Antidepressant Drugs: Additional Clinical Uses

Paul J. Orsulak, PhD, MBA, and David Waller, MD
Dallas, Texas

Three decades of psychiatric practice with tricyclic, tetracyclic, and heterocyclic antidepressants have shown that these drugs are effective not only for major depression, endogenous depression in particular, but also for a range of other disorders. Tricyclic and other antidepressants are now used to treat enuresis and attention-deficit disorders in children, bulimia and anorexia nervosa, panic disorder, posttraumatic stress disorder, obsessive-compulsive disorder, chronic pain, migraine, and peptic ulcer disease.

As with some of the antidepressants, the body of literature on the relationship between clinical response in these diseases and plasma or serum levels of the drugs is not complete or well understood, but for some of these disorders, sufficient preliminary serum level data are available to take advantage of therapeutic drug monitoring as an adjunct to treatment. Therapeutic monitoring can be particularly important where studies indicate that successful therapy occurs at blood levels substantially different from those used to treat depression. This paper presents a brief overview of antidepressant treatment of these disorders, focusing on the available pharmacologic data related to serum level measurements and their relation to clinical response.

Over the past 30 years antidepressant drugs have become the principal means of treating certain depressive disorders, especially endogenous depression. This broad group of medications includes the tricyclic antidepressants introduced originally in the 1950s, including imipramine, amitriptyline, nortriptyline, desipramine, doxepin, protriptyline, and trimipramine. Clomipramine (chlorimipramine) is also a tricyclic antidepressant used in Europe and Canada, but not approved for use (except as part of special protocols) in the United States. A new group of tetracyclic antidepressants represented by maprotiline and amoxapine was introduced in the early 1980s, as was the heterocyclic trazodone. Fluoxetine, a new, chemically distinct antidepressant, was introduced early in 1988, and bupropion, a monocyclic also with unique chemical properties, may become widely available soon. The triazolobenzodiazepine alprazolam, which is used primarily for its antianxiety action, is sometimes used as an antidepressant. The monoamine oxidase inhibitor (MAOI) drugs are also used to treat depression, but require certain dietary restrictions, and their use limits other medications that can be taken concomitantly. A wider use of these antidepressant drugs has developed, however, and they are now used to treat disorders other than major depression. Enuresis, migraine, chronic pain, the eating disorders anorexia nervosa and bulimia, panic disorders, posttraumatic stress disorder, peptic ulcer disease, obsessive-compulsive disorder, and attention deficit disorders have all been treated with one or more of these drugs.[1]

Over the past two decades numerous studies have also demonstrated correlations between plasma or serum concentrations of some of the antidepressant drugs and their therapeutic effectiveness.[2–4] Therapeutic monitoring of the tricyclic antidepressants, and to a lesser extent the other antidepressants in serum as an adjunct to clinical management of patients with depression, is being used more widely because the individual variability in the way that drugs are metabolized makes measurements of blood levels a useful tool to maximize therapeutic effectiveness and safety.

The measurement of tricyclic and other antidepressants in serum provides an accurate and useful means to obtain an optimal dosage and can enable the clinician to correct easily for differences in metabolism that are either genetically determined or brought about by disease states. Alterations in serum concentrations as the result of drug interactions and failure to achieve adequate serum concentrations as a result of noncompliance can also be iden-

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From the Departments of Psychiatry and Pathology, University of Texas Southwestern Medical Center, Dallas, Texas. Requests for reprints should be addressed to Dr. Paul J. Orsulak, Veterans Administration Medical Center (116A6), 4500 South Lancaster Road, Dallas, TX 75216.

