Depressive Disorders

Somatic Therapies of Depression

Steven Zavodnick, MD

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Steven Zavodnick, MD

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Somatic Therapies of Depression

For several decades, consensus has been building toward the idea that some physiologic disruption of brain function underlies the syndromes of severe unipolar and bipolar depression. While psychotherapy and somatic therapies may have additive effects in the treatment of depressive states (Weissman, 1979), most experienced clinicians agree on the value of somatically based therapies in the treatment of such symptoms as disordered sleep, appetite, energy, interest, and concentration, in moderate and severe depressions. This chapter is intended to provide an overview of the use of tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), second-generation antidepressants, lithium, and electroconvulsive therapy (ECT). The perspective will be practical, even impressionistic, rather than critical and quantitative. In an attempt to extract clues that might be useful in the treatment of patients prior to the complete resolution of controversial or theoretical issues, the benefit of clarity may be attended by the risk of oversimplification. Because the focus is on depression, no attempt to deal with possibly related conditions such as eating, panic, and obsessive-compulsive disorders will be made.

TRICYCLIC ANTIDEPRESSANTS

There is a rough specificity in the action of the various somatic treatments for depression. The most severe depressions, including psychotic or delusional depressions, respond best to electroconvulsive treatment or to a combination of tricyclic antidepressant and neuroleptic. Nonpsychotic, nonbipolar depressed patients are the group in which the response to tricyclic antidepressants is clearest. Bipolar patients may show antidepressant responses to lithium. Atypical depression marked by symptoms such as anxiety, phobia, reactive mood, and reversed vegetative symptoms is thought to be one syndrome that responds best to monoamine oxidase inhibitors. Dysthymic patients are viewed by a number of clinicians as exhibiting a preferential response to monoamine oxidase inhibitors or, perhaps, to a second-generation agent such as fluoxetine. This response specificity is only approximate. Tricyclic antidepressants may be helpful in some patients exhibiting atypical depression or dysthymia, monoamine oxidase inhibitors may be effective in some patients with severe depressions, and lithium may be useful as an adjunct to other drugs and in some unipolar patients. Nevertheless, in the absence of more rigorously defined predictors, fragmentary findings must serve as a guide to clinical intuition.

The efficacy of tricyclic antidepressants (TCAs) in the treatment of acute depression and the prevention of relapse has been well demonstrated (Davis, 1976; Klein & Davis, 1969). Patients with acute unipolar depression of at least

moderate intensity constitute the core group responding to these agents with reported rates of improvement ranging from 65 to 90 percent. This patient group may be considered a subset of the DSM diagnostic category Major Depression. Disagreements concerning both diagnosis and treatment increase as the focus moves away from this core group. Joyce and Paykel (1989) suggested that response to TCAs is less clear at both extremes of the spectrum of severity, with bipolar depression and with chronic depressions. Severe depressions with psychotic symptoms probably do not respond optimally to TCAs alone (Glassman, Kantor, Shostak, 1975), although TCA-neuroleptic combination treatment (Nelson & Bowers, 1978) and electroconvulsive therapy have been reported to be effective. Problems evaluating the specific efficacy of TCAs in mild depressions include identification of cases, a sizable placebo response rate, and weighing the benefits of alleviating mild distress against significant drug side effects. In bipolar depression the risks of TCA treatment include the induction of mania and the less common occurrence of rapid cycling. Although there is some disagreement about the frequency with which a switch into mania occurs (Lewis & Winokur, 1982), clinical experience suggests that this happens often enough and presents enough of a management problem to warrant considerable caution with this patient group. The drug treatment of chronic depressions has been little studied in any systematic fashion, although anecdotes suggest some responsiveness of patients in this group to both TCAs and monoamine oxidase inhibitors.

Tricyclic antidepressants and their usual dose range in physically healthy

adult patients are listed in Table 14.1. These drugs are a group of rather similar chemical structures; they include compounds related to imipramine, amitriptyline, and doxepin. The dose range of these drugs is 150-300 mg daily with the exception of nortriptyline and protriptyline, which are given in one-half and one-fifth of the usual dose respectively. Higher plasma levels of nortriptyline are associated with reduced response to the drug. Protriptyline is metabolized more slowly than the other agents in this series.

Table 14.1. Tricyclic Antidepressants

	Range of Daily Dosage (mg)
amitriptyline	150-300
nortriptyline	75-150
protriptyline	30-60
imipramine	150-300
desipramine	150-300
chloripramine	150-300

trimipramine	150-300
doxepin	150-300

In the past, putative differences between TCAs have been emphasized, based upon differing potencies in blocking the reuptake of norepinephrine and serotonin in the laboratory. Differential response of patient groups to hypothetically serotonergic and noradrenergic antidepressants has not been clinically demonstrated with sufficient consistency. Current thinking is that similarities among the various TCAs are probably more important than differences (Montgomery, 1987). The members of this TCA group with more pronounced in vitro effects on serotonin are typically biotransformed in vivo into metabolites—for example, nortriptyline and desmethylchlorimipramine—with pronounced noradrenergic effects. The entire class of TCAs is probably most accurately thought of as a group of agents predominately affecting norepinephrine. Rather than the common practice of sequential drug trials involving a series of similar agents, careful attention to dose and duration of a course with a single TCA seems a more effective treatment strategy.

