidence that untreated depression in pregnant women may adversely affect the development of the fetus. Depression-related alterations in the functioning in the hypothalamic–pituitary axis can lead to increased serum cortisol levels, and the neurotransmitter abnormalities that develop in depressed women can lead to increased catecholamine levels. These fluctuations may lead to abnormal development of the placenta, which can result in a reduced blood supply to the fetus, which in turn can cause intrauterine growth retardation and abnormal development of the nervous system *(29–34)*.

Untreated depression has clearly been linked with higher rates of mortality and morbidity, and discontinuation of antidepressant medication poses a threat for relapse and suicide *(35–37)*. There is ample evidence that discontinuation of antidepressant medication upon conception may also pose a risk for developmental and behavioral abnormalities in children of depressed mothers *(1)*.

6. PHARMACOLOGICAL TREATMENT OF DEPRESSION DURING PREGNANCY

The pharmacological treatment of depression during pregnancy is complicated and requires risk–benefit considerations for both the mother and fetus. Maternal factors include severity of depressive symptoms, medical history, and preferences of the patient. Potential fetal risks include intrauterine death, physical and structural malformations, growth impairment, neonatal drug withdrawal syndrome, abnormal central nervous system (CNS) development, and abnormal behavioral development *(38,39)*. It must be emphasized, however, that in cases involving moderate to severe or chronic depressive symptoms, withholding of antidepressant medication may result in detrimental effects on both mother and child.

Clinicians treating women diagnosed with MDD are presented with a number of challenges when making recommendations regarding the management of symptoms during pregnancy. The assessment of risks associated with medication use during pregnancy is complicated by variables that are difficult for physicians to control, including nutrition, substance use, exposure to environmental conditions, use of over-the-counter medications and vitamins, and patient compliance with prescribed medications. Also, the risks and benefits of many antidepressant medications have not been clearly established, and all antidepressant medications readily diffuse across the placental barrier.

The system established by the US Food and Drug Administration for classifying the safety of prescription medications into categories of risk of fetal damage (A, B, C, D, and X) serves as a guideline for physicians, but is often misleading and unclear. Although the first trimester of pregnancy, particularly between 2 and 8 wk after conception, is the period in which the fetus is most vulnerable to malformations resulting from drug exposure, the development of the CNS system continues throughout pregnancy and may be at risk for teratogenesis for a longer period of time *(40,41)*. The possibility of organ dysgenesis, neonatal toxicity or withdrawal during the acute neonatal period, and long-term behavioral sequelae also exist *(42–44)*. Other potential risks to the developing fetus include intrauterine death, growth impairment, and CNS defects *(38,39)*. Developmental CNS defects caused by antenatal drug administration could result in delayed behavioral maturation, impaired problem solving, and numerous learning disabilities. The lack of randomized, placebo-controlled studies of depression during pregnancy has resulted in a risk assessment system that is constructed from inconclusive or conflicting data. Most antidepressant medications are classified as category C agents: agents with insufficient or inconclusive reports regarding reproductive safety and agents for which "reproductive risk cannot be ruled out." However, some tricyclic antidepressants (TCAs) have been placed in category D, indicating "positive evidence of risk," despite the accumulating reports that these medications are safe for use *(45)*. Also, bupropion—a drug for which very little research has been conducted during pregnancy—is currently classified as a category B drug, indicating no evidence of risk in humans.

Physicians have been required to assess risk through the recommendations of colleagues, consensus opinions, and assessments of new research findings.

Women who present for consultation may or may not have a history of MDD, may or may not be currently taking antidepressant medications and wish to start a family, or may be currently pregnant and experiencing depressive symptoms. Within each group, the decision to begin, continue, or discontinue antidepressant drug therapy requires specific considerations. The ultimate goal of the physician and the patient is the same: to minimize the risk of fetal exposure to potentially adverse medication effects while limiting the morbidity of untreated depression in the mother.

6.1. Patients With a History of Major Depression Planning to Conceive or in the Early Stages of Pregnancy

With the guidance of their physician, women with a history of MDD who are currently taking antidepressant medication have the option of tapering the medication until eventual discontinuation before conception, abrupt discontinuation of medication upon learning about the positive results of a pregnancy test, or

maintaining therapeutic levels of medication throughout pregnancy. Although tapering to gradual discontinuation before conception minimizes the risk of fetal exposure, it does not rule out the possibility of severe consequences for the mother and child. Premature discontinuation of antidepressant medication administered for either acute depressive symptoms or during the maintenance phase of treatment may precipitate a recurrence of depressive symptoms. Investigators have reported that 75% of women with a history of recurrent MDD episodes during maintenance therapy who discontinued medication experience a relapse and 69% of the relapses occurred during the first trimester of pregnancy. Women experiencing these depressive episodes during the first trimester are often at risk for preterm delivery and delivering babies who are underweight for gestational age. It has also been shown that untreated depression during pregnancy triples the risk for MDD episodes during the postpartum period.

6.2. Patients Without a History of MDD Experiencing an Acute Onset of Depressive Symptoms

The acute onset of depressive symptoms during pregnancy may induce adverse effects in both the mother and the fetus. The severity of the depressive symptoms experienced by the mother will affect the treatment selection decision process. Expectant mothers should have an opportunity to discuss treatment options, including nonpharmacological treatment, pharmacological treatment, or a combination of both.

6.3. Maternal Pharmacokinetic Changes During Pregnancy

If it has been determined that pharmacotherapy is necessary, a number of important factors regarding drug selection must be considered, including efficacy of the drugs available, anticipated response of the individual patient, and the overall toxicity profile of the drug for both the mother and fetus *(46)*.

To determine the potential adverse effects of a particular drug, the pharmacokinetic variations that occur during maternal, placental, fetal, or neonatal absorption, distribution, metabolism, and elimination of the drug must be considered *(47,48)*. The rate of drug absorption in pregnant women can vary significantly because of reduced GI motility, increased gastric pH, and increased pulmonary alveolar drug uptake *(49)*. During pregnancy, significant changes occur in drug distribution as the total volume of body water increases by up to 50% *(49)*. The distribution of the increased body water—40% of which is distributed in maternal compartments and the remaining 60% to the amniotic fluid, placenta, and fetus—will also influence drug absorption and excretion rates *(49)*. At approx 40 wk gestation, serum albumin levels fall from an average of 40 g/L to 33 g/L, which results in a reduction of binding sites for acidic drugs. The effects of increased levels of unbound drug and the increased plasma volume during preg-

nancy usually offset each other, although there may be exceptions to this generalization *(45)*. Drug elimination rates are also affected during pregnancy. The fluctuation of maternal hormones, specifically progesterone and estradiol, during pregnancy can increase the rate of metabolism of some drugs in the liver and inhibit the hepatic metabolism of other drugs. For example, cytochrome P4501A2 (CYP1A2) and *N*-acetyltransferase 2 (NAT2) activity is altered during pregnancy *(50)*. Also, the potential for increased levels of estrogen to cause cholestasis can slow the clearance of drugs excreted into the biliary system. The clearance of drugs through the kidneys is potentially affected by a 25 to 50% increase of renal flow and increased glomerular filtration rate. In most cases, these changes do not result in clinically significant alterations requiring modification of drug dosing *(49)*, but some evidence indicates that the biological changes that occur during pregnancy may potentiate the need to modify medication dosages and that these changes will ultimately affect the level of fetal exposure and the risk of teratogenesis. For example, depressed women being treated with TCAs during the third trimester may require 1.6 times the mean dose required by nonpregnant women to maintain therapeutic serum levels during pregnancy *(51)*.

6.4. TCAs

TCAs, including nortriptyline and desipramine, are commonly prescribed to patients who have been diagnosed with MDD. Despite early reports that exposure to a TCA during the first trimester of pregnancy could result in fetal limb malformations *(52)*, recent data pooled from 414 individual cases indicate that there is no significant association between first trimester exposure to TCAs and infant teratogenesis *(42,53–57)*. In another study examining the birth outcomes for 209 infants exposed *in utero* to a TCA (amitriptyline, imipramine, doxepin, nortriptyline, or desipramine), investigators observed no differences in head circumference, birth weight, or Apgar score compared with infants who had not been exposed to TCAs. In a comparison group of 129 newborns exposed to a selective serotonin reuptake inhibitor (SSRI; fluoxetine, sertraline, or paroxetine), investigators found that exposed infants had a lower gestational age and lower birth weight compared with infants exposed to TCA. No congenital malformations or developmental delays were reported for either group *(58)*.

In some instances, perinatal syndromes consisting of short-lasting symptoms have developed in infants exposed *in utero* to TCAs, most commonly when the drug was administered close to or at the time of delivery. A withdrawal syndrome, manifested by jitteriness and irritability, has been observed. Seizures, occurring upon drug withdrawal, have also been reported with clomipramine exposure *(59–63)*. The anticholinergic effects of TCAs—which are associated with bowel obstruction, jitteriness, suckling problems, hyperexcitability, and urinary retention—have also been observed *(64,65)*. Nortriptyline and desipramine are prefer-

able to other TCAs during pregnancy because of their reduced likelihood of inducing anticholinergic and hypotensive effects. Maprotiline should be avoided because of an increased risk for maternal seizures compared with other TCAs *(66)*.

6.5. SSRIs

SSRIs are an effective treatment for patients diagnosed with MDD. Although data are reassuring regarding any risks associated with SSRI administration during pregnancy, it has been estimated that a minimum of 500 exposures must be monitored in order to demonstrate a twofold increase in risk for organ malformation compared with the regular population *(67)*. Most current studies have not enrolled this many individuals. In a study of 38 women taking sertraline, paroxetine, citalopram, or fluoxetine, antidepressant metabolites were detected in umbilical cord blood in 86.8% of their infants, albeit in much lower concentrations. Compared with the other SSRIs, mothers taking sertraline throughout their pregnancies had the lowest umbilical cord concentrations, suggesting sertraline may be advantageous for use in pregnancy *(68)*.

Currently, prospective studies monitoring the rates of congenital malformation in more than 1100 fluoxetine-exposed infants—gathered through a postmarketing surveillance registry established by the manufacturer of fluoxetine and a retrospective study of pregnancy outcomes—provide information about nearly 2500 cases regarding the possible fetal toxic effects of this drug *(52,53,55,69,70)*. These data indicate that there is no increased risk of teratogenesis in fluoxetine-exposed infants. However, information gathered from case reports and a prospective study has shown that *in utero* exposure to fluoxetine can lead to poor neonatal adaptation (biophysiological responses to new environmental stimuli), respiratory distress, feeding problems, and jitteriness *(52,71)*. Pastuszack and coworkers found no difference in teratogenicity when fluoxetine was compared with TCA and a nonteratogenic agent in matched groups. In other studies, the possible teratogenic risk of fetal exposure to sertraline, paroxetine, fluvoxamine, and citalopram has been monitored and investigators have found SSRIs to be a safe and effective for the treatment for depression throughout gestation. These studies had relatively small sample sizes, however *(53,72–74)*. In one prospective study of 531 infants with first trimester exposure to SSRIs, 375 of whom were exposed to citalopram, investigators did not find an increased risk of organ malformation *(74)*. In a retrospective study of 63 infants with first trimester exposure to paroxetine, investigators did not observe an increased risk for organ malformation *(72)*. In yet another prospective study monitoring *in utero* exposure to fluvoxamine, paroxetine, and sertraline in 26, 97, and 147 individuals, respectively, investigators determined that pregnancy outcomes (birth weight and gestational age), risk for organ malformation, and risk for complications (miscarriage or stillbirth) were the same compared with control

groups *(73)*. Data analysis in this study was done by grouping the three antidepressants together rather than by analyzing the data for each drug individually.

Although the previously mentioned studies demonstrate the relative safety of SSRI administration during pregnancy, one study has demonstrated the possibility of an increased risk for multiple minor malformations or structural defects with no cosmetic or functional importance in infants exposed *in utero* to fluoxetine *(52)*. Data gathered from this study also showed a correlation between late-term fluoxetine exposure and premature birth associated with poor neonatal adaptation. However, methodological defects in the study design—including the use of nonrandomized individuals due to ethical limitations, dissimilar control groups with differences in maternal age, and the possibility of bias due to unblinded researchers—have led many investigators to question the validity of these findings. This study also did not separate the effects of depression from possible adverse effects of medication. The last point remains an issue with all evaluations of the effects of medications. In a prospective, controlled study of 20 women taking citalopram or fluoxetine, infants exposed to either SSRI had a lower concentration of 5-HIAA, increased tremors, restlessness, and rigidity, as well as higher heart rates compared with the non-exposed group. Follow-up testing carried out 2 wk and 2 mo after birth indicated these symptoms had been transient, and no differences between the groups were reported *(75)*.

Data regarding the possibility of neonatal toxicity and withdrawal syndromes after prenatal exposure to fluoxetine and other SSRIs have been inconsistent. Symptoms of neonatal toxicity after *in utero* exposure to an SSRI—including poor neonatal adaptation, respiratory distress, feeding problems, and jitteriness—have been identified by some investigators *(52,71)*. However, other studies have been unable to identify significant rates of perinatal distress *(43,73,76)*. A more recent study of 53 infants exposed to paroxetine during the third trimester of pregnancy found that 12 infants in the paroxetine group vs three in the control group experienced complications that led to prolonged hospitalization. These symptoms, which improved within 1 to 2 wk, included hypoglycemia, respiratory distress, and jaundice *(77)*. Case reports of neonatal withdrawal following *in utero* exposure to SSRIs—most frequently paroxetine, but also with fluoxetine and citalopram—have been reported *(78,79)*. In one study, acute pain response in newborns exposed to an SSRI was attenuated *(80)*.

Because SSRIs are not associated with the negative cardiac, hypotensive, or sedative effects of TCAs, this decreased risk may make them more suitable for use during pregnancy.

6.6. The Motherisk Program

The Motherisk program is a service available to women, their families, and health professionals. that the program provides consultation and information

regarding possible risks of infant drug exposure during pregnancy and lactation. The service is most easily accessed through www.motherisk.org.