TABLE 1. SUGGESTED THERAPEUTIC RANGES FOR ANTIDEPRESSANT DRUGS WHEN USED TO TREAT MAJOR DEPRESSION

Drug	Trade Names	Compounds Measured	Therapeutic Range (μg/L)
Imipramine	Tofranil, Imavate, Antipress, Janimine, Presamine, SK-Pramine	Imipramine + desipramine	150–250
Nortriptyline	Aventyl, Pamelor	Nortriptyline	50–150
Amitriptyline	Elavil, Triavil, Endep, Etafon, Limbitrol, Amitril	Amitriptyline + nortriptyline	80–250
Desipramine	Norpramin, Pertofrane	Desipramine	125–300
Protriptyline	Vivactil	Protriptyline	70–260
Doxepin	Sinequan, Adapin	Doxepin + desmethyldoxepin	150–250
Trimipramine	Surmontil	Trimipramine	150–250
Clomipramine	Anafranil	Clomipramine,	70–200
		desmethylclomipramine	150–300
Maprotiline	Ludiomil	Maprotiline	200–600
Amoxapine	Asendin	Amoxapine + 8-hydroxyamoxapine	200–600
Trazodone	Desyrel	Trazodone	800–1600
Alprazolam	Xanax	Alprazolam	20–55
Fluoxetine	Prozac	Fluoxetine + norfluoxetine	NA

tified and corrected through measurement of serum drug concentrations.[5,6]

Contemporary methods for determination of tricyclic, tetracyclic, and heterocyclic antidepressants include gas chromatography and high-performance liquid chromatography. More recently, quantitative and relatively specific immunoassays have been introduced for some of the more widely used tricyclic antidepressants, ie, amitriptyline, its demethylated metabolite nortriptyline, imipramine, and its demethylated metabolite desipramine. The availability of robust and reliable assays for at least these most widely used antidepressants has made therapeutic drug monitoring of these drugs practical for most large clinical laboratories. The availability of these assays has increased the use of therapeutic drug monitoring as part of clinical practice when treating patients for depression[6] and has spurred development of methods for other antidepressants, although these are not as readily available.

For therapeutic drug monitoring to be useful and clinically beneficial there must be (1) a defined relationship between serum (or blood) concentration of the drug being measured and therapeutic response, and (2) a practical method to measure the drugs. When treating major depression—and in particular endogenous depression—therapeutic ranges for antidepressants such as amitriptyline, imipramine, nortriptyline, and desipramine are well defined, while the ranges for others are less well understood.[4–7] Expected serum concentrations[6] that occur in most successfully treated depressed patients have been suggested (Table 1), and can be used to aid treatment management.[6]

In contrast to the depressive disorders, the development of guidelines to support therapeutic drug monitoring for all of the other disorders treated with these agents has not evolved at so rapid a pace. Studies of the relationship between serum or plasma levels of antidepressants and clinical response in other disorders now being treated with these drugs are limited. Nevertheless, a few studies have been conducted, and this paper will review briefly the work that has been done on serum levels of antidepressants in these disorders. Because a comprehensive review of this area and a discussion of mechanisms are beyond the scope of this article, the focus will be on those treatments that use the tricyclic and related antidepressants and those studies where serum level monitoring has been used. It should be noted that medications should seldom, if ever, be used alone in the treatment of these disorders, but space does not permit other aspects of treatment to be considered in this review.

ENURESIS

Enuresis is defined as inappropriate voiding of urine occurring in patients over 5 years old, by which age awareness of bladder function and voluntary control are usually achieved. Treatment studies have usually been limited to nocturnal enuresis because most enuretic episodes occur at night and because daytime episodes are often the result of other disorders such as urinary tract infections.[8] Although behavioral conditioning is used to treat this problem, treatment with antidepressants is also frequent. Imipramine has been used most often,[9–12] but desipramine has been found to be equally effective.[12] The usual dose is in the range of 25 to 75 mg/d, but dose is dependent

on age and weight,[9] and the daily dose should not exceed 2.5 mg/kg. While these drugs are effective, clinical response is not long lasting; relapse rate is high,[13] so use of pharmacologic treatment is best reserved for situations where a short-term effect is desired—for example, when a child goes to summer camp.

