Pharmacology: New Antidepressants

By JOHN P. FEIGHNER, M.D.

The advent of psychotropic agents in the 1950s dramatically changed pharmacologic treatment and improved the quality of life for many patients suffering from psychiatric illness. Despite this major achievement, the available antidepressant drugs, even though clearly effective, have significant side effects, are potentially lethal when used for suicide attempts, and generally are slow in their onset of action. However, promising new classes of antidepressants are opening a new era in the treatment of depression. These agents have a more rapid onset of action, are biologically more specific, cause fewer side effects, and have been effective in patients with intractable depressive disease.

NEW ANTIDEPRESSANT DRUG CLASSES

During the past four years, our research clinic has been systematically studying these new classes of antidepressants:

- the new tetracyclic compounds, such as maprotiline, maprotiline analog (a specific inhibitor of norepinephrine re-uptake), and mianserin;
- a completely new psychotropic class of triazolopyridine derivatives that selectively inhibit serotonin re-uptake, e.g., trazodone;
- other serotonin re-uptake inhibitors, including zimelidine, fluoxetine, and fluvoxamine;
- the tetrahydroisoquinoline compound, nomifensine, which is a specific blocker of norepinephrine and dopamine re-uptake;
- buproprion, also a blocker of dopamine re-uptake, and alprazolam, which is a new triazolobenzodiazepine with antidepressant effects.

Data from these studies will summarize the pharmacologic profiles, clinical efficacy, and adverse effects of these new antidepressants. Incorporated into this research endeavor is an emphasis upon the development of greater diagnostic specificity correlated with diagnostic criteria, laboratory findings, and treatment response. Proper identification of the study population in order to achieve the greatest possible homogeneity is of the utmost importance. In all of these studies we have used the Feighner criteria for primary depression and the Research Diagnostic Criteria for major depressive disorders (Table 1).1,2

TETRACYCLIC COMPOUNDS

Maprotiline. The tetracyclic compounds will soon be available to the clinician. Maprotiline has been demonstrated in numerous double-blind, placebo-controlled studies to be an effective antidepressant when given in a single or divided daily dose ranging from 50 to 300 mg.1,4 It is a noradrenergic antidepressant with moderately low cardiovascular and cholinergic (or atropine-like) side effects, and, in general, is well tolerated by most patients. Its spectrum of antidepressant activity appears to be consistent with that of the currently available tricyclic antidepressants, such as imipramine and desipramine, and its major advantage is a reduced side-effect profile. Maprotiline Analog. At present we are studying a hydroxy analog of maprotiline. Animal studies have shown it to be five to 50 times more potent than the parent compound. Results from our recently completed study indicate that this tetracyclic can be taken once a day in doses ranging from 50 to 150 mg without any significant adverse effects.5 This compound was studied in 16 inpatients on an open-label basis, with appropriate baseline washout periods. Demographic data were consistent with our primary depression inpatient populations. Clinical assessment measures, including the brief psychiatric rating scale, Hamilton Depression Rating Scale (HAM-D), Zung self-rating scale, and Clinical

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**TABLE 1**
THE FEIGHNER CRITERIA FOR AFFECTIVE DISORDERS*

**PRIMARY AFFECTIVE DISORDERS**

Depression: "A" through "C" are required for a diagnosis of depression:

A. Dysphoric mood accompanied by such subjective symptoms as:

1. Depression
2. Sadness
3. The blues
4. Despondency
5. Hopelessness
6. Feeling down in the dumps
7. Irritability
8. Fear
9. Worry
10. Discouragement

B. At least five of the following criteria are required for a diagnosis of definite depression; at least four are required for a diagnosis of probable depression:

1. Poor appetite or weight loss of two pounds in one week, or 10 pounds or more in one year without dieting
2. Sleep disorder, such as insomnia or hypersomnia
3. Loss of energy, as noted by fatigability or tiredness
4. Agitation or retardation
5. Loss of interest in usual activities or decrease in sexual drive
6. Feelings of self-reproach or guilt, sometimes of delusional proportions
7. Complaint of or actual diminished ability to think or concentrate, as shown by slow thinking or mixed-up thoughts
8. Recurrent thoughts of death or suicide, including thoughts of wishing to be dead

C. A psychiatric illness lasting at least one month with no pre-existing psychiatric conditions, such as:

1. Schizophrenia
2. Anxiety neurosis
3. Phobic neurosis
4. Obsessive-compulsive neurosis
5. Hysteria
6. Alcoholism
7. Drug dependency
8. Antisocial personality
9. Sexual orientation disturbance (homosexuality)
10. Sexual deviation
11. Mental retardation
12. Organic brain syndrome

The presence of a life-threatening or incapacitating illness preceding and paralleling the depression should preclude the making of a diagnosis of primary depression.