Drug dosage is a critical variable in the clinical use of TCAs. Underdosing is the most common error, perhaps because of the difficulty many patients encounter in tolerating the side effects of the more sedating, hypotensive, and anticholinergic drugs of this group when given in adequate dose. A figure of 3.5

mg/kg has been suggested (Glassman, Perel, Shostak, Kantor, & Fleiss, 1979) for drugs with a 150-300 mg range yielding an average daily dose well over 200 mg/d. Plasma drug levels may be helpful in allowing for variability in patients' ability to metabolize TCAs (Gold, Lydiard, Pottash, & Martin, 1987). With nortriptyline, a better drug response has been associated with plasma levels between 70 and 140 ng/ml; responsiveness is reduced both below and above this therapeutic window. Improvement with imipramine has been associated with blood levels of imipramine plus desipramine over 225 ng/ml. Possibly, improvement with desipramine requires blood levels over 125 ng/ml (Nelson, Jatlow, Quinlan, & Bowers, 1982). The usual current methods of measuring TCA plasma levels do not yield information on other active, quantitatively important metabolites (e.g., 10-hydroxynortriptyline) or variations in drug-protein binding which may increase or decrease the active, free drug fraction. The author agrees with the suggestion of Gold et al. (1987) favoring the use of nortriptyline in most TCA trials, in view of the clearer dose response relationship with this drug as well as the significant reduction in side effects when the secondary amine metabolites (nortriptyline, desipramine) are used in preference to the tertiary amine parents (amitriptyline, imipramine).

One technique for prescribing TCAs consists of starting treatment with a dose of 75 mg h.s. and titrating upward, as tolerated, to the range of 200-300 mg nightly. Given the long elimination half-lives of TCAs, there is no need for multiple daily doses. Despite its higher milligram potency, nortriptyline is usually well

tolerated by healthy patients at a 75 mg starting dose. For many patients, upward titration is unnecessary because the effective dose is usually half that of most TCAs. Plasma levels may be obtained in the second or third week of treatment, ideally five to 10 days after reaching a stable dose level, and the drug dose can be adjusted with respect to the indicated range. Drug dose should be reduced with the occurrence of significant side effects, in the hope that tolerance will develop and permit the attainment of an adequate treating dose. For elderly patients and those with significant cardiovascular disease, starting doses should be lower and increases more gradual. The author's method is to start cardiac patients on 25 mg of nortriptyline daily and increase by 25 mg/week, with careful clinical assessment for the emergence of new cardiovascular symptoms, EKG, and nortriptyline plasma level determination prior to each new dose increase. There is some evidence suggesting that maintaining patients toward the lower end of the nortriptyline therapeutic window can minimize the likelihood of cardiac toxicity while preserving the possibility for the desired clinical response (Glassman & Bigger, 1981;Roose, 1987).

Response to antidepressant drugs of all types is usually not seen until three or four weeks after the therapeutic dose is reached. One group of patients has been described with a good response in week five or week six of a drug trial (Quitkin et al., 1987). There is little reason to continue TCA alone beyond six weeks if response has not been forthcoming. At this point the addition of an adjunctive agent such as lithium or triiodothyronine or an alternative

antidepressant treatment should be considered.

Drug side effects frequently present a limiting factor in the successful use of TCAs. Patients' inability to tolerate sedative, hypotensive, or other autonomic effects may interfere with the goal of achieving a satisfactory dose/plasma level and the desired clinical response. Secondary amine tricyclics, nortriptyline and desipramine, were initially explored in the hope that, by using the metabolite compounds rather than the parent drugs, response lag might be shortened. This hope was not realized. However, the secondary amines do have the advantage of markedly less severe side effects than the original agents in the TCA series. While there is no evidence for any difference in efficacy among any of the TCAs, the reduced propensity for side effects and the better understanding of the relationship between plasma level and patient response, in the author's opinion, render nortriptyline and desipramine the agents of choice within this group of drugs.

Central nervous system side effects include sedation, induction of psychosis, confusional states, and tremor. Sedation may be marked with tertiary amine TCAs, prolonging the time to reach the effective dose range. Tolerance to this side effect usually occurs with a more gradual increase in drug dose over a period of weeks. Sedation is typically mild or absent with nortriptyline or desipramine. Patients with a prior history of psychosis, either schizophrenia or mania, are at risk for the reactivation of psychotic symptoms with TCA treatment. The magnitude of the

risk for schizophrenic patients has not been assessed but is probably considerable. Some clinicians feel that adjunctive neuroleptics serve a protective function in this regard, although this has not been carefully studied. It has been estimated that 15 percent of the bipolar population may have an episode of mania in association with TCA treatment (Bunney, 1978). The induction of rapid cycling from mania to depression is another well-know risk with these agents (Wehr & Goodwin, 1979). Occasionally patients who were not previously known to be manic may exhibit mania or hypomania only while taking TCAs, leading some investigators to classify this group as part of the bipolar spectrum. Confusional states are commonly encountered with TCA overdose, especially in elderly patients, for whom doses used in younger patients prove to be excessive. These phenomena are related to the central anticholinergic effects of TCAs and to milder degrees of memory impairment that may be dose-related with the more strongly anticholinergic antidepressant drugs. Some patients given TCAs may exhibit a fine resting tremor. When necessary, low dose propranolol (e.g., 20-40 mg/d) may be prescribed to alleviate this.