As early as 1978, studies examined the antienuretic effect of traditional tricyclic antidepressants in relation to plasma levels.[14] Plasma concentration was measured in boys treated with 75 mg of imipramine or desipramine at bedtime. Plasma imipramine values ranged from 9 to 82 μg/L (mean = 33 μg/L) and plasma desipramine (a metabolite of imipramine) ranged from 11 to 249 μg/L (mean 94 μg/L) when imipramine was used. When desipramine was administered, concentrations were higher, ranging from 65 to 214 μg/L with a mean of 144 μg/L. Clinical response, measured by the number of dry nights, was correlated with plasma desipramine concentration regardless of which drug was used. Imipramine levels were not correlated with clinical response in a preliminary study[14] but were in a subsequent larger study.[12] As with depressive disorders, there were some patients who failed to respond even though they showed high levels of drug in plasma. A subsequent study[15] of imipramine therapy also found significant correlations between clinical response and plasma concentrations of both imipramine plus desipramine and desipramine alone. Optimal therapeutic effect occurred when the concentration of imipramine plus desipramine was greater than 60 μg/L, ie, about one quarter of the effective plasma concentration (125 to 280 μg/L) in depressed children.[16–18]

ATTENTION DEFICIT DISORDER

Attention deficit hyperactivity disorder is a syndrome beginning in childhood characterized by short attention span, impulsivity, and poorly organized behavior.[19] It was previously referred to as minimal brain dysfunction and hyperkinetic syndrome. Although it is usually treated with stimulant medication, tricyclic antidepressants are an alternative. Again, imipramine has been most widely used in treating this disorder.[20–22] Doses tend to be nearly as high as those used to treat depression,[23,24] but response is much more rapid.[25] Symptoms may recur immediately upon discontinuing medication. Desipramine[26] and clomipramine have also been used with limited success, being superior to placebo but less effective than methylphenidate.

Three studies examined desipramine plasma levels in young patients treated for attention deficit disorder.[26–28] Plasma levels of desipramine were correlated with dosage in individual patients. A tenfold range in plasma concentrations was seen across the subjects, but individual variability was narrower. At follow-up visits,[27] plasma levels of desipramine ranged from 33 to 291 μg/L (mean 156 ± 70 μg/L) in a group of 18 children who responded to this drug. Of significance is the notation by the authors that 10 of the 18 patients in this research study required doses higher than the 2.5 to 3.5 mg/kg/d, often considered to be an upper limit for this drug. Cardiac function should be monitored with electrocardiograms in this situation. Only one child achieved serum levels above 250 μg/L, but the wide interpatient variability pointed to the need for plasma level measurements to help avoid toxic levels as well as confirm medication compliance and adequacy of the drug trial.

BULIMIA

Bulimia is characterized by irresistible urges to binge eat, which recur frequently and are accompanied by behavior aimed at preventing weight gain (ie, self-induced vomiting, laxative abuse, and fasting). Depressed mood and self-reproach following the binging often accompany the disorder. This observation led to investigation of antidepressants to treat bulimia, and a subsequent double-blind study found imipramine superior to placebo in treating this disorder.[29] Initial studies with the MAO inhibitor phenelzine[30] showed this drug to be effective in reducing binge frequency when used at doses usually used to treat depression. Concerns over safety of MAOI therapy in a diet-related disorder, however, led to further studies with the tricyclic antidepressants. Studies using desipramine, imipramine, trazodone, and amitriptyline[31–33] have all showed some success, with the exception of one study that suggested that amitriptyline was not so effective in alleviating the eating behavior of bulimia.[32] A two-year follow-up study of patients with bulimia suggested that treatment response persists even after drug therapy is discontinued.[33]

Hughes et al[34] measured plasma levels of antidepressants in bulimia with significant results. Response to desipramine appeared most substantial when plasma levels were kept in the range of 125 to 275 μg/L. This range corresponds to the therapeutic range suggested for this drug in depression.[6] In addition, the authors noted the difficulty in monitoring medication compliance in patients who "binged and purged." For this reason, serum measurements may be a powerful adjunct to treatment in these patients. In the one study[32] that used amitriptyline without clinical benefit, the authors noted that plasma levels were very low (ie, less than 75 μg/L), implying that higher levels, possibly similar to those used for depression (greater than 90 μg/L) might be more effective.