In a study conducted at the Motherisk Clinic, 129 pregnant women taking a TCA were monitored for possible teratogenic effects. Of these women, 24 were unable to be contacted for follow-up, 8 did not choose to continue with follow-up treatment, 3 were exposed to known teratogens, 12 had spontaneous abortions, and 2 had therapeutic abortions. Of the remaining group of 80 women, 62 were treated for depression and 18 were treated for other indications. Among the 62 who were treated for depression, 40 chose to take the TCA throughout the first trimester, 36 throughout the entire pregnancy, 2 during the first and second trimester, and 2 during the first and third trimester. Of these women, 29 chose to take amitriptyline, 20 imipramine, 10 clomipramine, 9 desipramine, 8 nortriptyline, and 1 each maprotiline, doxepin, amoxapine, and trimipramine *(69)*.

Within this group, 88 women taking fluoxetine were also counseled by the Motherisk program. Of these women, 8 could not be contacted for follow-up, 8 chose not to continue follow-up treatment, 12 had spontaneous abortions, and 7 had therapeutic abortions. Among the 55 women remaining, 37 chose to take fluoxetine during the first trimester and 18 continued therapeutic doses throughout the entire pregnancy *(69)*.

The women being treated for depression, either with TCAs or with fluoxetine, had similar levels of depression; however, the women in the fluoxetine group had more previous pregnancies, more previous therapeutic abortions, and were of lower socioeconomic status. Also, the women in both drug groups consumed more alcohol and smoked more cigarettes than women in the control group *(69)*.

Upon birth and follow-up testing, the percentiles of weight, height, and head circumference were similar among all three groups. The rates of perinatal complications and incidence of major malformations were also similar among all three groups. In the TCA group, three children had major malformations: ventricular septal defect, hypospadias, and pyloric stenosis. In the fluoxetine group, two major malformations occurred: ventricular septal defect and patent ductus arteriosis. Among infants born to women in the control group, two had major malformations: cyanotic heart disease and ventricular septal defect *(69)*.

After adjusting for independent variables, mean global IQ scores were found to be comparable among the three groups, as were verbal comprehension and expressive language portions of the Reynell scales. Temperament—as measured by scores in mood, arousability, activity level, distractibility, and behavior problems—was also similar among the three groups *(69)*.

6.7. Monoamine Oxidase Inhibitors

The use of monoamine oxidase inhibitors (MAOIs) is often avoided during pregnancy because of an extremely limited amount of data regarding their risk

to fetal development. Because MAOIs may induce a hypertensive reaction in pregnant women—both throughout pregnancy and during delivery—and experimental data indicate numerous teratogenic effects, alternative methods of treating depression are recommended.

In a study monitoring the possible teratogenic risks of MAOIs, investigators found that an increased risk for congenital malformations after prenatal exposure to tranylcypromine and phenelzine *(81)*. However, because of a small sample size, more research needs to be done to verify these findings.

6.8. Lithium

Evidence accrued since the 1950s has consistently demonstrated that lithium is effective in the treatment of unipolar depression and BD. Because patients with BD are particularly vulnerable to recurrence of depressive symptoms with the discontinuation of maintenance therapy *(82,83)*, recognition of the disorder and methods to continue treatment during pregnancy are particularly important. Depending on the dose, method of delivery, and administration schedules, the use of lithium during pregnancy may pose potential problems for both the mother and the infant. However, it may be possible to prevent teratogenic effects and toxicity by careful observation of serum levels throughout the pregnancy, close monitoring of dietary intake and urinary excretion of sodium, and by creating an administration schedule that properly times doses throughout the day to maintain consistent concentrations. Weekly testing of serum concentrations throughout the pregnancy and daily testing during the last week of pregnancy are recommended. Because lithium toxicity can occur at levels of 1.5 to 2.0 mEq/L, the dosage should be adjusted to maintain levels between 0.5 and 1.2 mEq/L or the minimum serum level capable of providing a therapeutic benefit *(84–87)*. Renal clearance during pregnancy is increased from 50 to 100% and, thus, dictates the need for careful adjustments in the lithium dose throughout the pregnancy. A typical dose of 600 mg two or three times daily usually results in spikes in serum levels that can be toxic to the infant. Pregnant women should receive a dose no larger than 300 mg spaced evenly throughout the day and frequently enough to maintain the minimum serum levels. Other means of maintaining steady levels of lithium include the prevention of large variations in dietary sodium intake and avoiding activities that can lead to sodium depletion, such as ingesting diuretics (commonly prescribed to pregnant women to reduce fluid retention or ankle edema) or engaging in activities that will cause excessive perspiration. Fetal surveillance with regular ultrasonic cardiac monitoring throughout the pregnancy is also recommended.

Despite efforts to control the adverse effects of lithium administration, toxicity can occur in both the mother and the infant, most commonly when lithium is not discontinued during the final days prior to delivery. Lithium readily diffuses

across the placental barrier and high levels of drug concentrations can be found in fetal serum. Reports of maternal neonatal lithium intoxication with drug levels of 2.6 mEq/L and 2.1 mEq/L respectively have been reported *(88)* and often results in confusion, lethargy, diarrhea, muscle spasms; coma has been reported when lithium administration was continued throughout the final stages of pregnancy and beyond delivery. Lethargy, poor sucking, and poor swallowing reflex have been reported for infants exposed to lithium during the late stages of pregnancy. However, this too can be prevented by monitoring electrolyte balance and maintaining adequate renal function during the weeks prior to birth. It may be necessary to discontinue lithium 2 to 3 d prior to delivery or decrease the dose by one-half to one-fourth *(89–92)*.

With the creation of the Lithium Baby Register in 1969, retrospective data from a joint Danish–American–Canadian study of infant malformations occurring as a result of *in utero* exposure to lithium began to be documented *(91)*. Throughout the 10 yr this study was conducted, information regarding the birth outcomes of 225 babies born to mothers treated with lithium was recorded. Among these reports, 25 babies (11%) were born with visible malformations and 18 babies (8%) were born with cardiovascular anomalies, including Ebstein's anomaly (a cardiac defect of the tricuspid valve) in six cases. A small number of stillbirths and infants born with Down syndrome was also reported *(93)*.

Current research monitoring the toxicity of lithium during pregnancy is reassuring. After reviewing four case-controlled studies and two cohort studies analyzing the effects of *in utero* exposure to lithium, Cohen and associates determined that the risk of Ebstein's anomaly is between 0.05% and 0.1% and the rate of any other major birth defect is two to three times the expected rate. Data gathered from another multicenter study suggested that lithium is not a significant teratogen when no differences in pregnancy outcomes after lithium administration were found *(90)*.

6.9. Other Antidepressants

As new antidepressants are introduced to the market, their safety and efficacy when administered to pregnant or nursing women must be investigated. A paucity of anecdotal or research data are available for the use of mirtazapine, venlafaxine, trazodone, and buproprion during pregnancy; these drugs should be used with caution during pregnancy and only rarely as first-line agents.

6.10. Anticonvulsants

The use of anticonvulsants as an augmentation strategy or as a single use for BD-related depression during pregnancy is controversial. Neural tube defects (NTD) have been associated with the use of carbamazepine and valproic acid. The pathogenesis of NTDs involves an interaction between the maternal genetic

makeup, as reflected in the genes related to folate transport, and the folate metabolic pathway *(94)*. Anticonvulsant medications may have a role in the process as antagonists of folic acid, leading to an increased risk for NTD. The risk associated with these medications is not countered by the administration of folic acid and multivitamins *(95)*. Carbamazepine is associated with a twofold increase in major congenital abnormalities and low birth weight, as well as intrauterine growth retardation *(96,97)*. Lamotrigine, an anticonvulsant that has become increasingly utilized by physicians to treat BD-related depression, may increase the risk for congenital abnormalities when administered during pregnancy. When used in combination with valproic acid, lamotrigine was associated with chromosomal abnormalities *(98,99)*. In a study of 57 children experiencing symptoms of fetal anticonvulsant syndrome—34 of whom were exposed to valproate alone, four to carbamazepine alone, four to phenytoin, and the rest to multiple medications—investigators found that developmental abnormalities occurred throughout the pregnancy. The observed abnormalities included behavioral consequences, autism, learning disabilities, gross and fine motor delay, myopia, glue ear, and joint laxity *(100)*. Clonazepam and other anticonvulsants used together showed a significantly higher risk of congenital abnormalities *(101)*. Evidence indicates that topiramate passes freely through the placenta, but no adverse effects were reported in three case reports *(102)*.

6.11. Benzodiazepines

A review of the literature indicates that the use of benzodiazepines for the treatment of depression during pregnancy is safe, with the exception of some multidrug regimens and use during the first trimester *(103–107)*. In a study of 38 women taking clonazepam during pregnancy, of which 27 patient records were available, investigators found that clonazepam was not associated with increased risk for fetal toxicity or withdrawal. Two of the infants born to this study population who had been exposed to a combination of clonazepam and imipramine experienced hypotonia and respiratory distress *(107a)*.

Other data gathered from a database of 22,866 women who had delivered babies with congenital abnormalities also revealed that benzodiazepine use during pregnancy was relatively safe compared with a matched group of 38,151 women. Of the group of infants with abnormalities, 57 had been exposed to a benzodiazepine—nitrazepam, medazepam, tofisopam, alprazolam, or clonazepam. In the matched group, 75 had been exposed to a benzodiazepine, indicating no increased risk *(108)*. Only 2.3% of pregnant women were treated with benzodiazepines alone. All other drugs were used similarly in both groups, except for terbulaline, which was used more often in the group not treated with benzodiazepines.

6.12. Behavioral Consequences of Fetal Exposure to Antidepressant Medications

When monitoring the risks associated with antidepressant medications, it is necessary to assess the possibility of long-term neurobehavioral consequences after prenatal exposure to antidepressant medication. In one report, in which a cohort of children exposed *in utero* to TCAs ($n = 80$) and fluoxetine ($n = 55$) were followed through their preschool years, investigators found no significant differences in the IQ, temperament, behavior, reactivity, mood, distractibility, or activity level for these children compared with a control group ($n = 84$) *(4)* Although the results of this study suggest that TCAs and fluoxetine do not pose a significant risk for neurobehavioral consequences, further investigations are required.

6.13. Animal Models of Depression

The teratogenic effects of a particular drug in groups of animals are often used to make assumptions concerning the rates of teratogenic effects that will be found in humans. Although such models may be useful, they ignore substantial interspecies differences in drug metabolism and pharmacodynamics. Keeping these limitations in mind, investigators conducting laboratory studies of pregnant rats have reported concentrations of antidepressant medications in developing rat brains as high as 85% of the concentrations in the maternal brain, indicating that the developing fetus is at a risk for exposure to more than half of the therapeutic dose the mother receives. In vitro data indicate that although chronic exposure of cultured fetal rat cortical neurons to the SSRI citalopram did not produce alterations neuronal morphology or fine structure, changes did occur in the mitochondria and vesicular aggregation. These alterations suggest increased synaptic activity. Animal studies also indicate that untreated maternal depressive symptoms during pregnancy may lead to abnormal neuronal development in the fetus, dysfunction of the hypothalamic–pituitary–adrenocoritcal axis, and neuronal death.

7. USE OF PSYCHOTROPIC MEDICATION DURING LACTATION

Similar to women who experience symptoms of depression throughout their pregnancy, women in the postpartum period are susceptible to depressive episodes because of the numerous biological, neuroendocrine, and psychosocial changes that take place following childbirth, in addition to postpartum thyroiditis *(22,109–111)*. In a meta-analysis of 84 studies done in the 1990s, predictors of postpartum depression were prenatal depression, loss of self-esteem, child-care problems, anxiety, difficulties developing and maintaining social support systems, marital stress, past history of depression, newborn factors, “the blues,” socioeconomic status, and animosity toward the pregnancy *(112)*. Postpartum

depression—which can involve symptoms that persist for months, even years following childbirth—has been associated with an increased risk for adverse effects in both the mother and infant if left untreated *(113)*. These negative effects of maternal depressive symptoms may manifest through low social competence, cognitive disabilities, and emotional development impairments in their children *(113,114)*. These changes are associated with poor parenting practices by the depressed mother and negative changes in both the structure and functioning of the family system *(115)*. With 10% of women meeting diagnostic criteria for depression following delivery *(5)* and approx 59% of women indicating a desire to breast-feed their child after discharge from the hospital *(116)*, it is important to evaluate treatment options after assessing the risks of infant exposure to psychotropic medication through maternal breast milk vs the biological and psychological benefits of breast-feeding. With current reports indicating that 250,000 women per year in the United States consider the use of psychotropic medication while breast-feeding *(117)*, and recent data suggesting that this number will continue to grow *(118)*, research monitoring the safety of psychotropic medications during lactation is becoming increasingly important. When patients and physicians are discussing the administration of antidepressant medication to women who have recently given birth, several issues must be considered, including the potential benefits of breast-feeding on the infant development, the risk of infant exposure to the antidepressant medication and methods to minimize this exposure, possible subsequent adverse effects, the potential for an adverse impact on the mother–child attachment and cognitive–behavioral development, and the effects of untreated depression in the mother *(114,119–124)*.

7.1. Benefits of Breast-Feeding

The benefits of breast-feeding have been well documented and information regarding these benefits is widely distributed by numerous professional support organizations for new mothers and their families. The American Academy of Pediatrics has endorsed breast milk as the best source of nutrition for infants during the first 6 mo to promote optimal growth *(125)*. This endorsement, along with extensive reports indicating that breast-feeding newborns poses numerous advantages to the developing infant—including a lower incidence of GI disease, anemia, respiratory infections, otitis media, and sudden infant death syndrome *(125–128)*, as well as the possibility that exclusive breast-feeding may also enhance neurodevelopment of infants *(129,130)*—is sharply in contrast to the increasing amount of evidence that untreated maternal depression can adversely affect the attachment between the mother and her infant, which often begins during breast-feeding, as well as the child's development *(114,131,132)* and, thus, may increase the mother's risk for chronic depressive symptoms *(133,134)*.