Autonomic nervous system side effects include both antiadrenergic and anticholinergic actions. Orthostatic hypotension is the most serious of the antiadrenergic side effects; patients may be symptomatic with the ever present dangers of syncope, falls, and fractured bones. Nortriptyline has been reported as the TCA with the lowest incidence of orthostasis (Roose, 1981). The degree of orthostatic drop seen during treatment may be correlated with measured

orthostatic changes prior to the initiation of therapy. Curiously, there have been observations (Jarvik, Read, Minty, & Neshkes, 1983; Schneider, Sloan, Staples, & Bender, 1986) of a positive correlation between the magnitude of orthostatic hypotension noted prior to antidepressant treatment and a positive response to this treatment in geriatric patients. The theoretical implications of this are intriguing, suggesting some relationship between the responsiveness of the sympathetic nervous system to postural changes and the responsiveness of the brain to drug treatment. A recent report (Price & Heninger, 1988) described the use of yohimbine, a centrally active sympathetic agonist pressor agent, in the management of hypotension with TCAs. Impotence and ejaculatory difficulties are additional sympatholytic TCA side effects that may be encountered. While the autonomic mechanism is unclear, orgasmic dysfunction in women is not uncommon (Harrison et al., 1986). Dosage reduction may be helpful in some of these situations.

Peripheral anticholinergic effects include blurred vision, dry mouth, constipation, and urinary difficulties. These effects are less severe with the secondary amines. Tolerance may develop over a period of weeks with some patients; others may be aided with symptomatic measures (e.g., hard candies, citrus fruit slices for xerostomia, bulk laxatives for constipation). Frank urinary retention is not especially common, but many patients experience urinary hesitancy, dribbling, or a sensation of bladder fullness after voiding. Patients being treated for chronic glaucoma may be prescribed TCAs with ophthalmologic

consultation. Rarely, an attack of acute narrow-angle closure may be precipitated, typically in a patient not previously known to have ophthalmologic problems. Symptoms of an acute attack of narrow-angle glaucoma are a sharp pain in the eye and halos surrounding point sources of light. Immediate consultation is mandatory as delay may result in loss of vision. The treatment is surgical.

Cardiovascular side effects are a source of concern since the majority of depressed patients belong to an age group where concurrent cardiac disease is common. With proper attention, caution, and consultation when necessary, this need not be a bar to effective treatment, even in patients with known cardiac disease. Hypotension related to adrenergic blockade, heart rate increases with anticholinergic (antivagal) effects, and a quinidine-like effect consisting of antiarrhythmic actions at low to moderate plasma levels with increasing degrees of conduction blockade at higher dose levels have been described (Ziegler, Co, & Biggs, 1977). Once again, the secondary amine TCAs seem to be considerably safer with regard to the cardiovascular system because hypotensive and anticholinergic effects are less with these agents. Plasma level monitoring may help in determining the lowest effective doses to use with these patients. In addition to baseline and follow-up EKG, patients should be monitored for anginal symptoms, symptoms suggesting cardiac arrhythmia, and blood pressure measurements both sitting and standing prior to and during the course of treatment. If necessary, beta blocking agents may be used to protect against increases in heart rate and myocardial demand. Glassman's group (Giardina, Bigger, Glassman, Perel, &

Kantor, 1979) described decreases in premature atrial and ventricular contractions over a month-long imipramine trial in depressed patients. With TCA overdose, second- and third-degree heart block may be seen. TCAs are contraindicated in the acute phase following myocardial infarction. How long this contraindication must be observed is unclear. Six months would seem a reasonable and conservative, though entirely arbitrary figure.

TCA overdosage should be treated with considerable caution. Attention to possible suicidal ideation and intent is important in prescribing, since a 10-day supply of medication at usual doses may be lethal. Smaller medication supplies, more frequent physician visits, enlisting a family member or friend to control medication, or inpatient treatment are alternatives to manage this risk. Symptoms of overdose include delirium, mydriasis, flushing, dry mucosae, decreased bowel and bladder activity, cardiac arrhythmia, seizure, and coma. Patients should be treated in an intensive setting with cardiac monitoring for a 24-48-hour period because reduced gastrointestinal motility may lead to delayed absorption and late worsening of symptoms. Physostigmine 1-2 mg intravenously can produce dramatic, rapid reversal of central and peripheral anticholinergic toxicity. The duration of action of physostigmine is about two hours—rather brief relative to the half-life of the TCAs, which approximate 20 hours and may be prolonged with large overdoses. Physostigmine doses must be repeated frequently when patients exhibit clinical worsening a few hours after the last dose. Many emergency room and intensive care unit physicians prefer conservative management of TCA

overdoses, avoiding any concomitant and potentially complicating medications. The use of physostigmine is roughly analogous to the use of naloxone in opiate overdose—a maneuver that is both diagnostic and therapeutic and should be employed whenever the severity of overdose symptoms warrants.