ANOREXIA NERVOSA

Anorexia nervosa is a disorder characterized by disturbed self-image, fears of gaining weight, compulsive dieting and exercise, and excessive weight loss. To date, no specific treatment has been consistently successful. Various pharmacologic treatments have been tried with limited success, including chlorpromazine,[35] pimozide,[36] tetrahydrocannabinol (THC),[37] and naloxone.[38] Cyproheptadine has also been evaluated and may be effective at higher doses than usually used.[39] Amitriptyline has also been tried with some success, but again results have not been conclusive.[40–42] More recently,[43] several antidepressants including imipramine, desipramine, trazodone, amoxapine, and nortriptyline were tested in various combinations in a group of nine anorectic patients with some benefit to all but two of the patients. These findings point to difficulties associated with using these drugs in these patients. The low tolerance of these subjects for the anticholinergic side effects of tricyclic antidepressants and the extremely low weights of these patients (52 to 80 percent of ideal body weight) make management of a pharmacologic regimen difficult. Several of the studies used doses lower than those usually used to treat depression, so lack of response may be associated with inadequate trials of the drugs.

PANIC DISORDER

Several different tricyclic drugs, alprazolam, and MAO inhibitors are effective in treating anxiety disorders accompanied by panic attacks.[19] Imipramine is effective as evidenced by results of placebo-controlled studies.[44,45] Open trials show that desipramine[46] and clomipramine[47] may also be effective. Doses are generally in the same range as those required for depression,[48,49] but at least one study showed that imipramine at a dose of 50 mg/d was effective.[49]

Blood level measurements may be useful to guide such therapy even though a specific therapeutic range has not been established for phobic disorders.[49] Three studies examined the relationship of plasma levels and clinical response to tricyclic antidepressants in panic disorders. The first[50] included five patients who were treated with low doses (10 to 30 mg/d) of imipramine and who showed good clinical response after three weeks. Plasma levels of imipramine and desipramine at that time were 15 to 40 μg/L. Subsequent studies found slightly better clinical response[51] when plasma levels of imipramine plus desipramine were kept in the range of 100 to 150 μg/L, rather than the upper range of 200 to 250 μg/L usually suggested for depressed patients. Another study, however, found that clinical response correlated better with the concentration of imipramine alone, rather than imipramine plus desipramine,[52] with imipramine concentration ranging from 37 to 39 μg/L (mean, 42 μg/L). Total plasma levels were similar to those normally used in depressed patients (ie, imipramine plus desipramine = 241 ± 161 μg/L, X ± SD).

POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD) is characterized by symptoms of hyperalertness, sleep disturbance, survivor guilt, impairment of memory and concentration, avoidance of reminders and recollections of traumatic events, intensive daydreams or images, and recurrent nightmares. PTSD frequently presents with symptoms similar to those of panic attack, and both panic attack and PTSD frequently include a dysphoria resembling that seen in depression. Tricyclic antidepressants have been used to treat PTSD with moderate success.[53–55] Doxepin, imipramine, amitriptyline, and desipramine have been used to reduce the severity of symptoms associated with PTSD. Doses are similar to those used to treat depression, but data on serum or plasma levels were not included in the studies, so no recommendations can be made as to the utility of serum measurements.

OBSESSIVE-COMPULSIVE DISORDER

Obsessive-compulsive disorder is characterized by obsessive, recurrent, bothersome thoughts, ideas, and images or impulses or compulsions (repetitive, purposeful stereotyped behavior), with the patient being aware that these are abnormal but unable to resist them. Since this disorder, too, is defined as an anxiety disorder,[56] research eventually led to trials with antidepressants and other drugs used to treat anxiety.[57] Antidepressant drugs, in particular clomipramine, and behavioral therapy[58] are considered the most useful means of treating obsessive-compulsive disorders. Studies first found clomipramine to be successful,[58] followed by reports that imipramine was also useful,[59] but not amitriptyline or nortriptyline.[60,61] Doses of clomipramine are similar to those used for depression (150 to 300 mg/d), and a similar therapeutic range might exist as well. One of these studies[62] found that levels of both clomipramine and desmethylclomipramine correlated well with reduction of obsessional symptoms with maximal response occurring after three weeks of treatment. Patients most likely to benefit from this treatment appear to be those with plasma levels of clomipramine alone not exceeding 95 μg/L, which is near the lower limit of the therapeutic range for this drug used as an antidepressant (70 to 200 μg/L).

