Monoamine Oxidase Inhibitors Revisited

Jay D. Amsterdam, MD; and Mohit Chopra, MD

Monoamine oxidase inhibitors (MAOIs) were among the first compounds to show consistent antidepressant activity. The psychotropic benefits of MAOIs were initially discovered serendipitously as an adverse event of the use of iproniazid for tuberculosis. After the initial reports of mood enhancement resulting from iproniazid, West and Dally in the United Kingdom and Crane and Kline in the United States demonstrated the efficacy of iproniazid in the treatment of depression. These promising reports subsequently led to the introduction of MAOIs into psychiatric practice in the United States and the United Kingdom.

By the early 1960s, Sargent and Dally demonstrated the usefulness of MAOIs for the treatment of mixed depression and anxiety states, and even for the treatment of anxiety disorders in the absence of depression. However, hepatic toxicity with iproniazid led to the development of a second generation of MAOIs such as isocarboxazid, tranylcypromine, and phenelzine. The emergence of the biogenic amine hypothesis of depression and the ease of treating affective illness with a pill led to the early popularity of MAOIs.

However, along with the increasing use of MAOIs came reports of serious untoward effects, such as hypertensive events following the ingestion of certain foods. Subsequent reports of serious interactions with other medications and iproniazid-induced fatal hepatotoxicity substantially dampened enthusiasm for the routine use of MAOIs in clinical practice. The contemporaneous emergence of the tricyclic antidepressants (TCAs), coupled with a British Medical Research Council study questioning the efficacy of MAOIs compared with other somatic treatments for depression, finally led to disfavor with MAOIs and the rise of the TCA era in the 1960s.

Despite early enthusiasm over TCAs and concerns about the toxicity of MAOIs, many physicians now take a more considered approach to psychopharmacology. The initial high enthusiasm for TCAs has been tempered by the introduction of the selective serotonin reuptake inhibitors (SSRIs) and the recognition that TCAs were one of the leading causes of death by suicide among patients in treatment. More recently, the enthusiasm over the efficacy and simplicity of use of the SSRIs has eroded among some physicians who feel that these agents may be less effective for patients with severe and melancholic depression.

As a result, there has been a recent resurgence of interest in MAOIs not only for severe depression, but also for other affective disorders. This resurgence began with several reports that described enhanced efficacy of MAOIs for patients with mixed depression and anxiety symptoms. More recently, a reanalysis of the early MAOI studies, which often failed to demonstrate good efficacy, questioned the methodologic soundness of many of these trials and suggested...
that the lack of efficacy might have resulted from inadequate dosing and patient selection. Subsequent studies by Davidson et al. and White et al. have clearly demonstrated the effectiveness of MAOIs in the treatment of major depression with melancholic features. Other studies by Leibowitz et al. and Quitkin et al. have also demonstrated the usefulness of MAOIs in the treatment of major depression with “atypical” features of hypersonomolence, hyperphagia, weight gain, anergia, and mood reactivity.

In a dramatic reversal of the general opinion regarding MAOIs, the American Psychiatric Association recently stated in its guidelines for the treatment of patients with major depressive disorder that “…MAOIs may be particularly effective in treating subgroups of patients with major depressive disorder with atypical features such as reactive moods, reversed neurovegetative symptoms, and sensitivity to rejection.” Similarly, the recently published evidence-based guidelines for treating depression of the British Association for Psychopharmacology categorized the recommendation that “MAOIs [are] . . . more effective in non-hospitalized patients with ‘atypical’ depression” as level Ia (ie, based on a meta-analysis of randomized, controlled clinical trials).

In addition, investigators in the United States and Europe have repeatedly found MAOIs to be highly effective for as many as 50% of patients who were resistant to prior drug therapy. To this end, the practice guidelines for the treatment of patients with major depressive disorder of the American Psychiatric Association also stated that MAOIs have “…been shown to be effective treatments for some patients who have failed other antidepressant medication trials.” The guidelines of the British Association for Psychopharmacology report level Ib evidence for a positive response to a MAOI once a patient has failed a trial of an uptake inhibitor.

However, despite their demonstrated benefits during the past four decades in some of the most difficult cases of depression, MAOIs have not gained favor among most physicians.

**CLINICAL PHARMACOLOGY OF MAOIs**

MAOIs are thought to act by inhibiting the MAO enzymes responsible for the catabolism of monoamine and indolamine neurotransmitters, although other direct actions at the neuronal receptor level may also contribute to their antidepressant effect. There are two subtypes of MAO enzymes, designated MAO-A and MAO-B, that interact with selective chemical substrates (Table 1). It is still unclear whether the individual enzymes are isoenzymes of each other.