**Mania: "A" through "C" are required for a diagnosis of mania:**

A. Euphoria or irritability

B. A minimum of three of the following symptom categories must also be present:

1. Hyperactivity, including motor activity, social activity, and sexual activity
2. Push of speech—the pressure to keep talking
3. Flight of ideas—racing thoughts
4. Grandiosity, sometimes of delusional proportions
5. Decreased sleep
6. Distractibility

C. A psychiatric illness lasting at least two weeks with no pre-existing psychiatric conditions, such as:

1. Schizophrenia
2. Anxiety neurosis
3. Phobic neurosis
4. Obsessive-compulsive neurosis
5. Hysteria
6. Alcoholism
7. Drug dependency
8. Antisocial personality
9. Sexual orientation disturbance (homosexuality)
10. Sexual deviation
11. Mental retardation
12. Organic brain syndrome

MAPROTIENE ANALOG

CH₂CHOHCH₂NHCH₃

Global Impression Scale (CGIS), were performed at the baseline visit and repeated weekly for a total of four weeks. Anticholinergic side effects were assessed weekly by a specific anticholinergic scale, and electrocardiograms were also performed during weekly visits.

Eleven of the 16 patients showed clinically significant improvement. In addition, a total of nine patients fulfilled the criteria of moderate improvement or better, as defined by a 50% reduction of the HAM-D from baseline to endpoint and by an improvement on the global impressions of at least a moderate level or better. The average dosage was approximately 125 mg per day.

In addition to typical anticholinergic side effects of dry mouth, constipation, and orthostatic faintness, there was evidence of hyperactivity, including agitation, restlessness, and insomnia. However, it is important to note that despite these reported side effects, none of the 16 patients dropped out of the study as a result of adverse experience from this compound, which, in general, has a low side-effect profile. No clinically significant abnormal laboratory values or ECG changes were noted that could be attributed to maprotiline analog.

MIANSERIN. We are currently completing an extensive outpatient study with another tetracyclic compound, mianserin, which has already been extensively studied in Europe. Clinical efficacy has been evaluated in more than 25 double-blind, controlled studies with amitriptyline and imipramine as reference comparison drugs, but not in comparison with placebo. Mianserin has a much lower anticholinergic side-effect profile, and is very well tolerated by most patients. The most common side effects are drowsiness and lethargy. In addition, mianserin shows minimal cardiovascular toxicity, even with overdose, and minimal adverse drug-drug interaction with other psychotropic or cardiovascular drugs. The dosage range for this compound is 30 to 150 mg per day, usually given at bedtime. The spectrum of clinical activity appears to be similar to that of imipramine and amitriptyline.

SEROTONERGIC ANTIDEPRESSANTS

Trazodone. We are currently investigating numerous potent serotonergic antidepressants in our research clinic. Trazodone, which has been studied the most extensively, represents a completely new class of psychotropic drugs and is the first of the triazolopyridine derivatives to be used clinically. The pharmacologic profile of trazodone is unusual in that the compound fails to produce the usual typical results in classical laboratory tests for antidepressants. It does not antagonize reserpine, potentiate L-dopa, or inhibit monoamine oxidase (MAO), and it has no anticholinergic effects. Trazodone also lacks the anticonvulsant effects of antianxiety agents and has only weak muscle-relaxing activity. Like antipsychotic compounds, trazodone disrupts conditioned avoidance responses and protects mice from amphetamine-type toxicity; however, the drug lacks significant cataleptic properties, has weak hypothermic activity, does not inhibit the stereotypical behavior due to amphetamine or apomorphine, and has no demonstrable neuroleptic effect.

TRAZODONE

The antidepressant action of trazodone appears to be associated with its inhibition of brain serotonin re-uptake. It has been found to antagonize the depletion of brain serotonin induced by fenfluramine and to inhibit re-uptake of serotonin by rat platelets in vitro. Behavioral changes induced by the serotonin precursor 5-hydroxytryptophan are potentiated by trazodone.