7.2. Risk of Infant Exposure to Antidepressant Medication

The risk of infant exposure to antidepressant medication through maternal breast milk is determined by a number of factors, including the physiology of the mother, the stage of biological development of the infant, and the physiochemical properties of specific medications. By monitoring these factors, physicians can reduce infant exposure to high concentrations of medication and subsequently reduce the possibility of adverse effects.

The physiological characteristics of the mother are extremely important in determining the concentration of medication in breast milk. Current research has shown that all antidepressant medications can be found in maternal breast milk, with milk to plasma ratios ranging from 0.14 to 5.03 (*see* Table 1) *(135–137)*. Although the average amount of breast milk produced daily remains relatively constant at 600 to 1000 mL, individual variability in the chemical properties of the maternal breast milk—including pH and protein and lipid content—can influence the concentration of medication detectable in the breast milk *(138,139)*. The primary process by which medication enters breast milk is passive diffusion, although active transport processes, numerous maternal characteristics, and drug pharmacology also influence drug concentrations in the milk *(137,140–142)*. Because the pH of breast milk ranges from 6.35 to 7.65 and is generally more acidic than is plasma, medications that are weak bases diffuse diffuse into maternal breast milk more readily than others and are often found in higher concentrations in the milk *(140–142)*. Furthermore, medications that are poorly protein-bound and those that have higher lipid solubility are also found in higher concentrations *(140–142)*. Variations in the chemical properties of maternal breast milk can be found not only in different individuals, but also in the same individual at different times during a single feeding. Because hind milk (released during the second half each feeding period) has a higher lipid content than that of fore milk (released during the first half of feeding), it is likely to have higher concentrations of lipophilic medications. A number of other factors that can influence the chemical properties of maternal breast milk and alter medication concentrations in it include the concentration of lactose, serum albumin, lysozymes and other enzymes, prolactin, and minerals such as calcium and phosphates in the milk *(143)*.

The biological development of the infant plays an important role in determining the risk of exposure to antidepressant medication. The stage of development reached by the infant directly influences the infant's ability to metabolize medications and alters the levels of medication that will produce adverse effects *(49)*. In vitro studies have shown that infant capacity to metabolize medications in the liver through cytochrome P450 activity is approximately one-half of that in adults throughout the first 3 wk of life; additionally, because maturation rates for different liver enzymes vary, different substrates of the medications are metabolized at different points throughout infant development *(144)*. Glucuronidation

Table 1. Milk to Plasma Ratios of Selected Antidepressants *(137)*

Drug	*Reported Milk to Plasma Ratio*
Bupropion	5.03
Citalopram	1.0,1.8
Desipramine	1.34, 1.56
Fluoxetine	0.52
Fluvoxamine	1.32 (serum)
Nefazodone	0.27
Paroxetine	0.39, 0.69, 0.72
Trazodone	0.142
Venlafaxine	3.26, 3.99

Readers should note that published values are based on very small sample sizes, often one patient, with the largest samples for citalopram ($n = 8$) and paroxetine ($n = 7$).

and oxidation at birth occur at rates that are only 20% of those seen in adults *(145)*. Additionally, despite a kidney weight-to-body mass ratio nearly twice that of adults, the newborn kidney has a glomerular filtration rate of only 30 to 40% that of adults and only 20 to 30% of adult tubular secretion activity. This tends to result in toxic exposures over time owing to the accumulation of foreign compounds in the infant *(135)*. Finally, lipid-soluble agents can become 10 to 30 times more concentrated in cerebrospinal fluid than in serum because of an underdeveloped blood–brain barrier *(146)*. CNS concentrations of lipid-soluble substances are also higher in newborns compared with older infants owing to a limited number of body fat storage sites *(147)*.

Despite a seemingly complex interaction of physiological variations-resulting in variations in the rate of absorption of the particular drug into maternal circulation, diffusion of a drug from the maternal circulation into breast milk, and absorption of the drug by the infant—it is possible to use mathematical models to predict drug concentration levels at different times. It has been shown that infant exposure to psychotropic medications can be significantly minimized by implementing a schedule of drug administration. Research indicates that when medications are administered immediately following feeding, their concentrations are drastically reduced in subsequent feeding periods as a result of a maximum length of time being allowed for drug excretion *(148)*.

The physiochemical properties of individual drug compounds also influence the potential risk of infant exposure and subsequent adverse affects of that exposure. Although information is available about more than 30 psychotropic medications, the pharmacokinetic complexity of these drugs, coupled with defects in the study design, have made interpretation of the data difficult. The pharmacol-

ogy of antidepressant used during pregnancy and lactation was discussed by Burt and colleagues *(139)*, and readers are referred to that review for further details. An overview of their findings and data from more recent studies are presented later in this chapter *(139)*.

7.3. TCAs

Data regarding the safety of TCA administration during lactation is reassuring. Recent research has shown that infant serum levels of parent and active metabolites range from undetectable levels to less than 28 ng/mL; therefore, infant exposure to the medication is minimal *(139)*. Furthermore, in a combination of studies monitoring the health of 47 infants whose mothers were prescribed TCAs—including amitriptyline *(149–154)*, nortriptyline *(155–159)*, imipramine *(154,155,160)*, desipramine *(155,161)*, and clomipramine *(62,147,155,162)*—no adverse effects were reported. Wisner and coworkers reported that serum levels in 12 infants exposed to nortriptyline were undetectable; in 2 infants, 10-hydroxynortriptyline was found in detectable levels *(155–159,161,163)*.

Data based on a study of two mother–infant pairs prescribed doxepin indicate that milk to plasma ratios of parent and metabolite compounds of clomipramine were close to or greater than 1.0 and that serum metabolite concentrations were measurable *(139)*. In one of these cases, respiratory depression occurred *(163)*. After nursing was discontinued, the symptoms disappeared within 24 h. However, because nursing was not resumed, it is unclear if doxepin was responsible for the adverse effect or whether it could be attributed to some other cause. In one other case report of doxepin administration to nursing mothers, no adverse effects to the infant were observed. Wisner and Perle reported no adverse effects occurring in four infants exposed to clomipramine through maternal breast milk *(157,159,161)*.

7.4. SSRIs

The use of SSRIs, most commonly fluoxetine, in nursing women has been studied extensively. In 11 published reports monitoring the health of 190 breast-fed infants whose mothers were taking fluoxetine, no adverse effects were observed in 180 of the infants *(162,164–173)*. Although concentrations of the drug in the infants' serum were not recorded for 101 of the mother–infant pairs, among the 79 remaining cases, concentrations were in the range of undetectable to 340 ng/mL in one instance *(167)*. However, an association among serum concentrations in the infant, maternal dose of antidepressant medication, and infant age was not found *(139)*. The use of fluoxetine by nursing mothers may not be advisable because of its long half-life and slow elimination *(174)*.

One study monitoring the long-term (up to age 1 yr) neurobehavioral development of infants exposed to fluoxetine through maternal breast milk revealed no adverse effects *(170)*. Other studies have reported adverse effects occurring in infants exposed to this drug *(164,169,173)*. However, the symptoms observed in the infant were transient and may have been confounded by the administration of other medications. In one instance, fluoxetine serum levels in a 6-wk-old infant reached levels comparable to those found in the mother *(167)*. Adverse effects—e.g., excessive crying, decreased sleep, and GI effects (including increased vomiting and diarrhea)—were also reported. These effects were resolved after breast-feeding was discontinued. In a retrospective study of fluoxetine-exposed infants, incidences of lower rates of weight gain were reported; however, when compared with the national mean rate of weight gain, no significant reduction was found *(171)*.

The use of other SSRIs—including fluvoxamine *(175,176)*, paroxetine *(141,162,177–180)*, sertraline *(140,158,162,181,182)*, and citalopram *(183–185)*—by breast-feeding mothers has also been investigated. Serum levels were not reported for fluvoxamine. Serum levels of paroxetine were measured in 27 of the 37 breast-fed infants and found to be undetectable in 24 of the infants and below 20 ng/mL in the remaining three. Infant serum levels of sertraline were undetectable or below 5 ng/mL in all recorded cases, and concentrations of its metabolite were less than 10 ng/mL. In two case reports, citalopram concentrations were 2.3 ng/mL and 12.7 ng/mL; concentrations of the metabolite desmethylcitalopram were undetectable.

In another study of citalopram, drug and metabolite levels in maternal breast milk were two- to threefold higher than in maternal plasma. Concentrations in the tested infants were undetectable. No adverse effects were reported in any of the monitored infants. In a study monitoring 50 mother–infant pairs, Hendrick and associates found that fluvoxamine and paroxetine levels could not be detected in maternal breast milk. Data from this study indicates that sertraline was detectable in maternal breast milk and the likelihood of detection was increased when the maternal dose exceeded 100 mg *(68,180,186)*.

Investigations of both sertraline and desmethylsertraline concentrations in human breast milk and infant serum have revealed that concentrations are affected by the aliquot of milk sampled, time after maternal dose, and maternal daily dose *(140)*. Maternal serum levels 24 h after a 25- to 200-mg dose of sertraline and infant serum concentrations 2 to 4 h following nursing were detectable, with a gradient from fore milk to hind milk of both substances in maternal breast milk and infant's serum. The highest concentrations of sertraline were observed in hind milk 7 to 10 h following administration. The increase of maternal dose of sertraline also resulted in an increase of sertraline and desmethylsertraline in

both maternal breast milk and infant serum concentrations. Among the 11 infant–mother pairs participating in the study, detectable concentrations of sertraline were found in 3 of the infants and detectable levels of desmethylsertraline were found in 6. However, no adverse effects associated with this exposure were reported. Serotonin platelet levels in the infants were not affected by maternal treatment with sertraline, which suggests that breast-feeding would not affect CNS serotonin transport *(117)*.

In a study of paroxetine in human breast milk and nursing infants, investigators found that paroxetine concentrations are also dependent on the aliquot of milk sampled, time after maternal dose, and maternal daily dose *(141)*. When maternal breast milk and paired infant serum samples were collected after 10 d of maternal treatment with paroxetine (10–50 mg/d), paroxetine concentrations ranged from 2–101 ng/mL and were present in all 108 samples. Greater paroxetine concentrations were found in the hind milk and lower concentrations in the fore milk. Although a peak-and-trough pattern of drug concentration was found with reliable daily dosing, a specific time course of paroxetine excretion into breast milk could not be established. No detectable concentrations of paroxetine were found in the serum of nursing infants. No adverse effects were reported by any of the participants.

In the case reports of two women taking venlafaxine while nursing, the venlafaxine metabolite was detected in one infant but not in the other. No changes in behavioral development were observed, but changes in sleeping and eating patterns were noted *(68,180,186,187)*.

7.5. MAOIs and Other Antidepressants

Data are limited regarding the safety of bupropion *(188)*, mianserin *(189)*, and venlafaxine *(187)* administration among nursing women. However, no adverse effects were detected in the five infants monitored in these studies. Investigations of large samples are needed before definitive conclusions can be made. Other studies monitoring trazodone *(190)* and the reversible MAOI moclobemide *(174)* did not measure infant serum levels, and the safety of these medications remains unknown.

7.6. Lithium

Early investigations indicate that lithium concentrations in maternal breast milk can range from 30 to 100% of that in the mother's serum. It has also been shown that breast-fed infants ingesting the breast milk of mothers treated with lithium can have a serum drug concentrations close to those found in breast milk *(191)*. The ability of lithium to enter maternal breast milk and the increased vulnerability of the infant to lithium toxicity because of reduced renal clearance

creates a situation in which the benefits of breast-feeding must be evaluated against the risk of lithium exposure.

In a 2003 study monitoring the use of lithium by breast-feeding mothers, investigators found that despite large individual variability in the sample, large amounts of lithium can be excreted into maternal breast milk, with the actual range in that study being 0 to 30% of the maternal weight-adjusted dose *(192)*. This suggests that frequent monitoring of both maternal serum concentrations and maternal breast milk concentrations is necessary when administering lithium to lactating mothers. Further studies are required to monitor the long-term developmental and behavioral effects of lithium exposure during infancy.

7.7 Benzodiazepines

Multiple studies of benzodiazepine administration to nursing mothers have indicated minimal adverse effects. Cyanosis was reported in one infant exposed to clonazepam *(193)*. In another study of 35 infants whose mothers were treated with antidepressants and benzodiazepines, clonazepam was detected in the serum of these infants, but no adverse effects were reported *(162)*. One infant exposed to benzodiazepines through maternal breast milk experienced lethargy and weight loss *(194,195)*. Another report indicated the possibility of withdrawal syndrome in an infant after exposure to alprazolam through breast milk, despite medication tapering *(196)*.

8. NONPHARMACOLOGIC TREATMENT OF DEPRESSION DURING PREGNANCY

There has not been a significant number of clinical trials of the efficacy of the nonpharmacological treatment of depression during pregnancy. Interpersonal therapy (IPT) has been shown to be well suited for the treatment of depression in expectant families, particularly because of its attention to feelings of grief, interpersonal disputes concerning family relationships, role transitions occurring during and after pregnancy, and interpersonal deficits *(197)*. IPT has also been used by physicians to help depressed patients learn how to adjust to specific problems that arise within their relationships. IPT focuses on helping patients improve social functioning, communication techniques, and expression of emotions. A pilot study of 13 women showed that IPT significantly reduced the severity of depressive symptoms, reduced the number of depressive episodes, and induced remission in all of the patients *(197)*. Although the sample of this study was small, the success of the patients suggests that nonpharmacological treatment of depression is a possible treatment option for expecting mothers. Further research is currently being conducted.

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9 Antidepressant Treatments in Posttraumatic Stress Disorder

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Contents

1. POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD) is clinical syndrome that may follow a traumatic event. This disorder is characterized by three symptom clusters: (a) re-experiencing the traumatic event; (b) avoiding reminders of the traumatic event and emotional numbing; and (c) hyperarousal *(1)*. PTSD can result in significant distress and morbidity. For example, following an assault, a person may experience intrusive thoughts of the assault, nightmares of a threat or assault, or flashbacks of all or some portions of the assault. Avoidance of reminders is common and may include avoidance of the site of the assault or similar places, avoidance of people who are similar to the perpetrator, or avoidance of conversations about community or domestic violence. Following a traumatic event, emotional numbing may occur, which may be characterized by a sense of being unable to have loving feelings, feeling detached from others, or having decreased interest in normal activities.