MONOAMINE OXIDASE INHIBITORS

The antidepressant action of the monoamine oxidase inhibitors (MAOIs) was discovered as a result of the chance observation of euphoria in tuberculosis patients under treatment with isoniazid, an antituberculosis agent with MAOI activity. There has been a decided upsurge of interest in drugs of this class in the United States over the past 10 years (Quitkin, Rifkin, & Klein, 1979), although they have been available since the late 1950s. The new attention may be because of an improved understanding of the spectrum of activity of these agents, the dose-response relationship, and the management of dietary restrictions and other drug side effects. While there is clearly some overlap in the efficacy of MAOIs and TCAs, it is important to realize that there are subpopulations of patients who seem to respond preferentially to MAOIs. Some patients with the diagnosis of major depression may respond only to MAOIs; others, only to TCAs, or to both, or to neither drug group. Impressionistic observations such as these rest mainly on anecdotal reports rather than on controlled comparison studies so it is difficult to assign even rough quantitative estimates as to the size of these groups. Two other diagnoses for which specific MAOI responsiveness has been suggested are atypical depressions—mixed syndromes of anxiety and depression in patients with preserved mood reactivity and pronounced anxious, phobic, and hypochondriacal symptoms— and chronic or characterologic depression, that is, dysthymia. The responsiveness of atypical depression to MAOIs has been well studied and reviewed. The use of this group of drugs in chronic depressions is only hinted at

by suggestion of effectiveness in patients bearing the older diagnostic label *neurotic depression* (Nies, 1983). Another use of MAOIs has been in patients with bipolar depression in the hope, as yet unsubstantiated, that the tendency of TCAs to induce mania or rapid cycling in this patient group might be avoided.

In addition to a sharpened focus on groups of depressed patients who may preferentially respond to MAOIs, greater awareness of the effective dose range of these compounds (see Table 14.2) has contributed to their resurgence in clinical practice. It has been reported (Robinson Nies, Ravaris, Ives, & Bartlett, 1978) that 80 percent or greater inhibition of platelet monoamine oxidase is associated with a higher rate of response to MAOIs. As the measurement of platelet MAO inhibition is not generally available in routine clinical laboratories, the practical application has been an upward movement in the doses prescribed. The dose range of phenelzine is thought to be 60-90 mg daily and of tranylcypromine 40-60 mg daily, in order to attain this level of MAOI inhibition. Anecdotally, occasional patients are described tolerating and responding to doses two or three times higher! There has been interest in more specific MAOIs, with preferential affinity for one of several enzymatic subtypes. To date, the hopes for either reduced toxicity or enhanced clinical response have not been realized. Questions remain about efficacy and whether in vitro specificity is retained at the clinical doses required.

As with TCAs, the basic clinical technique in using MAOIs is to start patients

at a low dose, usually one or two tablets daily, increasing over a two- to four-week period to the presumed effective dose range, as tolerated. There is a three- to six-week lag between the time that the effective dose range is reached and clinical response is seen. Patients should be advised verbally and in writing about the specific dietary and medication incompatibilities, in order to reduce the risk of hypertensive crisis.

TABLE 14.2. Monoamine Oxidase Inhibitors

Drug	Dose (mg/d)
isocarboxazid	40-60
phenelzine	45-90
tranylcypromine	30-60

Although many physicians are duly concerned about the risks of using MAOIs, excessive caution is not warranted. Experience has shown that given proper instruction (Davidson, Zung, & Walker, 1984) most patients are able to observe adequate precautions regarding diet and medication and that, given this precondition, the risk of serious hypertensive crisis is low. Other side effects with MAOIs are frequently neither severe nor problematic and patients often tolerate

these agents better than TCAs (Nies & Robinson, 1982).

Central nervous system side effects of MAOIs include insomnia, sedation, nervousness, and psychotoxicity. Overstimulation may appear early in treatment with MAOIs. Susceptible patients complain that the medication makes them feel "hyper." This symptom is more frequently seen with tranylcypromine. Psychotoxicity refers to the ability of MAOIs to exacerbate the symptoms of schizophrenia and to induce mania or hypomania in bipolar patients. Whether these phenomena are seen less often with MAOIs than TCAs is uncertain; however, clinically it is not uncommon to encounter MAOI-induced elations, the absence of good statistical data notwithstanding. Some degree of insomnia or lesser sleep disturbance is quite common with MAOI treatment.