MAOIs can be classified according to the reversibility or irreversibility of their binding affinity to the enzymes. In this regard, some selective MAO-B inhibitors and most mixed MAO-A and MAO-B inhibitors irreversibly bind to the enzymes. This might partly explain the nature of their long pharmacodynamic half-life and extended interaction when coadministered with certain drugs and foods.

In general, the most potent antidepressant activity of MAOIs appears to be related to the degree of MAO-A enzyme inhibition, although l-deprenyl (a selective MAO-B enzyme inhibitor) may have antidepressant activity when prescribed at higher doses (Table 2).

Although the effective daily dose of most MAOIs is generally thought to be within a fairly narrow range, some observations suggest that there may be a dose-response relationship. Several studies have found that the generally recommended total daily dose of MAOIs may be too low for many patients, and that these agents should be prescribed the way that TCAs are prescribed. One early study with phenelzine showed that a minimum of 85% MAO enzyme inhibition was generally required for antidepressant efficacy, and that a substantial proportion of patients were receiving daily doses insufficient to inhibit this percentage of platelet enzyme.
TABLE 2

<table>
<thead>
<tr>
<th>Mechanism of MAO Enzyme Inhibition</th>
<th>MAO-A and MAO-B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Selective</td>
</tr>
<tr>
<td>Irreversible</td>
<td>Ciorglyline</td>
</tr>
<tr>
<td></td>
<td>Selective</td>
</tr>
<tr>
<td></td>
<td>Selegiline</td>
</tr>
<tr>
<td></td>
<td>Pargyline</td>
</tr>
<tr>
<td>Reversible</td>
<td>Moclobemide</td>
</tr>
<tr>
<td></td>
<td>Brofaromine</td>
</tr>
<tr>
<td></td>
<td>Toloxatone</td>
</tr>
<tr>
<td></td>
<td>Befloxatone</td>
</tr>
</tbody>
</table>

MAO = monoamine oxidase.

TABLE 3

<table>
<thead>
<tr>
<th>Recommended Daily Doses of MAOIs</th>
<th>Minimum Dose (mg)</th>
<th>Maximum Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAOI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Phendelzine</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>Isoxcarboxazid</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>I-diphenyl</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>300</td>
<td>900</td>
</tr>
</tbody>
</table>

MAOI = monoamine oxidase inhibitors.

Subsequent studies found that higher than recommended doses of MAOIs are often necessary to optimize enzyme inhibition (Table 3).

CLINICAL INDICATIONS FOR MAOIs

MAOIs are currently recommended for use in major depressions with atypical features and for patients with chronic, resistant major depression unresponsive to other antidepressant treatment. However, these agents have also been found to be highly effective for other psychiatric disorders.

One of the reasons MAOIs have had so little popularity in clinical practice is the fact that early studies failed to adequately articulate the therapeutic profile of these compounds and the clinical profiles of patients who might preferentially respond to MAOI therapy. However, this situation began to change with the publication of the meta-analysis of prior controlled MAOI studies by Davis et al. These investigators showed that MAOIs were superior to placebo in controlled clinical trials. Additional clinical reports demonstrating superiority of MAOIs over placebo and TCAs by McGrath et al. and others led to a clearer appreciation of the therapeutic role of MAOIs.

Major Depressive Episode With Atypical Features

Some researchers have suggested that MAOIs may produce a preferential response in certain subtypes of affective illness. In one early literature review of clinical predictors of response to MAOIs, White and Simpson suggested that these agents may be particularly effective for patients with anxious or neurotic (nonendogenous) depression. Shortly thereafter, Liebowitz et al. reported that MAOIs may be most suitable for patients with reverse neurovegetative or atypical symptoms. These investigators viewed the syndrome of atypical depression as an admixture of specific neurovegetative symptoms and personality traits characterized by hypersomnia, hyperphagia, weight gain, leaden paralysis, rejection sensitivity, and mood reactivity to environmental events (that can occur even in the absence of affective symptoms).

The DSM-IV's major depressive episode with atypical features has gradually come to be recognized as a syndromal subtype of major depression that sits at the opposite end of the clinical spectrum from major depressive episode with melancholic features. Moreover, Davidson et al. have suggested that major depressive episode with atypical features be considered as having two subtypes—anxious (type A) and reversed vegetative (type V)—that overlap. Both subtypes appear to be responsive to MAOI therapy.