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Hyperarousal is characterized by difficulty falling asleep, being easily startled, irritability, poor concentration, and hypervigilance (*see* fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* [*DSM-IV*] for criteria) *(1)*.

1.1. Acute Stress Disorder

Acute stress disorder (ASD), a recent addition to diagnostic nomenclature *(1)*, is characterized by dissociative, re-experiencing, avoidance, and hyperarousal symptoms that begin between 2 d and 4 wk following the index event. Dissociative symptoms—including derealization, depersonalization, being in a daze, numbing, and amnesia—frequently predominate. Some preliminary studies suggest that the presence of ASD predicts the development of PTSD *(2–4)*, while many studies show that peritraumatic dissociation is a risk factor for PTSD *(5–7)*.

1.2. Disorders of Extreme Stress

Disorders of extreme stress (DES), also known as complex PTSD, has been proposed by van der Kolk, Herman, and others *(8,9)* to define a posttraumatic clinical syndrome characterized by problems in self-regulation of affect and impulses, disordered interpersonal functioning, and somatization, as well as alterations in attention or consciousness, perceptions of the perpetrator, self-perceptions, and meaning systems. These symptoms are currently described as associated features of PTSD in the *DSM-IV (1)*. The field trials for the *DSM-IV* found that adult survivors of childhood sexual abuse were 4.4 times more likely to suffer from DES. Adults who suffered both childhood sexual and physical abuse were 14.4 times more likely to suffer from this symptom complex *(9)*.

2. EPIDEMIOLOGY OF TRAUMA AND PTSD

2.1. Prevalence of Traumatic Events

Traumatic events are common experiences. The National Comorbidity Survey *(10)* revealed that 60.7% of men and 51.2% of women in the United States have experienced a traumatic event that meets the *DSM-IV* stressor criteria. The *DSM-IV (1)* defines a traumatic event as one in which the person experiences, witnesses, or is confronted with actual or threatened death or serious injury or a threat to the physical integrity of oneself or others and responds to this event with intense fear, helplessness, or horror. The National Comorbidity Survey *(10)* noted that experiencing one or more traumatic events was not uncommon. Persons of both genders reported similar prevalence rates for witnessing a single traumatic event (26%) and two traumatic events (14%); however, men were nearly twice as likely to witness three events (9.5 vs 5%) or four events (10.2 vs 6.4%).

The most common traumatic events for members of both genders were witnessing someone severely injured or killed; being in a fire or flood, or other natural disaster; or being in a life-threatening accident. Men were more often involved in these common traumatic events, with 35.6% witnessing a threat to life; 18.9% experiencing a fire or flood, or other natural disaster; and 25% being involved in a life-threatening accident. In contrast, 14.5% of women had witnessed a threat to life; 15.2% had experienced a fire or flood or other natural disaster; and 13.8% had been in a life-threatening accident. A higher proportion of men than women reported experiencing a physical attack (11.1 vs 6.9%); combat (6.4 vs 0%); or being threatened with a weapon, held captive, or kidnapped (19 vs 6.8%). Women were more likely to experience rape (9.2 vs 0.7%), sexual molestation (12.3 vs 2.8%), childhood neglect (3.4 vs 2.1%), or childhood physical abuse (4.8 vs 3.2%) *(4)*. In general, men are at greater risk for an attack from strangers, whereas women and girls are at greater risk from family members or acquaintances.

Although more than half the US population has suffered a traumatic event in their lifetime, only 7.8% of those traumatized had a lifetime prevalence of PTSD (Table 1). Women, although experiencing fewer lifetime traumatic events, were more likely to develop PTSD (10.4 %) compared with men (5%). Events reported to be most upsetting more frequently resulted in PTSD. Rape was the most upsetting trauma for both men and women and most likely to result in PTSD. Following rape, 65% of men and 45.9% of women developed PTSD. Other traumatic events for men that resulted in PTSD included combat, childhood neglect, and childhood physical abuse; for women, they included sexual molestation, physical attack, being threatened by a weapon, held captive or kidnapped, and childhood physical abuse. Women were more likely to have experienced one of the traumatic events identified as most upsetting and resulting in PTSD (67.6 vs 44.6%). Excluding rape and childhood neglect, women had a greater exposure to high-impact events and a greater likelihood of developing PTSD following exposure, accounting for the 2:1 probability that women will develop PTSD *(10)*.

2.2. Comorbid Disorders

Comorbid disorders are common in people who develop PTSD *(10–12)* (Table 2). Data from the National Comorbidity Survey *(10)* reveals that 88.3% of men with PTSD and 79% of women with PTSD also had another disorder, in most cases three or more comorbid disorders. This is in sharp contrast to individuals with other psychiatric disorders, who were much less likely to have a comorbidity. The most common comorbid disorders for men with PTSD were alcohol abuse or dependence (51.9%), major depressive disorder (MDD) (47.9%), conduct disorder (43.3%), simple phobia (31.4%), drug abuse or depen-

Table 1. Prevalence of Trauma Experiences From the National Comorbidity Study

Trauma Type	*Men*	*Women*
Witness to life threat	35.6%	14.5%
Fire, flood, other natural disaster	18.9%	15.2%
Accident	25.0%	13.8%
Physical attack	11.1%	6.9%
Combat	6.4%	0%
Threatened with weapon, held captive, or kidnapped	19%	6.8%
Rape	0.7%	9.2%
Sexual molestation	2.8%	12.3%
Childhood neglect	2.1%	3.4%
Childhood physical abuse	3.2%	4.8%

Adapted from ref. *10*.

dence (26.9%), social phobia (27.6%), dysthymia (21.4%), generalized anxiety disorder (GAD) (16.8%), and agoraphobia (16.1%). The most common comorbid disorders for women with PTSD were MDDs (48.5%), simple phobia (29%), social phobia (28.4%), alcohol abuse or dependence (27.9%), drug abuse or dependence (26.9%), dysthymia (23.3%), and agoraphobia (22.4%)

The question of whether or not an individual with PTSD has a comorbid disorder is confounded by the overlap in diagnostic nomenclature for PTSD, other anxiety disorders, and MDD *(11)*. Symptoms of diminished interest, sleep disturbances, irritability, difficulty concentrating, and restricted affect are shared by MDD and PTSD. Arousal and avoidance symptoms are common in PTSD and other anxiety disorders, including GAD, simple phobia, social phobia, and agoraphobia.

An additional, often difficult, challenge is to identify the primary disorder. Evaluators of the National Comorbidity Survey *(10)* attempted to answer this by assessing the age at which each disorder was identified. The survey results suggested that PTSD was primary when MDD and substance abuse disorders were comorbid. In women, but not in men, conduct disorder was secondary to PTSD. PTSD was likely to be primary when an anxiety disorder was present, although the findings were less robust than for affective and substance abuse disorders. In clinical settings, it is often difficult to determine if PTSD is the primary or secondary disorder. Unfortunately, family history is usually not revealing, because a family history of an affective disorder is a risk factor for PTSD *(13)* and a family

Table 2. Comorbidity and PTSD From the National Comorbidity Study

Comorbid Disorder	*Men*	*Women*
Major depressive disorder	47.9%	48.5%
Dysthymia	21.4%	23.3%
Alcohol abuse or dependence	51.9%	27.9%
Drug abuse or dependence	26.9%	26.9%
Simple phobia	31.4%	29%
Social phobia	27.6%	28.4%
Generalized anxiety disorder	16.8%	15.0%
Agoraphobia	16.1%	22.4.%
Panic disorder	7.3%	12.6%
Conduct disorder	43.3%	15.4%

Adapted from ref. *10*.

history of substance abuse is a risk factor for childhood abuse or neglect *(14,15)*. The age at which the index traumatic event occurred is the most reliable indicator of the primary disorder. However, this does not preclude that the other disorder would have developed without a traumatic experience. The question is relevant in the context of medication management because many of the comorbid disorders are chronic, associated with significant morbidity, and are typically treated with maintenance medication.

3. NEUROBIOLOGY OF PTSD

Over the past decade, much has been learned about the neurobiological underpinnings of PTSD. However, questions remain stimulating ongoing research into the biological, neuroendocrine, and neurochemical mechanisms of psychological trauma and PTSD. An area of common interest to PTSD and other anxiety disorders is the biology of fear *(16–19)*. Fear and conditioned fear memories have been understood to be a component of PTSD and were the initial basis for the development of behavioral therapy for PTSD *(20)*. The current state of knowledge indicates that although fear conditioning is an important factor, PTSD is the result of more complicated neurobiological mechanisms. Investigations of fear and PTSD suggest that they share common pathways and neuroana-tomic sites with complex interactions between multiple sites that include the amygdala, hippocampus and prefrontal cortex, as well as the hypothalamic– pituitary–

adrenal (HPA) axis *(16–19,21–23)*. Neuroimaging studies reveal increased activity in the amygdala and along anterior paralimbic pathways in response to trauma-related stimuli *(24)*, and decreased activity in the anterior cingulate and orbitofrontal cortices *(25)*.

The amygdala—the "fear center" of the brain—has been shown to be intimately involved in both fear and PTSD *(16,18,19)*. During a fear response, the amygdala activates downstream brain nuclei and pathways leading to an increased startle response, increased release of catecholamines, and activation of the sympathetic nervous system. At the same time, projections from the central nucleus of the amygdala to the bed nucleus of the stria terminalis activate the HPA axis. These neurochemical activities prepare the body for a "freeze, flight-or-fight" response and then activate the subsequent negative feedback loop that attenuate this response *(26)*.

Yehuda and colleagues *(21,22,27)* have reported that patients with PTSD experience dysregulation of the HPA axis, resulting in hypocortisolemia but paradoxically high corticotrophin-releasing factor (CRH) levels in the cerebrospinal fluid (CSF). Additionally, patients with PTSD typically have an exaggerated suppression of cortisol in response to dexamethasone. These findings suggest an increased sensitivity of the negative feedback system in the HPA axis. Yehuda *(21,22,27)* hypothesized that PTSD is facilitated by the inability to turn off the normal stress response at the time of the trauma, which results in a cascade of neuroendocrine and neurochemical alterations that leads to the development of PTSD symptoms. Additionally, elevated cortisol levels at the time of the trauma have been proposed as the underlying cause of hippocampal damage that has been found in patients with PTSD *(27–29)*. However, findings in a recent study of twin pairs discordant for trauma exposure suggest that a smaller hippocampus is not the result of trauma, but may be a risk factor for the development of PTSD subsequent to a traumatic event *(30)*. CRH levels have been found to be higher in the CSF of veterans with PTSD compared with a healthy community sample *(31)*.

In addition to CRH and cortisol, neurotransmitters such as norepinephrine (NE) and serotonin (5-HT) play a role in PTSD *(19,21,32,33)*. Patients with PTSD have elevated circulating levels of NE and increased α_2-adrenergic receptor reactivity. Yohimbine, a centrally acting α_2-adrenergic antagonist, has been shown to exacerbate anxiety, panic, and PTSD-like symptoms in study participants *(19,33,34)*. Medications such as selective serotonin reuptake inhibitors (SSRIs) and dual-action antidepressants that increase both 5-HT and NE levels in the synapse have been shown to be effective in the management of some of the symptoms of PTSD *(28,32)*.

Glutamatergic and γ-amino butyric acid (GABA) systems are integrally involved in the encoding and recovery of memories and may have a role in PTSD, especially in the disturbances of memory *(28)*. Dysregulation in NE Systems and

the HPA axis, as well as hippocampal dysfunction and activation of the amygdala have also been implicated in memory disturbances common in patients with PTSD *(28,32,35)*. Van der Kolk and colleagues, in their study of memory for traumatic experiences, found that such memories are qualitatively different from memories of everyday events *(35–37)*. Traumatic memories typically have a substantial sensorimotor or affective quality with little or no narrative component and occur as nightmares, flashbacks, or intrusions accompanied by increased autonomic activity.

Accumulating evidence suggests that people with PTSD suffer from a global neurobiological dysregulation that primarily involves neuroendocrine, serotonergic, and adrenergic systems. Dysfunction of several brain regions—including the hippocampus, amygdala, prefrontal and cingulate cortex, and cerebellum—have been implicated in this disorder.

4. PHARMACOTHERAPY FOR PTSD

4.1. Antidepressant Treatment

Several recent reviews consider SSRIs as the first line agents in the medication treatment of PTSD because of efficacy and safety *(21,38,39)*. Clinical outcome studies have found that three SSRIs (fluoxetine *[40–42]*, paroxetine *[43,44],* and sertraline *[45–48]*) have efficacy in the treatment of individuals with PTSD. These medications also have been shown to be effective in the treatment of patients with some of the common comorbid disorders associated with PTSD, including MDD, anxiety disorders, and substance abuse disorders *(49,50)*. The 1999 Expert Consensus Guideline for PTSD considered venlafaxine and nefazadone as second-line medications *(39)*. However, the data supporting these opinions is not robust.

4.1.1. Fluoxetine

Fluoxetine was found to be effective in the treatment of individuals with PTSD in three open-label studies *(51–53)* and in three double-blind, placebo-controlled studies *(40–42)*. A 5-wk, double-blind, placebo-controlled trial reported efficacy in total PTSD symptoms and in the numbing and hyperarousal clusters, but not in the re-experiencing and avoidance symptoms *(40)*. A subgroup analysis revealed that efficacy for PTSD symptoms was robust for the community sample; however, in the veteran sample, differences between fluoxetine and placebo were not significant. In this study, flexible dosing was used (20–60 mg/d), with an average dose of 40 mg/d in the fluoxetine group. Symptoms of depression also improved in the fluoxetine group. Three fluoxetine treatment-emergent side effects (headache, diarrhea, and sweating) reached levels of significance.