The effectiveness of trazodone in the treatment of endogenous depression and related anxiety was first reported in 1967. Since that time, numerous other studies conducted primarily in Europe and Canada have confirmed the antidepressant properties of trazodone. Over the past 13 years, its therapeutic uses have been investi-

continued
gated internationally in more than 200 open and controlled clinical trials involving more than 10,000 patients. However, most of these studies are open-label, and very few international double-blind, placebo-controlled studies have been done. Results from these open-label and noncontrolled clinical trials indicate that trazodone is an effective broad-spectrum antidepressant with effectiveness in both bipolar and unipolar affective disorders and in depression accompanying schizoaffective disorders.7

Clinical trials comparing trazodone with imipramine, desipramine, chlorimipramine, and amitriptyline have shown that it is as effective therapeutically as the reference drugs. In addition, it is generally well tolerated, may have more rapid onset of action, and has virtually no anticholinergic effect and extremely low cardiovascular toxicity. As one would expect from its serotonergic activity, the compound is quite sedating. Therefore, the major portion of the therapeutic daily dosage, which ranges from 50 to 800 mg per day, is given at bedtime.

We have recently completed a double-blind placebo-controlled study comparing trazodone vs. imipramine vs. placebo in 45 hospitalized patients suffering from primary depression, who showed a minimum HAM-D entry score of 18 or greater on the 21-item rating scale for depression.10 Before entering the double-blind phase of the study, all patients underwent baseline evaluation for three to seven days, during which time they received placebo.

During this time, we also conducted a thorough physical examination and laboratory workup for each patient. Frequent clinical assessment of treatment response

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**FIGURE 1**

**MEAN TOTAL HAMILTON SCORES**

![Graph showing mean total Hamilton scores over days of treatment.](image)

- *significantly (p<0.05) better response than placebo.
- **significantly (p<0.01) better response than placebo.

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- **trazodone**
- **imipramine**
- **placebo**
was obtained from the HAM-D, structured clinical interview, CGIS, and global ward behavior scales. Those subjects who improved significantly during the baseline placebo washout period were not admitted to the double-blind portion of the study. There were no significant demographic differences among the study groups.

The remaining patients entered the double-blind phase of the study and were randomly assigned to receive trazodone, imipramine, or placebo. Initial total daily dosage was 200 mg of trazodone or 100 mg of imipramine on a divided schedule. Dosage titration by increments could be made every two to three days, as clinically warranted, up to a maximum of 600 mg of trazodone or 300 mg of imipramine. Chloral hydrate was permitted as needed for insomnia.

The mean total HAM-D score as early as day seven reveals that trazodone is superior to placebo at the p<.05 level (Figure 1). By day 28, trazodone’s superiority to placebo is statistically significant at the p<.01 level. Imipramine was consistently better than placebo, but produced an intermediate response between that of placebo and trazodone. The CGIS also showed trazodone to be more effective than placebo. With the criterion of at least a 30% reduction from pretreatment to endpoint HAM-D scores as a reflection of moderate improvement or better, the results demonstrate that 53% of the trazodone patients achieved this level of improvement, compared to only 28% of the imipramine patients (Table 2). None of the placebo patients showed significant levels of improvement.

Although other studies have shown that trazodone is an effective broad-spectrum antidepressant, our investigations indicate the greatest effectiveness for this compound is in symptom clusters relating to anxiety, somatization, sleep disturbance, and agitation.

Side effects of all treatments were systematically evaluated. Drowsiness was the most frequent complaint in the trazodone group, and for five of these patients the clinically significant side effects also included a drowsy feeling, lethargy, nausea, and headache.

Clinically significant anticholinergic side effects were most frequent in the imipramine group and included dry mouth, constipation, blurred vision, orthostatic faintness, increased agitation, tremulousness, and dizziness.

There were no significant abnormal laboratory tests associated with either of the treatment groups. However, one significant abnormal electrocardiographic change considered to be related to treatment was observed in a patient who developed a first-degree atroventricular block during treatment with imipramine.

These data indicate that trazodone is an effective antidepressant with a relatively rapid onset of action, and is generally well tolerated by most patients. Our results are consistent with those of numerous other studies suggesting that trazodone represents an effective new class of antidepressants. Further study and utilization of this compound should be rigorously pursued.

Zimelidine. Numerous international studies have demonstrated that zimelidine hydrochloride is a potent serotonergic compound.