Hypotension is the most frequent side effect encountered in routine MAOI use. This is of the orthostatic type and may be a limiting factor in treatment. The risk of syncope, falls, and related injuries is a serious consideration. The use of sodium chloride tablets (3-6 Gm daily) has been described anecdotally as a means of increasing intravascular fluid volume to reduce drug-induced orthostasis (Munjak, 1984). This measure is practical only in younger patients with good cardiovascular tone. Hypotension is more frequent with phenelzine.

Dry mouth, blurred vision, and constipation are seen with MAOIs. The mechanism of this is obscure as these drugs are devoid of anticholinergic activity.

Anorgasmia, ejaculatory inhibition, paresthesia, and myoclonus are occasional side effects seen. These may be dose-related and may reflect autonomic and peripheral nervous system toxicities.

Monoamine oxidase in the intestinal lining normally serves to protect against pressor effects of dietary amines derived from degradation of protein foodstuffs into component amino acids. MAOIs currently in use inhibit monoamine oxidase in a variety of tissues, including the gastrointestinal tract, permitting absorption of pharmacologically active quantities of dietary pressor agents. Prior to an understanding of this, the risk of hypertensive crisis and even rare cerebrovascular hemorrhage was a chief reason for the reluctance of many psychiatrists to employ MAOIs. With proper education, most patients are able to observe a MAOI diet reducing the risk of severe hypertensive crisis to acceptable levels. Foods to be avoided are listed in Table 14.3. These include most forms of cheese, preserved meats and fish, liver, fava beans, brewer's yeast products (not baked goods), red wines, and dark beers. Important interactions with medications include all sympathominetic amines (decongestants, appetite suppressants, stimulants, epinephrine in local anesthetics) and opiate analgesics. Antihistamines that are not combined with sympathominetic decongestants, acetylsalicylic acid, and acetaminophen may be permitted. TCAs should be avoided in combination with MAOIs except with special experience and close monitoring of patients. The combination of fluoxetine and MAOIs may be hazardous. Symptoms of hypertensive crisis include a pounding headache, sweating, pallor, and

palpitations. Patients should be directed to the nearest medical setting for blood pressure monitoring and possible intervention. Some psychiatrists advise patients to carry alpha adrenergic blocking agents (e.g., phentolamine 50 mg or chlorpromazine 50 mg) to be used in the case of inadvertent dietary indiscretion. Dietary and medication precautions should be continued for two weeks after MAOIs are discontinued as these are irreversible enzymatic inhibitors and the additional time is required for new enzyme synthesis.

Table 14.3. Foods and Medications to Avoid with MAOIs

Foods:	Cheese (except cream cheese, cottage cheese; includes cheese sauces)
	Pepperoni, salami, bologna, summer sausage
	Canned and smoked meats
	Chicken liver, beef liver
	Smoked salmon, anchovies, caviar, pickled herring, sardines
	Fava beans (broad beans, horse beans, Italian green beans)
	Yeast beverages (baked goods are safe)

	Red wine
	Beer (especially dark beers)
Medications:	Decongestants
	Cold, cough, allergy remedies
	Appetite suppressants
	Stimulants
	Epinephrine (in dental, other local anesthetics)
	Antidepressants
	Meperidine, morphine

SECOND-GENERATION ANTIDEPRESSANTS

During the 1980s a series of unrelated, nontricyclic, non-MAOI antidepressants were introduced to American psychiatry (Table 14.4). These have been referred to as heterocyclic or second-generation antidepressants, although neither term is particularly informative in either a chemical or clinical sense. In this section these agents will be compared to TCAs from the standpoint of target patient population, efficacy, and side effects.

Amoxapine is a demethylated derivative of the neuroleptic drug loxapine. It is not a TCA although there are rough structural similarities (a three-ring central moeity with a nitrogen-containing albeit cyclical side chain attached to the central ring). The pharmacology of amoxapine is similar to that of the TCAs: it affects norepinephrine reuptake and receptors as well as the ability to block dopamine receptors, which it shares with the neuroleptic agents. Efficacy was similar to that of TCAs in a patient population that included inpatients and outpatients with the diagnosis of major depression (Feighner, 1983). The side effect profile is very similar to that of the TCAs, with the addition of the entire spectrum of acute extrapyramidal effects occasionally reported with this drug. It appears to be no safer than TCAs in the overdose situation.

Maprotiline is described as a tetracyclic antidepressant. The structure of this drug is quite reminiscent of desipramine: an extra ring is found attached to the center ring of the tricyclic structure perpendicular to the plane of the molecule.

The pharmacology is also rather like that of desipramine, with specific effects on norepinephrine reuptake and postsynaptic receptors. The population in which maprotiline has been used, its efficacy, side effects, and overdose lethality are quite similar to those of the TCAs. Because this drug has an elimination half-life more than twice as long as that of the TCAs, there is a tendency for this agent to accumulate to rather high blood levels if given in the usual TCA dose range. After several years on the United States market, the drug's dose recommendations were changed by the manufacturer to suggest slower dose increases and a maximum dose about two-thirds that of the TCAs.