At the same time, a second study[63] of clomipramine in 40 obsessive-compulsive ritualizers found that plasma levels of both clomipramine and its desmethyl metabolite correlated well with clinical response but not with side effects. The results suggested a "therapeutic window" for this disorder. Patients with plasma levels of clomipramine between 100 and 250 μg/L and desmethylclomipramine between 230 and 550 μg/L were found to respond better than patients with plasma levels outside this range.

Fluoxetine has also been used in limited studies[64,65] to treat obsessive-compulsive disorder successfully and is currently undergoing clinical trials for this indication. While one study noted variable response to this drug,[64] the other[65] reported that all of its seven patients responded to fluoxetine without any of the adverse effects observed when these same patients were treated with clomipramine.

CHRONIC PAIN

Many antidepressant drugs including imipramine, amitriptyline, doxepin, and clomipramine as well as the MAO inhibitor phenelzine[66] are known to be effective in treating chronic pain[67,68] associated with arthritis,[69] diabetic neuropathy,[70] tension headache,[71–73] facial pain syndrome,[66] back pain,[74] pain of mixed etiology,[75] postherpetic neuralgia,[76] and cancer pain.[77] About 25 percent of patients who exhibit pain associated with chronic physical illness also experience at least moderate depression,[77] and conversely, many patients with depression complain of pain.[78–81] Of interest here is the finding that imipramine was effective for painful neuropathy at lower doses and lower serum levels than are required to treat depression. Serum levels of amitriptyline plus nortriptyline above 100 to 120 μg/L were effective in most patients[70] compared with the levels usually required in depression of 200 to 250 μg/L.[5] Similarly, lower doses of amitriptyline have been shown to be effective against chronic pain.[76] (The mechanism of action was probably different from that found in depression,[82] and the evidence for a lower therapeutic window was based on dosage required.) Maximum analgesia occurred when doses were in the 20- to 100-mg range, with a return of pain at doses above this level. Although blood levels were not measured, this study suggests that effective plasma concentrations might be lower than those used to treat depression.

The analgesic effect of amitriptyline in patients with chronic pain was studied in relation to amitriptyline plasma levels and plasma levels of its metabolites.[83] Plasma levels of amitriptyline, nortriptyline, and 10-hydroxy-nortriptyline (the principal metabolite of nortriptyline) were not correlated with clinical response. There was also no difference in plasma levels between responders and nonresponders, but in both groups plasma levels were much lower than those usually associated with response to this antidepressant in depressive disorders. Mean plasma concentrations were 33 μg/L, 53 μg/L, and 38 μg/L, respectively, for amitriptyline, nortriptyline, and hydroxynortriptyline in responders, compared with levels of amitriptyline plus nortriptyline of 100 to 250 μg/L in depressed patients treated successfully. Of note, however, is not only that responders had higher nortriptyline levels (53 μg/L) than nonresponders (32 μg/L), but that the level in responders is within the therapeutic window reported for nortriptyline when used to treat depression (50 to 150 μg/L),[6] while the level in nonresponders fell below this range. When taken together, these studies suggest that chronic pain without depression may require lower doses, with response occurring at lower blood levels than the dose (and blood level) required to treat either depression or chronic pain with depression.

Doxepin has been used to treat chronic low back and cervical pain.[84] In a study of 60 patients, the administration of 200 mg/d of doxepin was successful in alleviating both pain symptoms and associated depression by maintaining plasma levels of doxepin plus desmethyldoxepin of about 90 μg/L. As with other tricyclic antidepressants, this level of doxepin in the blood is lower than that usually associated with treatment of depression (150 to 250 μg/L). Similar to studies in depression, conflicting results can also be found. A second study with doxepin reported significant relief of pain and remission of depression with plasma levels of doxepin plus its metabolite throughout a range of 28 to 388 μg/L.