In a 12-wk, double-blind, placebo-controlled study, 53 civilians were randomly assigned to fluoxetine (20–60 mg/d) or placebo *(41)*. This study of primarily female patients (91%), found significant improvement in PTSD symptoms and overall functioning with fluoxetine. A subsequent report of an analysis of PTSD symptoms and the three PTSD symptom subscales indicated that fluoxetine had efficacy across all subscales, with the greatest improvement in the symptoms of avoidance and numbing *(54)*.

A recent double-blind, placebo-controlled trial of fluoxetine was conducted in patients from several war-torn areas in Europe, Israel, and South Africa *(42)*. The patients were predominately male (81%) and white (91%), and had experienced multiple combat-related events (48%) and/or were survivors of war or witness to wars (47%) and/or witnessed another person's death (33%). The study participants were randomized to fluoxetine (n = 226) titrated from 20 to 80 mg (mean dose: 57 mg) or placebo (n = 75). Based on clinician-rated measures, fluoxetine resulted in significant improvement in total PTSD scores as well as the intrusive and hyperarousal subscales, but not the avoidance and numbing subscale. These findings were statistically significant by week 6 and maintained significance throughout the 12-wk study. Additionally, clinician-administered measures of depression found significant improvement in symptoms of depression in the fluoxetine group. Patient-rated measures of both PTSD and depression failed to show a difference between placebo and fluoxetine. Fluoxetine was well tolerated with no treatment-emergent side effects reaching statistical significance; however, patients in the fluoxetine group had a slight decrease in erythrocyte count.

A recent study of combat veterans with chronic, severe PTSD failed to show any benefit from treatment with fluoxetine *(55)*. Combat veterans appear to be more challenging to treat, as suggested by two studies in which combat veterans did not respond well to fluoxetine treatment.

4.1.2. Paroxetine

Paroxetine has also been found efficacious in the treatment of PTSD. An open trial in a community sample of 17 patients reported that 65% of study patients had demonstrated improvement in total PTSD symptoms and all three PTSD subscales *(56)*. Patients also demonstrated improvement in symptoms of anxiety, depression, and dissociation.

In a 12-wk, double-blind, randomized placebo-controlled trial of paroxetine (20 or 40 mg) in 551 patients with chronic PTSD *(43)*, 62% of those who received the 40-mg dose and 54% of those who received the 20-mg dose had significant global improvement. There was a significant reduction in total PTSD symptoms and across all three symptom subscales. Paroxetine was well tolerated, although treatment-emergent side effects of asthenia, diarrhea, abnormal

ejaculation, impotence, nausea, and somnolence reached significance as compared with placebo.

A double-blind, randomized, placebo-controlled study of paroxetine using flexible dosages (range: 20– 50 mg/d; mean dose 27.6 mg/d) *(44)* found PTSD in the treatment group were significantly improved at weeks 4, 8, and 12. Patients in the paroxetine group were significantly improved in overall functioning in occupational, social, and family life. Paroxetine was well tolerated, with nausea, dry mouth, asthenia, and abnormal ejaculation as significant treatment-emergent side effects.

4.1.3. Sertraline

Sertraline has been investigated in three open-label studies *(50,57,58)* and in four double-blind, placebo-controlled studies *(45–48)*. Nearly 60% of treatment-refractory combat veterans in an open-label trial responded to sertraline with decreased symptoms of arousal, intrusions, and explosive behaviors *(57)*. An open-label study of rape victims revealed that four of five women with chronic PTSD had a greater than 30% reduction in PTSD symptoms following a 12-wk trial *(58)*. Brady and colleagues reported that sertraline resulted in symptom improvement in a small sample with comorbid alcoholism and PTSD *(50)*.

A double-blind, placebo-controlled study of 187 patients with PTSD using flexible dosing of sertraline (range: 50–200 mg/d) reported that sertraline resulted in a 53% reduction in total PTSD symptoms *(46)*. Significant efficacy was determined for two of three symptoms clusters—avoidance and numbing and increased arousal—but not in the re-experiencing/intrusion cluster. Sertraline was well tolerated, with insomnia being the only side effect to reach significance compared with placebo.

In another 12-wk, double-blind, placebo-controlled trial in 200 patients, investigators reported that sertraline achieved a greater reduction in PTSD symptoms (60 vs 38% in the placebo group) *(47)*. Across the three symptoms clusters, re-experiencing /intrusions symptoms were reduced by 50%, avoidance and numbing symptoms by 47%, and increased arousal symptoms by 40%. Sertraline treatment resulted in a marked improvement in quality of life and functional measures, with 58% of patients within 10% of community norms *(48)*. Sertraline had several side effect that reached significance compared with placebo (insomnia, diarrhea, nausea, fatigue, and decreased appetite) *(47)*.

A 24-wk open-label continuation study of patients who completed the initial study reported a 25% improvement rate for PTSD symptoms after 12 wk of treatment *(59)*. In addition, 54% of patients who did not respond to therapy during the initial 12-wk study became responders with continued sertraline therapy *(48)*. The 24-wk continuation phase resulted in an additional 20% improvement in quality of life and functioning. A follow-up study enrolled con-

tinuation-phase responders in a double-blind, placebo-controlled maintenance study for an additional 28 wk *(45)*. Sertraline was dosed flexibly from 50 to 200 mg/d. Continued treatment with sertraline resulted in lower relapse rates (5 vs 26% in the placebo group), with significant findings across all three PTSD symptom clusters. Patients who received placebo were 6.4 times more likely to relapse with recurrences of significant PTSD symptoms and an accompanying reduction in quality of life and functioning, although less than at time of initial study entry.

4.1.4. Citalopram

Citalopram has not been studied in double-blind, placebo-controlled trials for the treatment of PTSD. A case report *(60)* and one open-label study *(61)* suggest that citalopram is well tolerated and may reduce PTSD symptomatology.

4.1.5. Fluvoxamine

Fluvoxamine has been studied only in open-label trials, all of which revealed improvement in some or all clusters of PTSD symptoms *(62–65)*. A recent open-label study of 15 veterans with combat-related PTSD resulted in a nearly 50% dropout rate due to side effects *(62)*.

4.1.6. Venlafaxine

An open-label, study compared sertraline, paroxetine, and venlafaxine in 32 Bosnian refugees living in the United States and experiencing PTSD *(66)*.This 6-wk study randomly assigned the participants to three treatment groups. The first group received 50 mg/d sertraline for 14 d and then increased to 100 mg/d as tolerated. The paroxetine group received a fixed dose of 20 mg/d. Venlafaxine was initiated at 37.5 mg twice daily for 2 wk and then increased to 75 mg twice daily as tolerated. A significant decline in the number of PTSD symptoms was reported for all three treatment groups, although at the end of the study, all remained sufficiently symptomatic to continue to meet diagnostic criteria for PTSD. Sertraline and paroxetine were associated with a significant decrease in depressive symptoms and increased overall functioning. Sertraline and paroxetine were better tolerated than venlafaxine, which had a high dropout rate. None of the patients in the sertraline or paroxetine group dropped out of the study. Conclusion from this study are limited as a short 6-wk trial and low dosages of medications were used. Expert consensus guidelines *(38)* indicate that in clinical practice, venlafaxine is considered efficacious for the treatment of PTSD. However, to date few research data are available to support this clinical opinion.

4.1.7. Nefazadone

Nefazadone, an SSRI and 5-HT_2 antagonist, has shown efficacy in an open-label study in combat veterans *(67)*. Treatment responses included improved sleep and decreased anger. However, the recent black box warning of the risk of

hepatic failure and the current level of research data do not allow the initial expert consensus in favor of nefazadone to be sustained.

4.1.8. Monoamine Oxidase Inhibitors

Phenelzine—an irreversible monoamine oxidase inhibitor (MAOI) has been reported in case studies, two open-label studies *(68,69)*, and two randomized studies—to be effective in the treatment of patients with PTSD *(70,71)*. In one open-label study, investigators failed to observe any benefit for this drug *(72)*. A review of the literature on MAOIs indicates that 82% of patients with PTSD obtained moderate to good improvement, with the greatest reduction in symptoms observed for re-experiencing and insomnia *(73)*. Avoidant, numbing, and hyperarousal symptoms, as well as symptoms of depression and anxiety did not improve. The use of MAOIs raised clinician concern about patient adherence to necessary dietary restrictions, as a hypertensive crisis could result following the ingestion of foods or beverages that are rich in tyramine. The risk of serotonin syndrome is high if patients prescribed MAOIs use meperidine. These concerns limit the extent to which MAOIs are used. However, meclobemide, a reversible MAO-A inhibitor, does not share these features and has been associated in an open-label trial with a reduction in the PTSD symptoms of re-experiencing and avoidance *(74)*. There is conflicting evidence for the effectiveness of brofaromine (a reversible MAOI) in the treatment of PTSD. In two studies *(75,76)*, researchers found that brofaromine may provide some benefit in patients with less severe symptoms of PTSD. Baker and colleagues *(77)* conducted a large, multicentered, double-blind, placebo-controlled trial of brofaromine, in which they observed no difference between groups. Meclobemide and brofaromine are not currently available in the United States.

4.1.9. Tricyclic and Tetracyclic Antidepressants

In randomized clinical trials, investigators found that imipramine *(70)* and amitryptyline *(78)* were effective for the treatment of PTSD, but despiramine was not*(79)*, An analysis of 15 case reports and both open-label and randomized clinical trials revealed that 45% of patients treated with tricyclic antidepressants (TCAs) reported improvement in PTSD symptoms *(73)*. These findings were less robust than the comparison of MAOIs. Overall, TCAs were more effective for reducing symptoms of re-experiencing than for avoidance/numbing or hyperarousal. The side effects of TCAs include those associated with the blockade of muscarinic cholinergic receptors (dry mouth, constipation, urinary retention, and mydriasis), blockade of histamine H1 receptors (sedation and weight gain), and α_1-receptor blockade (orthostatic hypotension). These side effects are not well tolerated by many patients with PTSD. Given their side-effect profile and efficacy status, TCAs hold no advantage over SSRIs or MAOIs. However, their efficacy

may not be as negative as is suggested by these studies, which were performed primarily in combat veterans with PTSD as combat veterans did not respond as well as community patients in PTSD treatment studies with SSRIs *(40)*. It is possible that TCAs may play a role in the patient who is refractory or unable to tolerate SSRIs or MAOIs. In general, the tertiary amine TCAs which have strong serotonergic effects have shown greater efficacy in the treatment of individuals with PTSD than the secondary amine TCAs, which have both serotonergic and NE effects.

4.1.10. Trazadone

Trazadone, an SSRI and 5-HT_2 antagonist, is commonly used as a hypnotic because it is highly sedating effect. In one open-label study, investigators found only mild effectiveness for PTSD symptoms *(80)*. However, trazadone is often used in combination with SSRIs as a hypnotic. Its usual dosage range is 25 to 500 mg once daily at bedtime.

4.1.11. Bupropion

Bupropion was reported effective against hyperarousal in patients with PTSD in a small open-label study *(81)*

4.1.12. Mirtazapine

In a single open-label study of six adults with chronic, severe PTSD, investigators reported that three patients had a 50% decrease in PTSD symptomatology *(82)*. In a recent double-blind, placebo-controlled pilot study, mirtazapine was found to be efficacious for PTSD *(83)*.

4.1.13. Summary

SSRIs are considered first-line treatment for PTSD, whereas MAOIs and tertiary TCAs may have a role in the treatment of nonresponders or patients who cannot tolerate SSRIs. Treatment studies of fluoxetine, sertraline, and paroxetine indicate that all are effective in the treatment of patients with PTSD. SSRIs have several advantages, including efficacy in the treatment of disorders that may be comorbid with PTSD, including MDD and various anxiety disorders (GAD, social phobia, and panic disorder). Additionally, prelimary studies suggest that the SSRIs may be helpful in the treatment of patients with comorbid alcohol disorders. These medications are well tolerated. Venlafaxine may have some role; however, the data on this antidepressant are derived from case reports and open-label studies, only. Nefazadone has been suggested as having a role in PTSD therapy, but there are little data to support this.

5. ADJUNCTIVE THERAPY

5.1. Anxiolytics/Hypnotics

The use of benzodiazepines in the treatment of PTSD continues to be debated. In an open-label study of two benzodiazepines, alprazolam and clonazepam, investigators did not find any global improvement in PTSD over placebo *(84)*. However, there was improvement in physiological arousal. For patients with persisting anxiety or sleep disturbance in the aftermath of a traumatic event who have not benefited from acute psychological interventions, judicious short-term use of a benzodiazepine may calm the patient sufficiently to allow engagement in psychological interventions. Given the degree of comorbid substance abuse in patients with PTSD, benzodiazepine therapy beyond a brief period may complicate the treatment. In addition, withdrawal symptoms—reported as severe in a study of eight combat veterans with PTSD—may develop, including increased symptoms of PTSD and rage *(85)*. Trazadone may be a preferred alternative for sleep.

5.2. Mood Stabilizers

Lithium was investigated in two open-label trials in combat veterans, with both investigators in both trials reporting improvement in emotional control and hyperarousal *(86,87)*. Data in support of the use of anticonvulsants in patients with PTSD is based primarily on case reports and open-label studies. The theoretical premise for their use is based on the kindling theory, which suggests that symptoms of PTSD begin with an irritable limbic focus that expands to recruit larger areas of the brain, resulting in more symptoms *(28)*. Anticonvulsants appear to raise the neuronal threshold for arousal by stimulating GABA receptors and increasing chloride conductance. Thus, it was hypothesized, intrusive thoughts and hyperarousal symptoms would diminish with anticonvulsant therapy. In an open-label trial and case reports, valproic acid was associated with a diminished number of intrusive thoughts and diminished hyperarousal symptoms *(88)*. In two open-label trials of carbamazepine in veterans with complex PTSD, anger, substance abuse, and Axis II disorders, investigators reported improvements in impulse control *(89,90)*. Both of these anticonvulsants may cause a range of side effects, including sedation, dizziness, nausea, and vomiting. Two potentially serious adverse reactions to carbamazepine—blood dyscrasias and hepatitis—require monitoring during treatment. Valproic acid has also been found to elevate cholesterol and liver enzymes. Both carbamazepine and valproic acid are contraindicated during pregnancy.