TABLE 14.4. Second-Generation Antidepressants

Drug	Dose (mg)
amoxapine	150-300
maprotiline	75-225
trazodone	150-300
fluoxetine	20-80
bupropion	200-450

Trazodone is both structurally and pharmacologically distinct. A triazolopyridine, it is thought to exert effects mainly by blocking the reuptake of and receptors for serotonin and may be viewed as a mixed serotonin agonist-antagonist. The drug also exhibits effects upon postsynaptic beta adrenergic receptors. In patients with major depression, trazodone is described as having similar efficacy to the TCAs (Schatzberg, Dessain, O'Neil, Katy, & Cole, 1987). It has enjoyed fairly extensive use in geriatric depressed patient groups. Two major areas of advantage for this drug are side effects and overdoses. Main side effects for trazodone are limited to sedation and occasional gastrointestinal discomfort. Priaprism is an infrequent side effect, noted as a curiosity and because there have been cases with permanent loss of erectile function. Immediate drug discontinuation and urological consultation are recommended. Although there are sporadic reports of cardiac arrhythmia, trazodone is generally well-tolerated from the cardiovascular standpoint and should be considered one of the drugs of choice for the medically fragile depressed patient. Overdose lethality is low.

Fluoxetine has been described (Fuller & Wong, 1987) as the most specifically serotonergic antidepressant currently available in the United States. It is a potent inhibitor of serotonin reuptake with little effect on other neurotransmitter systems. Fluoxetine has a long elimination half-life (in the range of one to three days) with an active metabolite, norfluoxetine, whose half-life is on the order of one to two weeks. Two practical consequences of this are that the drug need not be given every day (e.g., if lower doses are desired) and that

fluoxetine is recommended to be discontinued five weeks prior to an MAOI trial. This drug has been used in a patient population that is different from the patients usually treated with TCAs. Patients who responded to fluoxetine were mainly outpatients with symptoms of moderately severe, chronic depression as opposed to the more severe, acute depressions that tend to respond to TCA treatment. This patient group probably includes a mixture of patients with a diagnosis of major depression in the mild to moderate range of severity as well as patients with dysthymia. Fluoxetine is generally quite well tolerated. A minority of patients may experience nervousness or insomnia and for this reason the drug is generally given in the morning. Headache and nausea, the other common side effects, usually abate with dose reduction. Although experience is limited, the drug is thought to be safe after overdoses. Overall, fluoxetine is a drug with major advantages over TCAs from the standpoint of patient tolerance and safety and a different spectrum of activity that is skewed toward the less severe, less acute depressed patient.

Bupropion is another novel antidepressant drug which has structural similarities to the psychomotor stimulants. The mechanism of action is thought to involve the neurotransmitter dopamine, setting it apart from the TCAs, MAOIs, and other second-generation antidepressants. This drug has been as effective as TCAs in research trials involving inpatient and outpatient groups with major depression (Zung, 1983). Clinical experience suggests that there are patients who respond to this agent after failing to improve with MAOIs, TCAs, and other second-

generation antidepressants. Side effects are usually not problematic and are quite similar to those seen with fluoxetine—occasional nervousness, insomnia, headache, or nausea—although the drugs are dissimilar. Because of the modest risk of seizure with doses higher than 450 mg daily, these doses are not recommended and the manufacturer suggests that this drug be reserved for patients who fail to respond to other antidepressants.

LITHIUM

Lithium salts are generally considered to be either second-line or adjunctive agents in the treatment of depression in unipolar patients. Evidence for lithium's ability to prevent the recurrence of depression in the maintenance treatment of bipolar patients is clear (Davis, 1976). There is some support for the use of lithium as an acute antidepressant in bipolar patients, in maintenance treatment of recurrent unipolar depressions, and, occasionally, in the acute treatment of unipolar depression (Jefferson, Greist, Ackerman & Carroll, 1987; Ramsey & Mendels, 1980). There is little published work on the use of lithium in atypical depression or dysthymic disorder. An area that has excited considerable interest in recent years is the use of lithium as an adjunct to TCAs, MAOIs, and second-generation antidepressants in the acute treatment of unipolar depression. Dramatic responses have been described within 2 to 14 days after the addition of lithium to standard antidepressant treatment in patients who initially appeared to be treatment-refractory (de Montigny & Cournoyer, 1987). Patients responding included a small number with psychotic symptoms, a group who may not respond well to TCA alone. Lithium doses were in the 900-1,200 mg daily range with few additional side effects seen and no clear correlation between serum lithium levels and clinical response. It is not clear how long to continue combined treatment after a positive response; some patients maintained their improvement after the early discontinuation of lithium. The number of patients studied in a controlled fashion has not been large and, in some cases, lithium was added to another agent

after trials lasting only three weeks so that it is difficult to be accurate about the likelihood of response with this treatment. It may be on the order of 50-75 percent. In view of the low risk and the usual need for a four- to six-week trial when switching from a failed antidepressant treatment to another, an intervening two-week period of adjunctive lithium therapy seems a reasonable second step prior to initiating a new antidepressant in any patient not responding to the first drug selected.