Results of these studies indicate that zimelidine has clinical efficacy in a dosage range of 50 to 130 mg per day. It appears to be well tolerated by most patients, does not seem to have anticholinergic side effects, and has low cardiovascular toxicity. Extensive studies are now in progress in our research center and elsewhere to compare zimelidine, in double-blind, placebo-controlled trials, to established tricyclic antidepressants.

Fluoxetine. Fluoxetine hydrochloride is another of the new potent and specific inhibitors of serotonin re-uptake. Fluoxetine, to date, has been studied in limited open-label clinical trials in both inpatients and outpatients with major depressive disorders. Results from these preliminary studies indicate that fluoxetine has clinical efficacy in a dosage range of 20 to 80 mg per day. It appears to be well tolerated by most patients, does not seem to have anticholinergic side effects, and has low cardiovascular toxicity. Extensive studies are now in progress in our research center and elsewhere to compare fluoxetine, in double-blind, placebo-controlled trials, to established tricyclic antidepressants.

### TABLE 2

<table>
<thead>
<tr>
<th>IMPROVED*</th>
<th>%</th>
<th>UNIMPROVED</th>
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<td>9</td>
<td>53</td>
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<tr>
<td>IMIPRamine</td>
<td>5</td>
<td>28</td>
<td>13</td>
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*at least 50% reduction from pretreatment to endpoint scores
clinical trials indicate efficacy with 40 to 80 mg per day in divided or single doses. At the present time, we are participating in a double-blind, placebo-controlled, multicenter study comparing fluoxetine to amitriptyline.

Fluvoxamine. Fluvoxamine is also a potent specific serotonergic compound of the family of (2-amino-ethyl) oxime ethers of the aralkyl ketones. It possesses a high serotonin re-uptake-inhibiting activity, with negligible, if any, effect upon norepinephrine re-uptake. It has no MAO-inhibiting effect and no amphetamine-like effect. In addition, fluvoxamine and its relative, clovoxamine, are further characterized by an absence of anticholinergic activity. Studies in healthy human volunteers have not produced any serious or unwanted side effects.

**FLUOXAMINE**

\[
\text{Fluvoxamine structure}
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In humans, its oral half-life is approximately 15 hours. Three open-label clinical studies have shown that fluvoxamine has a specific antidepressant effect, with a minimum of significant side effects. The average daily dose ranges from 50 to 300 mg, which, because of the long half-life, can be administered to many patients in a single dose. At the present time, we are involved in a double-blind, placebo-controlled, comparative study of fluvoxamine versus imipramine in patients with primary depression.

With the exception of trazodone, the other potent serotonergic compounds, such as zimelidine, fluvoxamine, and fluoxetine, still require extensive clinical trials to establish efficacy. Nonetheless, preliminary results appear to indicate that these highly specific compounds are effective and well tolerated, with no anticholinergic side effects and minimal cardiovascular toxicity.

**NEW DRUGS OF OTHER CLASSES**

Nomifensine. Nomifensine is a tetrahydroisoquinoline compound and is of particular interest because, unlike the tricyclic antidepressants, it is a specific blocker of dopamine re-uptake and represents another entirely new family of antidepressant compounds. Extensive international studies have demonstrated its antidepressant activity.

We recently completed a 28-day multicenter trial with nomifensine in 106 patients suffering from primary depression. This was a double-blind comparison of nomifensine maleate vs. placebo, with a dosage range of 100 to 200 mg per day. There were no significant demographic differences between the nomifensine and placebo study groups.

**Nomifensine**

The overall HAM-D scores indicate greater activity for nomifensine vs. placebo at the p<.05 level. The most striking findings were that nomifensine was most effective for those patients with psychomotor retardation and that this difference was significant at the p<.01 level. Even though the overall difference between nomifensine and placebo was significant at only the p<.05 level, in no instance was there a statistically significant difference favoring placebo. Results from the CGIS also favor nomifensine for overall improvement at the p<.05 level. Fifty-six percent of the nomifensine group vs. 17.4% of the placebo group showed marked or moderate improvement.

Evaluation of the laboratory and physical examination data revealed no significant difference for either group. No significant drug-related ECG changes were noted. However, five times the number of patients who received nomifensine reported side effects, compared with those receiving placebo. This difference was highly significant at p<.001. The most frequently reported side effects for nomifensine were dry mouth, nervousness, restlessness, and insomnia.