Several newer anticonvulsants have been investigated for their usefulness in patients with PTSD. A retrospective open-label study of gabapentin reported

reduction in sleep disturbances as well as a decrease in the frequency of nightmares *(91)*. A small, 12-wk, double-blind study of lamotrigine found improvement in re-experiencing and avoidance/numbing symptoms *(92)*. Topiramate has been reported to be effective as an adjunct or as monotherapy for patients with chronic PTSD. A recent open-label study showed that nightmares, flashbacks, and intrusive thoughts occurred less frequently in patients taking topiramate *(93)*. All of these newer agents share certain side effects—somnolence, fatigue, dizziness, and ataxia. Additionally, lamotrigine has been associated with serious rashes, primarily in the pediatric population. However, a rash in any age group resulting from lamotrigine use warrants discontinuation.

5.3. Antipsychotics

As with several other psychopharmacologic interventions in current clinical use for PTSD, few studies have investigated the use of either typical or atypical neuroleptics. Sernyak and colleagues *(94)* reviewed data from two large outcome studies to examine the role of neuroleptics in PTSD, finding that patients with more severe PTSD symptoms (particularly intrusive symptoms) were commonly treated with a neuroleptic medication. However, treatment outcomes were no different than those observed in patients who did not take neuroleptic medication.

Several recent trials indicate that atypical antipsychotics may have a role in treating patients with PTSD *(95–98)*. In a 6-wk open trial in combat veterans, quetiapine significantly reduced PTSD symptoms and was very well tolerated *(95)*. In a 6-wk, double-blind, placebo-controlled study in combat veterans with high arousal symptoms, investigators found risperidone reduced irritability and the number of intrusive thoughts *(96)*. Hamner and colleagues *(97)* assessed the efficacy of risperidone in combat veterans who had PTSD and comorbid psychotic symptoms. In this 5-wk, double-blind, placebo-controlled trial, they found risperidone to be more effective than placebo for reducing psychotic symptoms and re-experiencing symptoms. In an 8-wk open trial of combat veterans, investigators found that olanzapine reduced symptoms of PTSD, depression, and anxiety *(98)*. However, the dropout rate was higher in this trial than in other trials of atypical antipsychotics. A 10-wk, double-blind, placebo-controlled trial of olanzapine, did not show a significant difference by the end of treatment *(99)*. A small open trial of risperidone in burn patients with acute stress disorder found improvement in sleep and re-experiencing and hyperarousal symptoms *(100)*.

5.4. Other Medications

Clonidine, an α_2-agonist, has been reported in open-label trials in adults *(101,102)* and children *(103,104)* to reduce PTSD symptoms, including re-experiencing and hyperarousal. Harmon and Riggs *(103)* caution against the use of clonidine in children, noting cardiac concerns. Clonidine is sedating, and this

side effect may be helpful for patients with sleep disturbances. Clonidine is used to treat menopausal symptoms, particularly night sweats, and, thus, may be an excellent choice for symptomatically menopausal women with PTSD. Propranolol, a β-blocker, has been found to reduce re-experiencing and hyperarousal symptoms in adults *(101)* and children with PTSD *(105)*. In a recent double-blind, placebo-controlled pilot study designed to determine whether propranolol has a role in the prevention of PTSD *(106)*, patients were treated with propranolol within the first 6 h of the index event and treatment continued for 10 d. At the 1-mo follow-up assessment, there was no significant difference in PTSD scores; however, at 3 mo the propranolol group exhibited a lower level of physiological arousal to script-driven imagery. Clonidine and propranolol, commonly used to treat patients with hypertension, may result in hypotension in normotensive persons. Additionally, propranolol is contraindicated in persons with asthma and has been reported to induce or exacerbate major depressive episodes.

6. PSYCHOSOCIAL TREATMENTS

In addition to pharmacotherapy, psychosocial therapy is indicated for patients with PTSD. According to recently published PTSD treatment guidelines *(38,39)*, both exposure-based therapy and pharmacotherapy are efficacious. Among the exposure-based therapies, cognitive behavioral therapy is given the highest rating, with eye movement desensitization and reprocessing proposed as an alternative treatment option.

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10 Antidepressant Therapy in Children and Adolescents

An Overview for the Generalist

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Contents

1. INTRODUCTION

In this chapter, we present an overview of antidepressant pharmacotherapy for depressive disorders in children and adolescents. Our intended audience is the generalist, who may be called on to treat older adolescents for whom the demarcation between adulthood and adolescence may not be clear-cut. From the vantage point of the clinical psychopharmacologist who treats adults, several areas require special attention in adolescents, including (a) recognition, diagnosis, and differential diagnosis; (b) selection of the psychosocial intervention used with pharmacotherapy; (c) dosing strategies based on pharmacokinetics and pharmacodynamics; (d) pharmacotherapy in the context of common comorbid conditions; and (e) duration of antidepressant therapy. One of the most startling differences between the fields of adult and childhood antidepressant therapy is the relative paucity of research data from clinical trials in children that can be used to make informed clinical decisions.

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Depression in children and adolescents is both common and underrecognized by generalists. Accurate diagnosis and effective therapy can measurably improve the lives of children and teens with this potentially serious illness. An estimated 2.5% of children and up to 8.3% of adolescents in the United States suffer from depression *(1–3)*. In a 6-mo study of 9- to 17-yr-olds, the prevalence of depression was estimated at more than 6%, with 4.9% having major depression *(4)*. Additionally, research indicates that the onset of depression is earlier in life today than in past decades *(5)*. During childhood, the number of boys and girls affected is almost equal. In adolescence, twice as many girls as boys are diagnosed with this disorder. Among both children and adolescents, depressive disorders confer an increased risk for illness and interpersonal and psychosocial difficulties that persist long after the depressive episode is resolved; in adolescents, the risk for substance abuse and suicidal behavior is also increased *(6)*. Psychopharmacological treatment must be part of a comprehensive plan that includes psychotherapy and family intervention. Prescribing practices in children and adolescents have typically been based on clinical experience, with few controlled clinical trials available. Despite this, the number of antidepressant prescriptions, especially selective serotonin reuptake inhibitors (SSRIs), has increased dramatically in children younger than 18 yr *(7)*.

2. RECOGNITION, DIAGNOSIS, AND DIFFERENTIAL DIAGNOSIS OF CHILD AND ADOLESCENT DEPRESSION

The behavior of depressed children and teenagers may differ from the behavior of depressed adults; however, the *DSM-IV* criteria for childhood and adult Major Depression are the same *(8)*, which require five or more of the specific symptoms during a 2-wk period, with at least one of the symptoms being "depressed mood or loss of interest or pleasure" (*see* also Table 1). Other symptoms, according to the *DSM-IV*, include persistent depressed mood or irritability, weight changes, sleep disturbance, psychomotor agitation or retardation, fatigue, guilt, concentration difficulties, suicidal ideation, attempts, or frequent thoughts of death.

Children often lack the ability to verbalize their feelings. Instead, their behavior is an indication of how they feel. Children with depression may appear persistently sad, may no longer enjoy activities they normally enjoy, or may frequently appear agitated, "hyper," or irritable. Depressed children may frequently complain of physical problems such as headaches and stomachaches and often have frequent absences from school or poor performance in school. They may appear bored or low in energy and frequently have problems concentrating. A major change in eating or sleeping patterns is a frequent sign of depression in children and adolescents. Children may mask or hide their depressive feelings with aggressive behaviors such as severe, recurrent temper tantrums. In older

Table 1

Symptoms of Major Depressive Disorder Common to Adults, Children, and Adolescents

- Persistent sad or irritable mood
- Loss of interest in activities once enjoyed
- Significant change in appetite or body weight
- Difficulty sleeping or oversleeping
- Psychomotor agitation or retardation
- Loss of energy
- Feelings of worthlessness or inappropriate guilt
- Difficulty concentrating
- Recurrent thoughts of death or suicide

Five or more of these symptoms must persist for 2 or more weeks before a diagnosis of major depression is indicated.

Signs That May Be Associated with Depression in Children and Adolescents

- Frequent vague, non-specific physical complaints such as headaches, muscle aches, stomachaches or tiredness
- Frequent absences from school or poor performance in school
- Talk of or efforts to run away from home
- Outbursts of shouting, complaining, unexplained irritability, or crying
- Being bored
- Lack of interest in playing with friends
- Alcohol or substance abuse
- Social isolation, poor communication
- Fear of death
- Extreme sensitivity to rejection or failure
- Increased irritability, anger, or hostility
- Reckless behavior
- Difficulty with relationships

Source: National Institute of Mental Health

children and adolescents, classic signs and symptoms include low self-esteem, guilt, loss of interest in school and work-related activities, decrease in school performance, boredom, and apathy, in addition to sleep, appetite, and weight changes. Younger children also may manifest similar characteristics. However, it is common for young, school-age children to present with irritability, restless-

Table 2

Biological Measure	*Children*	*Adolescents*	*Adults*	*Comments*
Basal Cortisol	Usually normal, but if elevated occurs at night	Usually normal, but if elevated occurs at night	Often elevated (50%)	24-h serial collections necessary
Cort to CRH	Normal	Normal	Blunted	
DST	Nonsuppression rates comparable to adults	Nonsuppression rates slightly lower than children or adults	Nonsuppression rates highest in psychotic, endogenous	Dosing and procedures vary greatly across studies; differences between groups may not be valid
GH	Blunted to clonidine GHRH, L-dopa	Blunted to desipramine, but not clonidine, dextroamphetamine, L-dopa	Most studies report blunted response to common probes	
PRL	Augmented PRL after fenfluramine	Blunted after clomipramine, augmented after mCPP	Most studies reported blunted response to serotonergic challenge	Small numbers of subjects
Thyroid	Insufficient data	Insufficient data	Decreased T3, TSH Increased T4	
TSH to TRH	Insufficient data	Insufficient data	Blunted	
Sleep	Three studies showed no sleep changes in children. One study reported increased sleep latency, decreased REM latency	Similar to adults; most studies showed increased sleep latency, decreased REM latency, increased REM density, no Stage 3/4 changes	Increased sleep latency, reduced REM latency, increased REM density decreased Stage 3/4	
Immune Function	Relationship to depression not established	Relationship to depression not established	Reduced	
TCA Response	Superiority to placebo not established	Superiority to placebo not established	Efficacy established	
SSRI Response	Evidence to support efficacy	Evidence to support efficacy	Efficacy established	

Key to Abbreviations
CORT: Corticotropin
CRH: corticotropin releasing hormone
DST: dexamethasone supression test
GH: Growth hormone
GHRH: Growth hormone releasing factor
PRC: Prolactin
TSH: thyroid stimulating hormone
TRH: thyrotropin releasing howmone

ness, and hyperactivity, which frequently leads professionals to suspect attention deficit with hyperactivity disorder (ADHD) instead of depression *(9)*.

In addition to different symptom patterns, neurobiological correlates of mood disorders may not be the same in children and adults. Table 2 summarizes some of the findings of Kaufman and colleagues *(10)* who compared the differences between biological factors associated with depression in children, adolescents, and adults. Taken as a whole, the differences in the biological correlates of depression in children and adults suggest that antidepressant treatment of children may require a different approach from that used in adult patients. Unfortunately, there is not a clear, biologically based rationale for antidepressant treatment in children.

Early-onset depression may differ from adult-onset depression in two fundamental ways: early-onset depression may be a different illness (or several different illnesses) than adult depression, or early-onset and adult-onset depression may be the same illness at different stages of progression *(10)*. Whichever is the case, pharmacotherapy targeted for a specific condition cannot selected until the underlying neuropharmacology is elucidated, and this process is only in the preliminary stages of development.

It is generally believed that the neural pathways and monoamines systems that regulate mood are not fully developed in childhood. Whereas serotonergic activity in the prefrontal cortex matures relatively early in childhood, dopamine innervation of the prefrontal cortex is not complete until young adulthood *(10)*. One complicating factor is that very little is known about the postnatal maturation process of the human brain. Most data are extrapolated from rodent models, some from non-human primates, and a handful from human studies *(10a)*. These studies have established that neurotransmitters, such as 5-HT, may function as neurotrophic factors initially, and only later develop as neurotransmitters *(10b)*. Such a characteristic not only supports a changing function of neuromodulators during maturation, but may also provide evidence that these neurotransmitters could act as neurotrophic agents in the presence of antidepressant medications *(10c)*.

It is also known that different neural systems mature at different stages of postnatal development and that the same neurotransmitter systems mature at different rates depending on their location in the brain, with patterns varying not only in particular cortical regions but also depending on the cortical layer and type of synapse *(10a)*. For example, in monkeys, dopamine concentrations increase in all areas of the brain postnatally; however during puberty patterns of increase and decrease vary depending on cortical region *(10d)*. The same may be said of neuroreceptors, neurotransporters *(10e)*, and enzymes responsible for oxidative deamination of monoamines *(10f)*. Neuroimaging studies have identified several potential deficits in childhood depression, including left cortical anterolateral hypoactivation *(10a)*. To the extent that these deficits are associated with alter-

ations in neurotransmitter function, a rationale for pharmacotherapy may eventually evolve. Magnetic resonance spectroscopy has identified increased choline compounds in the left orbitofrontal *(10h)* and dorsolateral prefrontal cortex *(10i)* in adolescents with major depression compared to healthy adolescent volunteers. Future research must carefully address the issue of depressive subtypes and comorbidity in childhood depression as clinical trials of antidepressants proceed.

2.1. Diagnosis

The psychiatric interview should be conducted by a clinician who is experienced in developing therapeutic relationships with children and adolescents. The diagnostic process should include interviews of the parents and the child. Parents are more likely to report outward signs of depression and the child may be more aware of inward signs. A comprehensive family psychiatric history may also help the therapist identify a child at high risk for bipolar disorder, which may influence pharmacotherapy. A recent physical examination and laboratory studies designed to rule out medical etiologies of behavioral disturbances is essential, and may be done in collaboration with a pediatrician or family medicine physician. A neurological examination and neuropsychological testing should be included, the latter to rule out ADHD, which has a high comorbidity with depression. Other commonly associated conditions should be considered, including substance abuse, anxiety disorders, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and conduct disorder.