Maintenance treatment for the prevention of recurrent depression has been described with lithium levels toward the lower range of those used in the treatment of bipolar disorders, 0.5-0.8 mEq/l (Hullin, 1980). Side effects should be mild in this range and can include tremor, thirst, polyuria, and possibly some of the subtler central nervous system complaints such as decreased concentration and memory. The typical patient will experience no side effects at this dose. Suppression of thyroid function indices and occasional hypothyroidism are to be expected with chronic treatment. Lithium intoxication is the most severe problem to be encountered with the use of this agent. This may occur with intentional or accidental ingestion of excess lithium, acute renal disease impairment of lithium excretion, or conditions causing sodium depletion with compensatory renal retention of both sodium and lithium (e.g., thiazide diuretic use, febrile illness, sodium loss through perspiration with heavy exercise). Symptoms are a combination of gastrointestinal and central nervous system toxicities: nausea, vomiting, or diarrhea combined with tremor, incoordination, dysarthria, or

drowsiness. The serum lithium level is usually, but not always, above the range of 1.0-1.5 mEq/l. The diagnosis of lithium intoxication should be made clinically. Early recognition and discontinuation of lithium treatment while underlying causes are explored and corrected usually leads to resolution of symptoms in a few days without sequellae.

Medical conditions complicating lithium therapy include hypothyroidism, decreased renal function, congestive heart failure, and pregnancy. Hypothyroid patients may be treated with lithium so long as thyroid function is monitored closely and additional thyroid hormone supplementation is provided as necessary. Patients with decreased renal function will exhibit proportionately decreased ability to excrete lithium ion. Prescribed lithium doses must be lowered accordingly. In patients with congestive heart failure, it must be recalled that lithium behaves much like sodium physiologically. The lithium dose may act like a salt load, exacerbating the degree of failure if this is not taken into account. Additionally, thiazide diuretics may raise serum lithium levels via a mechanism involving increased proximal renal tubular resorption. Lithium treatment, when indicated, must proceed cautiously with closer than usual attention to both fluid balance and serum lithium levels. Lithium is probably teratogenic (Sitland-Marken, Rickman, Wells, & Mabie, 1989) and should be avoided during pregnancy, particularly during the first trimester. Lithium is excreted in therapeutic concentrations in breast milk. Breast feeding is contraindicated while lithium treatment is in progress.

Evaluation of the patient prior to lithium therapy should include a medical history and physical exam, including urinalysis, CBC, creatinine, BUN, thyroid function studies, and chest X-ray. Women of childbearing age should have a pregnancy test as it is lithium exposure during early, often undiagnosed pregnancy that carries the greatest risk. Patients may be started on 600-900 mg lithium salt daily with plasma lithium levels obtained every four or five days. As noted above, a target level of 0.6 mEq/1 is probably adequate for the treatment of depression. Once stable lithium levels are attained, monitoring every one to three months is sufficient. For long-term maintenance, thyroid stimulating hormone, serum creatinine, and urine specific gravity should be monitored semiannually. At the present the optimal time period for continuing lithium used to potentiate another antidepressant is not certain. It might be reasonable to discontinue either the lithium or the antidepressant after a month or two.

THYROID POTENTIATION

Thyroid potentiation with triiodothyronine has been found useful for the past 20 years in converting TCA nonresponders to responders and in shortening the lag period for TCA response (Prange, 1987; Prange, Wilson, Rabon, & Lipton, 1969). Triiodothyronine is used rather than thyroxine as the shorter half-life (one day vs. seven days) allows for more rapid clearance should discontinuation become necessary. This treatment is not dependent upon a diagnosis of frank or subclinical hypothyroidism. Indeed, in hypothyroid patients, often correction of the endocrine abnormality is the only treatment needed to modify associated psychiatric symptoms. In euthyroid depressed patients the dose range for antidepressant potentiation is usually 25 to 50 meg triiodothyronine daily in the morning. Response may be seen within two weeks and supplemental thyroid medication is usually discontinued after a month. Side effects may include sympathetic nervous system overactivity and cardiac arrhythmia. Despite impressive results in controlled trials with as many as 75 percent of nonresponders improving with T3 addition (Goodwin, Prange, Post, Muscattola, & Lipton, 1982), this treatment has not been as enthusiastically utilized as might be expected. The reasons for this are unclear. Whether there is overlap, nonoverlap, or some other relationship between patients responding to lithium or thyroid potentiation has not been investigated.