Advocacy for the use of MAOIs among patients with major depressive episode with atypical features has primarily come from investigators at Columbia University and the New York State Psychiatric Institute. In a series of trials conducted in the 1970s and 1980s with more than 400 patients who had major depression with mood reactivity and at least 2 associated atypical
symptoms from a group of 4 (ie, rejection sensitivity, leaden paralysis, hypersomnia, and hyperphagia), these investigators found phenelzine to be slightly, but consistently, superior to imipramine (with both treatments being superior to placebo). Among the patients with major depressive episode with atypical features, the overall response rate to phenelzine was approximately 70%, compared with approximately 60% for imipramine and approximately 20% for placebo. Moreover, the initial response with phenelzine appeared to be maintained among the patients with atypical features, but was less evident among the patients who had only the behavior pattern of mood reactivity without the associated atypical symptoms.

Other studies have specifically examined the effect of MAOIs on reverse neurovegetative symptoms. For example, in an initial report, Himmelhoch et al. showed that tranylcypromine was effective for 81% of anergic depressed patients with bipolar major depression, whereas imipramine was effective for 48%. A subsequent report by Thase et al. indicated that tranylcypromine was effective among anergic depressed patients with bipolar depression who were initially resistant to imipramine. A related report also found a good response to tranylcypromine among patients with reverse neurovegetative symptoms initially resistant to imipramine.

Chronic Depression and Dysthymic Disorder

Several studies have shown that MAOIs may be particularly effective for the treatment of patients with chronic major depressive episode, dysthymic disorder, and “double depression,” in which major depressive disorder and dysthymic disorder are intermittently superimposed on each other. In one noteworthy study, phenelzine was found to be superior to imipramine for 30 outpatients with dysthymic disorder, whereas imipramine tended to be more effective for patients with melancholic features. Similarly, phenelzine was found to be more effective than both imipramine and placebo for patients with double and chronic major depressive episode, whereas phenelzine and imipramine were of comparable efficacy among patients with “pure” dysthymic disorder.

In a meta-analysis that examined the relative efficacy of several reuptake inhibitors and MAOIs for patients with dysthymic disorder, Nolen et al. found MAOIs to be superior to TCAs and SSRIs during short-term treatment, with a more favorable side effect profile and a lower study dropout rate compared with TCA treatment. In contrast, another meta-analysis reported similar efficacies among the various MAOIs for depressed outpatients, but less overall efficacy than that seen with TCAs for depressed inpatients.

Bipolar Major Depression

Some investigators have suggested that MAOIs should be considered as a first-line treatment for bipolar I and II major depression. Himmelhoch et al. found the antidepressant efficacy of tranylcypromine to be superior to that of imipramine for patients with bipolar I and II depression who were taking mood stabilizers. In this study, the side effect burden with tranylcypromine was similar to that seen with imipramine. Others have used lithium carbonate to augment the antidepressant effect of MAOIs for patients with bipolar depression who are resistant to treatment. It is not surprising, therefore, that patients with bipolar depression who experience a “break through” depression while receiving lithium prophylaxis appear to respond rapidly to the addition of a MAOI, with less induction of mood swings and affective cycling.

More recently, we have suggested that MAOIs should be considered as a primary antidepressant treatment for patients with “phenotypic variants” of bipolar disorder. In this context, MAOIs should be considered for patients with (1) early onset, highly recurrent (apparent) “unipolar” depression; (2) “unipolar” depression with a history of cyclothymia; (3) bipolar not otherwise specified depression; (4) postpartum depression; (5) “unipolar” depression with a history of TCA-induced hypomania; (6) “unipolar” depression with a history of TCA-induced mood swings; (7) “unipolar” depression with a family history of bipolar disorder; (8) early onset chronic depression with a prominent seasonal distribution (worse in the autumn and winter); (9) early onset depression with a history of treatment resistance; and (10) childhood major depression.
Treatment-Resistant Major Depression

Numerous studies have shown MAOIs to be beneficial for depression resistant to prior antidepressant drug therapy.13,52 As many as 50% of patients with treatment-resistant depression are consistently reported to respond to treatment with a MAOI,24-26,44-46 and response rates approaching 70% have been reported for patients with typical28 and atypical41 depressive features and treatment-resistant depression.

Nolen et al.24,49 examined the efficacy of non-TCAs compared with MAOI compounds for patients with treatment-resistant depression. In both open-label and double-blind, crossover studies, these investigators showed a significantly higher response rate with tranylcypromine compared with nomifensine for patients who had failed to respond to at least two prior adequate treatments with antidepressants from different drug classes.