2.2. Comorbidity

Since childhood depression is associated with high psychiatric comorbidity, it is imperative that other psychiatric disorders be considered when assessing a child. Comorbidity has been found to exist in 40% to 70% of depressed children and adolescents. These comorbidities include the "double depression" and anxiety disorders which are 2 to 25 times more likely to occur in depressed children than nondepressed children. Disruptive disorders such as conduct disorder, which is estimated at five times more likely to occur in depressed children than nondepressed children, and ADHD are both commonly occurring comorbidities. Major depressive disorder is also associated with substance abuse and personality disorders. Comorbidities are negative prognostic factors because they increase the duration and severity of episodes of major depressive disorder, and the likelihood of recurrence and suicidal tendencies *(11,11a,11b)*.

3. TREATMENT

3.1. Psychosocial Interventions

Most authorities agree that psychotherapy is the preferred initial treatment in depressed children, except in cases where depressive symptoms are so severe that immediate relief is necessary *(7)*. Medication is usually considered only after an adequate trial of psychotherapy. Proponents of this position argue that combined use of medications and psychotherapy at the onset of treatment can make it difficult to evaluate treatment effectiveness and identify the specific source of change. Few empirical data are available that support this approach, but it is intuitively appealing because it limits exposure to the risks of medications. Research in adults has revealed that combined psychotherapy and medication is often necessary, beneficial, and superior to either modality alone. A definitive answer to the question in childhood depression must await the results of more clinical trials. A variety of psychotherapeutic techniques have been shown to be effective, including cognitive behavioral therapy, multisystemic therapy, interpersonal psychotherapy, and family therapy. No reliable data are available to suggest that any one type is superior to another in combination with antidepressant therapy in children.

3.2. Pharmacotherapy

The antidepressant agents available and approved for adults are also used in children. The most active area of clinical research is the use of SSRIs, with fewer studies of the mixed action or noradrenergic antidepressants. In contrast to adult pharmacotherapy, the efficacy of tricyclic antidepressants (TCAs) in children and adolescents has been difficult to demonstrate, whereas clinical trials of SSRIs have reported efficacy compared to placebo. Prior to discussing individual drug classes, pharmacokinetic and pharmacodynamic factors are briefly reviewed.

3.2.1. Pharmacokinetics and Pharmacodynamics

Based on data available at the present time, the cytochrome P450 (CYP) system reaches maturity by the third year of life, at which time the distribution of metabolic genotypes and phenotypes appear to be similar to that in the adult population *(11c–13)*. Antidepressant pharmacokinetics, when body mass index is taken into consideration, is similar in adults and children. The primary reason for dose adjustment (i.e., reduction) in children is based on body weight, not on alterations in drug metabolism.

Alterations of drug biotransformation across the life cycle are complex, and the relationship between aging and drug metabolizing capacity is not linear. Research data are expanding rapidly in this field; the following discussion will emphasize only the most important issues. For details, the reader is referred to two excellent reviews by Leeder and associates *(12,14)*.

The pharmacokinetics of antidepressants in fetuses, children, and adolescents has been studied using in vitro models, drug challenges using cytochrome probes, and drug serum levels from clinical studies *(14)*. At the risk of oversimplification for the sake of clarity, we will discuss only general trends. With respect to CYP2D6, fetuses have 1% of adult activity; infants during the first month of life have 20% that of adults; full adult activity is reached between 3 and 5 yr of age *(14)*. Clinicians should be mindful that genetic polymorphisms exist; e.g., up to 10% of whites metabolize 2D6 slowly, whereas the rate in Asians is much lower (1–2%) *(14)*. Limited data suggest that CYP2C19 and CYP2C9 have little or no activity in fetuses, although they are detectable during the first few wk of life, reaching adult levels by 6 mo and actually exceeding adult activity by approximately one- to twofold until the end of puberty, when they decline to adult levels. CYP1A2 activity reaches adult rates by 4 mo of age, but may continue to rise in children until the end of puberty, although some gender differences have been reported *(14)*. Compared with adult activity, CYP3A4 is lower during the first year of life, higher from age 1 to 4 yr, and equivalent by the end of puberty *(14)*. Glucuronyltransferases (UGTs) conjugate medications and drug metabolites with glucuronic acid to facilitate excretion. These enzymes are of great importance in clinical practice and exhibit genetic polymorphism (e.g., mutation of UGT1 is responsible for Gilbert's disease). Despite a lack of data, UGT activity is known to be low or absent in fetuses (depending on the subtype) and gradually increases after birth. UGT1A1 reaches adult levels by 6 mo of age. *N*-acetyltransferase 2, which is responsible for acetylation, shows low activity in fetuses through the first 2 mo of life and reaches adult values between 1 and 3 yr of age. The activities of metabolizing enzymes are influenced by genetic polymorphisms, age, and drug–drug interactions; clinicians should consider these factors when prescribing antidepressants for children and adolescents.

Wilens and colleagues *(15)* used population pharmacokinetics data to describe the pharmacokinetic parameters of fluoxetine and norfluoxetine in 10 children aged 6–12 yr and 11 adolescents aged 13–18 yr. Mean steady-state fluoxetine and norfluoxetine levels were 127 ng/mL and 151 ng/mL, respectively, after 4 wk of 20 mg of oral fluoxetine. Fluoxetine serum concentrations in adolescents were twice that in children; norfluoxetine levels were 1.7 times higher in adolescents. When normalized to body weight, concentrations were similar in both groups. Unless future studies reveal tolerability problems in younger age groups, the findings of this study suggest that a 20-mg starting dose

in adolescents, and 10 mg in children, should produce serum levels comparable to those seen in adults. Wide interindividual variability in metabolism of fluoxetine occurs in both adults and children.

Thirty depressed individuals between the ages of 6 and 17 yr (mean age: 11.2 ± 2.9 yr) were studied to establish the pharmacokinetics and safety of paroxetine in this age group *(16)*. The mean elimination half-life of a 10-mg dose of paroxetine was 11.1 h, approximately half the value recorded for adults. Other pharmacokinetic parameters, including T_{max}, and fraction excreted unchanged in the urine, were similar to published values for adults. During the chronic dosing portion of the study, nonlinear pharmacokinetics was observed, again similar to those observed in studies of adult populations. Activity of the CYP2D6 locus correlated directly with both the apparent steady-state volume of distribution (divided by bioavailability) and total body clearance (divided by bioavailability) and inversely with the fraction excreted unchanged in urine. A trend suggested that the elimination half-life correlated with catechol-O-methyl-transferase (COMT) activity. Paroxetine appeared to be well tolerated in this study, with the only adverse event leading to medication discontinuation being hypomania in two study participants, one of whom did not metabolize CYP2D6 well. In summary, this study suggested that paroxetine may be cleared more rapidly in adolescents and children; however, the typical doses of 10 to 20 mg should be used in the absence of evidence that a specific individual is a poor metabolizer of CYP2D6.

The pharmacokinetics and safety of sertraline were studied in children and adolescents after a single 50-mg dose, followed by 35 d of treatment using two different titration schedules *(17)*. Elimination half-life, 24-h area under the curve (AUC), and C_{max} were similar for adults and children. Although C_{max} and 24-h AUC were greater in the 6- to 12-yr-old subgroup compared with the 13- to 17-yr-old subgroup, the elimination half-life and time to maximum concentration did not differ. Furthermore, when pharmacokinetic parameters were normalized by weight, there were no group differences for sertraline vs desmethysertraline. Adverse effects were typical for sertraline, i.e., headache (21%), nausea (21%), insomnia (21%), somnolence (15%), dyspepsia (12%), and anorexia (12%), with dyspepsia occurring more often in the younger subgroup (21 vs 6%). These findings suggest that neither the adult rate of dose titration or maximal dose needs to be altered in most children and adolescents. Dose adjustments should be based on body mass, but the wide safety and tolerability profile of sertraline should present few clinical problems.

The issues concerning the enantiomers of citalopram were discussed in Chapter 2. One study examined the steady-state concentrations of enantiomers in adolescents (mean age: 18 yr; range: 15–20 yr) and found ratios similar to those in adults *(18)*.

The most comprehensive pharmacokinetic study of desipramine was conducted by Cohen and associates *(19)* in a clinical sample of 173 patients (90 children aged 6–12 yr and 83 adolescents aged ≥12 yr) referred to a pediatric psychopharmacology clinic. The desipramine dosage was adjusted to maintain a serum concentration of 300 μg/L. No difference in dose or weight- and dose-normalized serum concentrations and clearance was seen between children and adolescents, nor was a sex effect detected. All values were similar to published data for desipramine pharmacokinetics in adults. This is quite consistent with data on the maturation of CYP2D6 activity discussed earlier. The investigators stress that these findings may not apply to the tertiary parent compound of desipramine—imipramine—which may have a more complex involvement of different cytochromes. Imipramine may demonstrate increased clearance during childhood and adolescence, which is again consistent with our earlier discussion of greater activity for CYP3A4, CYP2C19, and other cytochromes during childhood compared to adulthood.

Nefazodone biotransformation is also complicated, with at least three active metabolites metabolized via CYP2D6 and CYP3A4; in addition, the parent compound is also inhibits CYP3A4 activity. In a study of single-dose and steady-state kinetics of 100 mg of nefazodone twice daily in 28 patients—15 children with a mean age of 10 yr, (range: 7–12 yr) and 13 adolescents with a mean age of 14.2 yr (range: 13–16 yr)—plasma nefazodone concentrations were substantially higher in children compared to adolescents*(20)*. Similar elevations were found in the hydroxynefazodone metabolite, with smaller increases in the dione and *m*CPP metabolites. Of note, the younger group had a mean weight of 44.7 kg and the older group 68.5 kg, representing a 53% greater body mass, which may explain the group differences. The nefazodone elimination half-life was more rapid in children and adolescents (3.5 and 3.9 h, respectively) than in published reports of 7 h for adults. The nefazodone dose should be adjusted to body mass when used in children or adolescents.

Pharmacodynamic differences between adults and children have not been carefully studied. The most important clinical findings are that TCAs do not have established efficacy in early-onset depression and that children may be more susceptible to the cardiac adverse effects of TCAs. Clinical studies reporting adverse effects are discussed below.

3.2.2. SSRIs

The combination of SSRIs and psychotherapy is now recommended for first-line treatment in depressed children and adolescents due to better tolerability than with the TCAs *(21)*.

Open-label trials of sertraline *(22)* and paroxetine have suggested these drugs are efficacious in early-onset depression. A 10-wk, multisite, double-blind, placebo-controlled study assessed the safety and efficacy of sertraline (50–200 mg/d) in the treatment of 376 children and adolescents with major depressive disorder (MDD) *(23)*. The sertraline group experienced clinically significant improvements, as indicated by the Children's Depression Rating Scale-Revised (CDRS-R) score compared to the placebo group, and sertraline was found to be both efficacious and well-tolerated.

In an early study, Simeon and associates *(24)* found a nonsignificant trend for fluoxetine to be superior to placebo in adolescents with depression; however, the small number of completers ($n = 30$) may have minimized group differences. In a large multisite study, Keller and associates compared 20 to 40 mg of paroxetine, 200 to 300 mg of imipramine, and placebo in 275 adolescents with major depression. The paroxetine group showed greater efficacy than placebo on the primary outcome measures of depression; no differences were found between imipramine and placebo groups *(25)*. Paroxetine was well tolerated and adverse events—including headache, nausea, dizziness, dry mouth, and somnolence—appeared to be similar to those reported in adults . Of these, only somnolence occurred at a rate substantially higher than that observed with placebo (17.2 vs 3.4%). Of the subjects in the imipramine group who were terminated from the study owing to adverse effects, nearly one-third were terminated because of cardiovascular symptoms including tachycardia, postural hypotension, and prolonged QT interval. The mean dose of paroxetine in this study was 28.8 mg/d and for imipramine it was 205.8 mg/d. Of special note is that this study replicated earlier findings that TCAs are not superior to placebo in clinical trials in childhood depression. Also of importance is the fact that imipramine was associated with high rates of treatment discontinuation. An unpublished multisite, double-blind, placebo-controlled study in children and adolescents with major depression did not show superior efficacy for paroxetine compared to placebo *(26)*.

Another study compared paroxetine to clomipramine in adolescents with major depression in 121 adolescents aged 12 to 20 yr *(27)*. Both drugs had similar outcomes on Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression (CGI) scale scores; however, clomipramine was less well tolerated.

Recent reports have indicated a potential for "increased risk of suicidal thinking and suicidal attempts in children and adolescents under the age of 18" being treated with paroxetine for MDD *(28)*. In response to these reports, the US Food and Drug Administration (FDA) issued a statement recommending that paroxetine not be used to treat children and adolescents with MDD, although

paroxetine not be used to treat children and adolescents with MDD, although their safety assessment has not been completed *(28)*.

An FDA public health advisory issued March 22, 2004 states the following: 'FDA is asking manufacturers to change the labels of ten drugs to include stronger cautions and warnings about the need to monitor patients for the worsening of depression and the emergence of suicidal ideation, regardless of the cause of such worsening. The drugs under review include bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, escitalopram and venlafaxine. It should be noted that the only drug that has received approval for use in children with major depressive disorder is fluoxetine (Prozac). Several of these drugs are approved for the treatment of obsessive-compulsive disorder in pediatric patients, i.e., sertraline (Zoloft), fluoxetine (Prozac), and fluvoxamine (Luvox). Luvox is not approved as an antidepressant in the United States.'

The UK Department of Health issued a broader statement disallowing the use of paroxetine for the treatment of depressive illness in children and adolescents under the age of 18 yr, because they found increased rates of "self harm and potentially suicidal behavior in this age group, when paroxetine is used" *(28)*.