ELECTROCONVULSIVE THERAPY

Electroconvulsive therapy (ECT), first used by Ugo Cerletti in 1938, continues to be among the most demonstrably effective treatments for severe depressive states (Klein & Davis, 1969). Severe depressions— including those in patients with psychotic symptoms, catatonia, acutely suicidal depressed patients, and patients failing to respond to drug treatments—constitute the main indication for ECT. ECT is generally not used for mild, atypical, or chronic depression. In severe depression, the response rate to ECT often exceeds 80 percent (Fink, 1987). The main drawbacks to the use of this treatment are availability and relapse. Surveys have demonstrated (Asnis, Fink, & Saferstein, 1978) a pattern that suggests underutilization of ECT in public hospital settings when compared to university and private hospitals. While diagnostic differences between the populations served may account for some of these findings, it is suspected that ECT, with its modestly increased demands for equipment, staff, and training is less often available to patients in public mental hospitals. Relapse is a major issue in treating all patients with affective disorders. In a review (Davis, 1976) of maintenance treatment in depression it was shown that over 50 percent of treated patients suffer relapse within a few months without continuation of treatment. A similar number of patients experience relapse after a successful course of ECT (Kiloh, 1982). The clinician is left with the choice of attempting maintenance treatment with a drug whose efficacy is uncertain or maintenance ECT. Anecdotal reports suggest that maintenance ECT at intervals ranging from once weekly to

once every four to six weeks is often effective.

The addition of barbiturate anesthesia and muscle relaxation agents 20 years ago reduced the subjective distress and physical trauma associated with older convulsive techniques. Recent modifications include unilateral ECT treatments, reduction in the electrical stimulus used, close physiologic monitoring, and electroencephalographic monitoring. While there are still unresolved controversies regarding the efficacy of unilateral versus bilateral treatment and brief-pulse, square-wave stimuli versus sine-wave stimuli, the overall result is a tendency toward less associated memory disruption, lower exposure of the brain to electricity, better control of oxygenation and hypertension during treatments, and more attention to the adequacy of the cerebral seizure for effective treatment.

There is general agreement (Fink, 1979;Snaith, 1981) that a majority of patients will respond to six to eight ECT treatments, although individualization of the number of treatments based upon clinical response is the basic principle. Two factors contributing to longer courses of ECT may be the not uncommon occurrence of missed or abbreviated seizures and the poorly substantiated practice of prescribing several treatments beyond the point of clinical response in the hope that they will solidify patient recovery. Fink (1979) observed that the induction of adequate generalized seizures may be more difficult with unilateral electrode placement and brief-pulse stimulation, which led some physicians to resist these modifications. The practice of some experienced clinicians is to begin

a series of treatments with unilateral, brief-pulse ECT and then switch to bilateral ECT if there is no response by a certain point in the treatment course or to sine wave stimuli if difficulty in producing a generalized convulsion is encountered.

The main side effect of ECT is the acute confusional state which is related to the number of treatments, patient age, and whether the stimulus is administered to the dominant cerebral hemisphere. Memory dysfunction is minimal with unilateral, nondominant hemisphere ECT. With bilateral treatments, the severity of anterograde amnesia usually increases with increasing number of ECT treatments. Memory function is typically recovered one to two months after the cessation of ECT, although recall of events occurring during the acute amnestic period is usually lost. Delirium during the immediate post-ECT, postanesthesia recovery period may be encountered. This typically resolves spontaneously in under an hour. Benzodiazepines or neuroleptics have been used to manage this when necessary. Transient elevation in blood pressure and cardiac arrhythmias are usually managed quite easily by anesthesia personnel. Fatalities with ECT are rare. Kalinowsky (1975) cited a series greater than 100,000 treatments with a death rate of 0.003 percent despite the fact that many treated patients were elderly with concomitant cardiovascular and other medical problems. Caution is in order in the acute period following myocardial infarction, although most psychiatrists would consider ECT to be safer than TCAs here. Uncontrolled elevation in intracranial pressure is the strongest contraindication to ECT.

SUMMARY

The somatic treatment of depression is far from ideal. Tricyclic antidepressants have a fairly wide spectrum of action, being effective in major depressions of varying degrees of severity, some atypical depressions, and some dysthymias. The addition of neuroleptics may extend the range of these agents to psychotic depression. Potentiation with lithium or thyroid hormone may improve efficacy; however, it remains considerably less than complete. Side effects with TCAs are significant. Monoamine oxidase inhibitors are particularly efficacious in the treatment of atypical depression. Some patients with major depression and some with dysthymia may respond, although the statistics for this are quite uncertain. Side effects with these drugs may be bothersome and the adverse interaction with foods and medications render this a not uncomplicated treatment. Lithium has a special place in the treatment of bipolar patients, as a potentiator of other antidepressants, and, perhaps, in continuation therapy. Side effects are usually mild, but effectiveness is clearly less than complete. The second generation of antidepressants has yielded a number of chemically distinct agents, typically with fewer and less severe side effects than the TCAs and MAOIs. The clinical range of these agents is not clear at the present time. There are no suggestions that effectiveness is greater than that of TCAs when patients are considered as a group. Electroconvulsive therapy is quite effective for a narrow range of severe depressions. It is not indicated in dysthymia or atypical depression. Underutilization, management of relapses, and emotional resistance

to electrical stimulation of the brain are the major problems with this treatment. The biological treatment of depression is just beginning. Psychiatrists are called upon for diagnostic acumen and clinical perspicacity in the selection and management of problems in treatment. Many of the conditional statements in this section need to be addressed by clinical research. There is much to do while awaiting the millenium.

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