AUGMENTATION AND COMBINATION STRATEGIES FOR MAOIs

However, despite the best efforts of physicians to convert patients who do not respond to SSRIs and TCAs into patients who do respond to MAOI therapy, at least 50% of patients will remain depressed. There are numerous aggressive augmentation and combination strategies for patients who have failed to respond to adequate MAOI monotherapy.13,51-53 In general, most of these studies report an additional approximate 50% salvage rate. Several of these strategies have received considerable attention for use in treatment-resistant depression.

Lithium Carbonate and MAOIs

One of the most successful approaches to enhancing MAOI responsiveness among patients whose conditions are resistant to treatment is the addition of lithium carbonate to augment a failed MAOI trial. In several studies, lithium carbonate potentiation has been found to be effective for MAOI-resistant depression.24,55 The empirical use of lithium carbonate as an adjunctive treatment with MAOIs is based on its ability to enhance postsynaptic serotonin receptor sensitivity.56-58

The therapeutic benefit of lithium carbonate augmentation has been repeatedly demonstrated for patients with unipolar major depression.13,54,56,57,59 Similarly, Price et al.55 and others54,53 have reported a rapid synergistic response when lithium is added to a failed MAOI regimen. Tranylcypromine has also been shown to be an effective augmentation therapy for patients with bipolar depression who experience break through depression during maintenance therapy with lithium.51 In this regard, Himmelhoch et al.44 reported good efficacy when tranylcypromine was prescribed for patients with bipolar I and II depression in a double-blind study. These investigators found tranylcypromine to be superior to imipramine, with a low rate of induction of mania.

Combination TCA and MAOI Therapy

The combination of a TCA and a MAOI has been used successfully for more than three decades.52 Studies dating back to the 1960s and 1970s have repeatedly shown efficacy rates of approximately 60% to 90% for this combination among patients who are unresponsive to either medication alone.13,52,60-64

However, the initial optimism regarding this combination was tempered by reports of adverse events,63 especially when MAOIs were combined with chlorimipramine.64 Despite these reports, the safety of the combination of a MAOI and a TCA (except chlorimipramine) for refractory depression has been repeatedly demonstrated.13,52

Although most reviews of the combined use of a TCA and a MAOI suggest that these drugs should be either initiated simultaneously or the MAOI added to the failed TCA regimen,52 we60,51,64 and others39 have reported no ill effects from the judicious addition of a TCA to a failed MAOI regimen. We have reported the successful addition of most TCAs to a MAOI regimen without any increase in blood pressure. However, the addition of chlorimipramine, a tertiary amine TCA with significant inhibition of the serotonin reuptake site, should be avoided due to a significant likelihood of precipitating a "serotonin crisis."64

Finally, patients with treatment-resistant depression who have responded to combination antidepressant therapy should be encouraged to continue this therapy. Given the presence of a "therapeutic decrement" of approximately 20%, whereby each successive drug trial is 20% less
likely to be effective than the preceding unsuccessful treatment, it is critical that effective therapy not be altered. To this end, Berlanga and Ortega-soto performed a 3-year follow-up of patients with previous treatment-resistant depression who received the combination of a TCA and a MAOI as maintenance therapy. They found that 50% of these patients required that both drugs be continued to maintain remission of symptoms.

Other MAOI Augmentation Strategies

A variety of augmentation strategies have been suggested for patients who have failed to respond to adequate MAOI monotherapy and to combination TCA and MAOI therapy. Cautious augmentation of MAOI treatment with triiodothyronine (T₃), trazodone, carbamazepine, divalproex sodium, L-tryptophan, fenfluramine, methylphenidate, dextroamphetamine sulfate, and even SSRIs has been described for patients with exceedingly refractory conditions.

High-Dose Tranilcypromine Therapy

We and others have employed a more parsimonious approach for patients with highly resistant depression that is unresponsive to maximized MAOI therapy. In our study, high-dose tranilcypromine was administered during the current episode to 14 patients whose conditions were refractory to at least five prior treatment regimens (including tranilcypromine therapy). All of these patients had failed to respond to a prospective trial of tranilcypromine at a dose of 80 mg/d for at least 3 weeks. Doses of tranilcypromine were then gradually increased up to 180 mg/d in an open-label fashion. The mean (SD) maximum daily dose of tranilcypromine was 128 ± 27 mg. Seven patients (50%) had near complete remission, and 3 additional patients (21%) had a partial response. Response was unrelated to the duration of the episode or the prior number of treatments. Side effects were generally mild and well tolerated without any evidence of hypertensive events.