Emslie and associates *(29)* studied the efficacy of an 8-wk regimen of 20 mg/d of fluoxetine in 96 children and adolescents (ages 7–17 yr) with major depression. Fluoxetine demonstrated greater improvement on the CDRS-R after 5 wk of treatment. Drug placebo differences were not significant on several other self-report measures. Furthermore, complete remission was uncommon, despite the significant decline in the CDRS-R.

In a multisite study of fluoxetine therapy (week 1: 10 mg/d; weeks 2–8: 20 mg/d) in depressed children and adolescents, researchers found that the active drug was associated with greater decline in the CDRS-R than placebo *(30)*. The fluoxetine group was also superior to placebo on the CGI scale. Headache was the only adverse effect reported more often in the active drug group.

3.2.3. TCAs

Two factors limit the clinical use of TCAs in children: efficacy and safety. The efficacy of TCAs in childhood and adolescent depression has not been established. In two comprehensive reviews *(31,32)* of 15 studies that reported the results of randomized, placebo-controlled clinical trials of TCAs in depressed children and adolescents, 13 were presented in sufficient detail to allow pooling of data. The TCAs studied were imipramine (5), amitriptyline (4), desipramine (2), and nortriptyline (2), which were all compared with inactive placebo. The pooled data found no statistically significant differences in the groups treated with TCAs compared with the placebo groups. In a subgroup analysis, a nonsignificant trend toward efficacy was found in adolescents, but not in children. Adverse effects were comparable to those seen in adult populations, with a statistically significant difference seen for vertigo, orthostatic hypotension, tremor, and dry mouth compared to placebo.

Many authorities have put forth explanations for the lack of efficacy of TCAs in this population. These can be summarized as developmental differences in neurotransmitter function in children, a serotonergic-mediated depression in children, or a different underlying neuropathology in early-onset depression.

Despite clinical trial findings suggesting that adverse effects were similar in children and adults, a substantial controversy has developed concerning the cardiac safety of TCAs, especially desipramine, in children. During the early 1990s, four cases of sudden death in children taking desipramine were reported *(33)*. These reports led some authorities to advise against the use of desipramine in children *(34)*, whereas others argued that evidence for an association between

desipramine and sudden death in children was weak *(34)* although desipramine may increase the risk of sudden death by a factor or 2 to 3 relative to the general population aged 5 to 14 yr *(35)*.

The cardiac effects of TCAs in adults were reviewed in Chapter 2. To summarize briefly here, TCAs may prolong the QT_C interval, induce arrhythmias, and lead to sudden death. The etiology of these effects in adults has been linked with their monoamine effects, anticholinergic activity, antihistamine effects, and blockade of ion channels. There are some specific differences in children that may make them more susceptible to cardiac effects of TCAs.

While studying cardiac autonomic regulation in children and adolescents who were taking a variety of psychotropic medications, Mezzacappa and colleagues *(36)* proposed that the major cardiac effect of TCAs is inhibition of high-frequency heart-rate variability, which is controlled by vagal input. They suggested that this produces "a relatively unchecked sympathetic modulation ... similar to (other) risk factors associated with tachyarrhythmias" *(36)*. Although this may be a risk factor, given the low incidence cited by Biederman *(35)*, it cannot entirely explain the phenomenon. The rate of development of the vagal and sympathetic control of cardiac function is age dependent, and it varies substantially among individuals. In tissue slices taken from the right atrium, desipramine produced greater positive inotropic effects in response to norepinephrine (NE) in tissue taken from children compared to samples taken from older patients *(37)*. Thus, in addition to evidence suggesting that the TCAs produce a greater loss of vagal modulation in children, youths may also have greater sensitivity to a drug affecting NE reuptake. On the other hand, stress, anxiety disorders, depression, and other factors may lead to an imbalance in autonomic regulation of cardiac function. For example, one study reported a relative increase in sympathetic tone and a decrease in cardiac vagal activity in children with anxiety disorders *(38)*.

Wilens and colleagues *(39)* reviewed 20 human studies involving 636 children and adolescents taking TCAs (imipramine, desipramine, nortriptyline, amitriptyline, and clomipramine) with 12-lead electrocardiogram (ECG) monitoring. Although only a minority of these studies compared baseline and therapeutic ECGs, those that did found an unexpectedly high baseline incidence of abnormalities, including sinus tachycardia (5–15%), prolonged intraventricular conduction delay (up to 10%), and prolonged QTc interval (5–15%). In general, TCAs were associated with lengthening of the P-R, QRS, and QTc intervals. Depending on the criteria used, first-degree AV block was reported in 0.9% (criterion: P-R = ≥200 msec) or 10 to 14% (criterion: PR = 180 msec) of children. Increases in QRS ranged from 7 to 24% for incomplete intraventricular conduction delay (100–120 msec) and was less than 0.5% for complete block (≥200 msec). QTc interval was associated with an average 4 to 10% increase in duration with TCA therapy. Desipramine was associated with higher rates of QTc intervals

lasting longer than 440 msec (30%), but somewhat lower rates using different criteria (18% using a criterion of 450 msec; 8% using a criterion of ≥460 msec), compared with other TCAs. Intermittent abnormalities from TCAs that were not found on routine ECG were identified using Holter monitoring. Higher doses and serum concentrations of TCAs have been associated with prolonged conduction, and investigators using Holter monitoring reported that children with higher desipramine concentrations had greater rates of paired premature atrial contractions and supraventricular tachycardia compared to those with lower levels *(40)*. Exercise does not appear to increase cardiac risk in children taking TCAs. There is not a consensus on the relative risk of different TCAs. Although some have proposed that the relatively greater noradrenergic effects of desipramine may increase toxicity *(33)*, all TCAs are associated with cardiac effects.

The clinical implications of these findings are that TCAs should not be first-line agents in childhood or adolescent depression, although they may be used as second- or third-line agents in older adolescents. Some studies have suggested that the response to TCAs is better in older adolescents than in children. The risk:benefit ratio of TCAs must be considered, especially in terms of cardiac effects. When TCAs are used, baseline and periodic ECG monitoring is necessary to identify changes in conduction delays, particularly QTc prolongation, a serious effect that should prompt discontinuation. Less serious conduction delays and persistent tachycardia may respond to dose reduction or require discontinuation of therapy; a consultation with a pediatric cardiologist should be used to guide therapeutic decisions. Sudden death is rare and idiosyncratic *(40)*; even with close monitoring, it may not be preventable. Prior to prescribing a TCA, clinicians should consider genetic susceptibility to impaired drug metabolism (e.g., 10% of whites have impaired CYP2D activity) and the possibility that the drug exposes someone with a genetic predisposition to long QT syndrome (see Chapter 2). Serum level monitoring may be helpful in identifying slow metabolizers of the drug.

4. IMPLICATIONS FOR PRACTICE

Given the relative paucity of clinical trial data available to guide pharmacotherapy for depression, standard treatment algorithms rely heavily on clinical experience and extrapolation from adult studies. Two of the better known algorithms, the Texas Children's Medication Algorithm Project *(7)* and the Practice Parameters of the American Academy of Child and Adolescent Psychiatry (AACAP) *(21)*, will be discussed briefly. Both emphasize the necessity for assessing and treating the child within the context of the family and social environment, as well as the importance of psychotherapeutic interventions.

With respect to pharmacotherapy, there is concurrence that SSRIs are the first-line agents. The Texas Algorithm is more specific in its guidelines, suggesting that failure of monotherapy with one SSRI should be followed by monotherapy with another SSRI. Although it recommended fluoxetine, paroxetine, and sertraline as preferred agents, it recognizes that other SSRIs may be effective and predicts that even mixed agents could be used as first-line agents in the future, if supporting data are forthcoming (the FDA caution regarding paroxetine was issued after the publication of the algorithm). It also recommended augmentation strategies with lithium or buspirone for partial SSRI responders, but did not reach consensus on augmentation with stimulants, bupropion, or thyroid. Failure to respond to this strategy moves the process to monotherapy with a different drug class (TCAs or mixed-action agents), although there are no adequate clinical trials to support this strategy. Only clinical experience and adult data are available to support the additional approaches that are recommended when depression remains refractory, including combination of antidepressants or monotherapy with monoamine oxidase inhibitors (MAOIs). In cases of psychotic depression, the Texas Algorithm adds an atypical antipsychotic agent. The AACAP concurs with this recommendation, and both recommend the use of electroconvulsive therapy in severe depressions that are resistant to pharmacotherapy.

The algorithms differ in their approach to comorbid major depression and ADHD. The AACAP guidelines suggest that initial use of a TCA, bupropion, or venlafaxine may be more appropriate than first-line use of SSRIs. The Texas Algorithm proposes an initial 2-wk trial of a stimulant, and if both depression and ADHD respond, it advises clinicians to proceed with monotherapy. If ADHD improves but not depression, it recommends continuing the stimulant and following the depression algorithm. If neither ADHD nor mood improves with stimulant therapy, the Texas Algorithm recommends discontinuing the stimulant and using an SSRI. The AACAP suggests that comorbid depression and ADHD may respond better to TCAs, bupropion, or venlafaxine than to SSRIs.

Behavioral therapy for comorbid anxiety disorders is recommended in the Texas Algorithm, whereas the AACAP guidelines point out that antidepressants are also useful agents in anxiety disorders. In approx 67% of patients with OCD, there is comorbid major depression *(41)*. The SSRIs are effective in both OCD and depression in combination with behavioral therapies, although the effect size in some studies have been small *(17,42–47)*. In treatment-resistant cases, some clinicians report success with venlafaxine *(48)* or SSRI augmentation with noradrenergic antidepressants *(49)*.

Few data are available to guide antidepressant use with major depression and comorbid PTSD or substance dependence, but most authorities would agree that SSRIs are the first-line agents if drug therapy is chosen. The results of an open-

label study supported the short-term efficacy of fluoxetine in adolescents with alcohol abuse and depression *(50)*. Naltrexone has been used successfully in the treatment of alcohol abuse in adolescents in a small number of clinical reports *(51,52)*, and it is commonly used in combination with SSRIs in adults, but the safety and tolerability of the combination in younger patients are unknown. SSRIs have been proposed as a first-line therapy for comorbid depression and PTSD in children and adolescents *(53)*, and the results of open trials *(54)* are encouraging. As with adult PTSD, combination therapy and other classes of medication may be necessary *(55,56)*.

Recommendations for long-term pharmacotherapy of childhood depression are based on clinical experience and adult data. After successful treatment of the acute phase, continuation therapy is recommended from age 6 to 9 mo. The decision to proceed to the maintenance phase is based on the severity and frequency of depressive episodes. Maintenance therapy continues the antidepressant is taken at full therapeutic dose for periods ranging from 1 yr to lifelong treatment.

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Index

Pharmacotherapy of Depression

Edited by

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Recently acquired knowledge about the various subtypes of depression, the introduction of novel antidepressant medications, and the functioning of the brain during depression have led to a complexity of treatment options that did not exist a decade ago. In *Pharmacotherapy of Depression,* well recognized clinician-scientists who have worked extensively in both basic and clinical research, as well as in clinical practice, explain in detail the welter of therapeutic options available to frontline physicians who prescribe antidepressants. Single-mindedly concentrating on information of high relevance to their daily clinical use, the authors review the latest developments concerning these medications and demonstrate how experts in the field approach the treatment of depression. Their clinical recommendations cover a wide range of uses in special populations, including geriatric depression, bipolar depression, psychotic depression, substance abuse and depression, HIV/AIDS-related depression, depression associated with pregnancy, posttraumatic stress disorder, and depression in children. As necessary background to optimal prescribing, the authors also survey the biological theories of depression, explain their implications for current and new treatments, and clarify the clinical pharmacology and therapeutics of today's antidepressant medications. An accompanying compact disk allows the downloading of an ebook version to the reader's PC or PDA.

Comprehensive and state-of-the-art, *Pharmacotherapy of Depression* offers busy clinicians from many disciplines a gold-standard practical guide and reference to the safe and effective use of the latest antidepressant medications.

Features

- Comprehensive overview of antidepressant therapy for clinicians from many disciplines
- Up-to-date guidelines designed for the busy physician who prescribes antidepressants
- Based on time-tested courses given by the editors in their own teaching programs
- Review of the biology of depression and the clinical pharmacology of drugs to treat it

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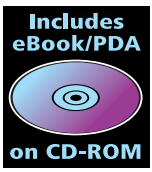

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Pharmacotherapy of Depression Edited by Domenic A. Ciraulo, MD Richard I. Shader, MD / Biological Theories and Treatments 1 1 Biological Theories of Depression and Implications for Current and New Treatments David J Goldstein, MD, PhD and William Z. Potter, MD, PhD CONTENTS INTRODUCTION NEUROENDOCRINE SYSTEMS ALTERATIONS IN PHYSIOLOGICAL FUNCTION: CIRCADIAN RHYTHMS, SLEEP, PAIN PERCEPTION, AND APPETITE CONCLUSION REFERENCES 1. INTRODUCTION Unipolar major depressive disorder is a common condition that has both emotional (mood and anxiety) and physical aspects (1). The physical manifestations are common features of depression present in up to 80% of depressed patients (2). These physical symptoms occur in nearly all body systems and are often the presenting features in the nonpsychiatric setting. However, many of these investigations have not been replicated, or show significant overlap between depressed and nondepressed groups leading to From: Edited by: D. A. Ciraulo and R. I. Shader © Humana Press Inc., Totowa, NJ 10 Table 1. Hormones and Neurotransmitters That Demonstrate Alterations in Depression and the Potential Effects on Producing Symptoms a Hormone or Neurotransmitter ...

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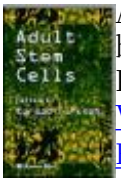

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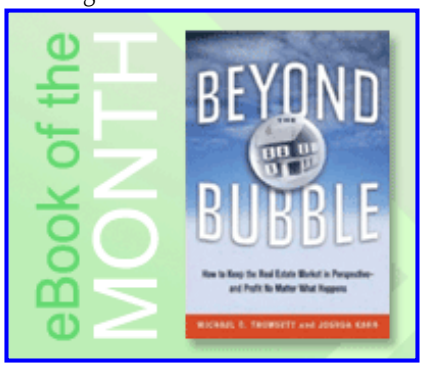

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