In contrast to the high levels of clomipramine and its metabolite required to treat depression and obsessive-compulsive disorder, pain syndromes respond to lower concentrations of this drug as well. A therapeutic window for clomipramine between 20 and 85 μg/L has been observed for analgesia with this drug.[85] Levels above the threshold of 85 μg/L were associated with poor clinical response. This study, however, might have underestimated steady-state plasma concentrations because blood specimens were drawn 22 hours after last dose of medication.

MIGRAINE

Migraine is distinguished from other forms of headache on the basis of its episodic occurrence, and its occurrence usually being unilateral with a throbbing quality. It is frequently accompanied by visual phenomena and nausea.[86,87] Numerous studies[88–91] have shown that the tricyclic antidepressant amitriptyline is far superior to placebo for the prophylactic treatment of migraine and can be as effective as ergotamine.[92] The effectiveness of

amitriptyline, however, may be confounded by the fact that while it is better than placebo, it is barely as effective as the more traditional treatment with methysergide maleate (50 percent improvement in frequency and severity compared with 58 percent for methysergide and 34 percent for placebo).[93] Nevertheless, the significant potential for fibrotic or vascular complications from long-term treatment with methysergide may favor treatment with amitriptyline in many patients.

PEPTIC ULCER DISEASE

The tricyclic antidepressants were initially considered for treating this disease because the anticholinergic properties might attenuate gastric acid secretion.[94] The tricyclic antidepressants doxepin at about 50 mg/d[95] and trimipramine at 25 to 50 mg/d[96–100] have been successfully used in treating peptic ulcers. In one trial of doxepin,[101] a daily dose of 50 mg/d was effective in treating seven of eight patients who did not respond to cimetidine. In a more recent study,[102] doxepin treatment was associated with a more rapid decrease in ulcer size compared with cimetidine treatment, but after six weeks of treatment both drugs were equivalent. Because of the lack of well-controlled trials, it is premature to suggest that this drug be used preferentially to cimetidine, even in patients with depressive symptoms.[1]

CONCLUSIONS

A review of the use of tricyclic and other antidepressants in both psychiatric and nonpsychiatric disorders points out that these drugs can be effective, but that they are decidedly beneficial in only some of the diseases. Although it would be too simplistic to assume that pharmacologic or pharmacokinetic differences alone could account for the lack of efficacy when numerous different mechanisms[1] are probably involved, consideration of blood levels and pharmacologic variables might improve clinical response in some patients who fail to respond to the initial treatment with medication.

Serum measurements of antidepressants are particularly important in cases such as chronic pain, where levels well below those seen in patients treated for depression are seen. Careful titration of dose up to the plasma levels required may be necessary, since the usual oral doses of antidepressants may lead to excessive blood levels and possibly poor clinical response. Where plasma or serum level information is available, these measures should be used to ensure compliance, avoid excessive doses and toxicity, and ensure that each patient receives an adequate medication trial.

Measurement of antidepressants for these psychiatric and nonpsychiatric disorders will also present new challenges for the laboratories providing therapeutic drug-monitoring services. Clearly, additional studies of efficacy of antidepressants in the diseases summarized here are needed to better develop treatment and management of these disorders. These studies should include complete pharmacokinetic and pharmacologic data obtained through serum level measurements. In this way, guidelines for use of serum measurements of antidepressants in these disorders can be developed. The introduction of new drugs, such as clomipramine and fluoxetine, will require new analytical methods. The introduction of new therapeutic ranges, such as the lower levels required in enuresis, will broaden the analytical ranges, and reports will have to take such new information into account. It will no longer be sufficient to report only a therapeutic range for one disease such as depression. Therapeutic ranges for each use will need to be developed and incorporated into laboratory information. The uses for antidepressant measurements outlined here will also require a broader understanding of the pharmacology and diagnostic information surrounding their use so that the laboratory can provide information that will maximize clinical benefit and cost effectiveness.

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