These data indicate that this agent may not have broad-spectrum antidepressant activity. Further research with nomifensine should focus on specific depressive subtypes to define its role as an antidepressant more clearly.

Bupropion. Bupropion is a chloropropiphenone compound. It is a specific dopamine re-uptake inhibitor, with no anticholinergic effect and no MAO inhibitory effect. Dosage range is from 200 to 600 mg per day in divided doses.

Numerous national and international studies have been done on both an open-label and double-blind basis. To date, this compound has demonstrated antidepressant ef-
ficacy, but may also lack a broad-spectrum effect. Careful attention must be directed to specific depressive subtypes in evaluating its antidepressant effect.

BUPROPION

We are now conducting an extensive double-blind, placebo-controlled study of bupropion in inpatients with major depressive disorders. Preliminary results indicate the greatest effect is seen in those patients with psychomotor retardation.

Alprazolam. A recent review by Schatzberg and Cole on the antidepressant activity of benzodiazepines states that there is limited evidence to indicate that drugs of this class may have specific antidepressant effect. Alprazolam, which appears to have this specificity, represents a totally new family of triazolobenzodiazepines evaluated in a series of double-blind, placebo-controlled studies.

In one multicenter trial involving over 500 patients with unipolar depression of the anxious/agitated/insomnia subtype, alprazolam demonstrated more rapid onset of action than imipramine, with equivalent antidepressant effect. It also produced fewer side effects and was better tolerated by patients.

The antidepressant potential of this new class of benzodiazepines, with its advantages of a low side-effect profile, lack of anticholinergic effect, and minimal danger of mortality upon overdose, certainly warrants further investigation.

The imminent availability of the innovative antidepressants described here, as well as other new compounds currently being studied, portends that pharmacotherapy in the 1980s clearly will be much more specific, more effective, and safer than in the past.

REFERENCES

Is trazodone particularly useful in any specific depressive subtype, including atypical depression?

Trazodone has been shown to be a broad-spectrum antidepressant in many, many studies. Our own work confirmed this, but also showed that it was most effective in patients with symptoms of anxiety—such as agitation and insomnia. We also had a good response in some very ill, intractably depressed patients. It appears that all types of depression may respond to trazodone. However, we have not tested it in atypical depressives.

Did you find any imipramine failures that responded to trazodone?

We did, but those data have not yet been analyzed.

Because of its effect on the serotonin system, one would expect trazodone to be effective in relieving chronic pain. Are there any data on this?

It has not been studied, but I would expect it to work.

The issue may not be related to serotonin, because various tricyclics have been shown to be useful in treating chronic pain, and it is not clear whether or not they are predominantly serotonin uptake compounds.

Do any of the new agents have a therapeutic window effect?

This is a very difficult thing to establish; techniques for measuring blood levels of the newer compounds are still being developed. Even with nortriptyline—the most extensively used agent—there are many conflicting data concerning a therapeutic window effect.

Much of this symposium has involved the untoward side effects of the established antidepressant medications. In light of that, can you compare the newer compounds with the established ones, in terms of the problems that exist with the latter?

Certainly the tricyclics are effective, all of the drugs we have been discussing have a place in the treatment of depression. But the problems are manifold: tricyclics and MAO inhibitors can precipitate and aggravate mania in bipolar disorders; tricyclics are lethal when taken in overdose, and their onset of action takes two to four weeks. Beyond that, cardiotoxicity can be a side effect, although I think this is somewhat overplayed. The atropine side effects are the most troublesome.

Did you observe any manic episodes following trazodone administration?

In our long-term studies with trazodone, only one patient has had a clinically significant manic episode. This drug, you will recall, represents an entirely new class of antidepressant, whose effect is thought to be related to its inhibition of serotonin reuptake in the brain. It does not antagonize reserpine, potentiate L-dopa, or inhibit monoamine oxidase. Also, it has no anticholinergic effects and extremely low cardiovascular toxicity.

The newer compounds, as a group, have some tremendous advantages over the tricyclics. Many of them have little or no atropine effect, and many are effective in patients whom nothing else has helped. Some are quite sedating and others are minimally sedating. Weight gain—a real problem with tricyclics—does not occur with the newer agents, with the exception of mianserin, a tetracyclic.

Do you envision the established drugs being largely replaced by the newer agents?

I certainly do; the advantages of these newer compounds cannot be ignored, and I think the research with tetracyclic compounds and the triazolopyridines may alter some of our concepts about the psychopharmacology of depression.