Reversible MAO-A Inhibitors

Selective and reversible MAO-A inhibitors have long been available in Europe and Canada. They appear to be largely devoid of the side effect burden of the irreversible MAOIs and generally require far fewer dietary and medication restrictions. Two compounds, moclobemide and buproprion, have received the most attention as antidepressants.

Moclobemide

Moclobemide is a reversible MAO-A inhibitor that is currently indicated for the treatment of Parkinson's disease. It is a selective MAO-A inhibitor that has been demonstrated to have antidepressant efficacy compared with placebo. Although dietary restrictions are not necessary when moclobemide is used at recommended doses (<10 mg/d)
to treat Parkinson’s disease, the doses of oral selegiline generally needed to achieve antidepressant activity are considerably higher and result in loss of MAO-B enzyme selective activity.

Recently, however, a selegiline transdermal system has been developed with a pharmacokineti
c profile that is distinctly different from that of oral selegiline. The selegiline transdermal sys
tem patch delivers sustained blood levels of selegiline, which produces central nonselective, irreversible MAO-A and MAO-B enzyme inhibition without traversing the gastrointestinal mucosa. As a result, the need for a tyramine-restricted diet is obviated. A recent prospective, double-blind, placebo-controlled trial was undertaken with 177 outpatients who had major depression (89 receiving the selegiline transdermal system at 20 mg/cm² and 88 receiving placebo) for up to 6 weeks. The selegiline transdermal system was superior to placebo from weeks 1 through 6 on the 17-item Hamilton Depression Rating Scale (HAM-D) (P < .02) and the 28-item HAM-D (P < .02), with a side effect profile similar to that of placebo (with the exception of more application-site reactions with the selegiline transdermal system versus placebo [36% vs 17%]).

**DIETARY AND MEDICATION RESTRICTIONS**

Interactions between nonselective MAOIs and tyramine in certain foods and beverages became apparent shortly after their introduction. Over time, the list of dietary restrictions has grown, and potential food interactions have now become the main stumbling block to the widespread clinical use and research development of MAOIs. Patients often express dismay over the food restrictions, and physicians are apprehensive about possible adverse events resulting from dietary indiscretions.

More recent research regarding the tyramine content of food and beverages has suggested that some foods initially thought to be contraindicated are not likely to produce hypertensive events and need not be completely excluded from the diet. Many of these foods can be classified based on the degree to which they need to be avoided. Some of them are listed in Table 4. Hypertensive events resulting from tyramine interactions are often characterized by progressively severe headaches, neck stiffness, palpitations, and a flushed sensation. Often there are few prodromal signs and the event appears precipitously.

**Table 4**

<table>
<thead>
<tr>
<th>Degree of Interaction</th>
<th>Foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>Aged cheeses, aged and fermented</td>
</tr>
<tr>
<td></td>
<td>meats, broad bean pods, spoiled</td>
</tr>
<tr>
<td></td>
<td>meats and fish, marmite, soy sauce,</td>
</tr>
<tr>
<td></td>
<td>and tap beer</td>
</tr>
<tr>
<td>Moderate</td>
<td>Red or white wine and canned beers</td>
</tr>
<tr>
<td>Mild to none</td>
<td>Avocados, bananas, bouillon, chocolate, fresh cheeses and meats, peanuts, soy milk, and yeast extracts</td>
</tr>
</tbody>
</table>

Interactions between nonselective MAOIs and numerous medications have also been reported. Similar to foods containing tyramine, certain medications can be classified according to their relative risk of precipitating an interaction with a MAOI. Two types of drug interactions are of concern for psychiatrists. The most feared is the hypertensive crisis that can result from the concomitant administration of medications containing indirectly acting sympathomimetic amines. Some examples include decongestants with pseudoephedrine, such as over-the-counter cold and allergy preparations. Other medications that should generally be avoided in combination with MAOIs include L-dopa, methyldopa, cocaine, anorectics, meperidine, epinephrine, norepinephrine, and some local anesthetics with vasoconstrictors.

The other interaction of concern is the one that occurs with the concurrent use of an SSRI and a MAOI. The “serotonin syndrome” has been reported to have substantial morbidity and mortality rates, in part due to the fact that there is no specific antidote to reverse the progressive central and peripheral serotonin-related pathology. The serotonin syndrome can occur gradually or acutely with rapid progression to involve changes in cognition, behavioral disturbances,
confusion, delirium, autonomic instability with hyperpyrexia, neuromuscular rigidity and rhabdomyolysis, blood pressure instability, cardiac arrhythmias, and visceral hemorrhage, as well as other neurovegetative symptoms. In addition to SSRI interactions, a recent study found that a high rate of serotonin-related symptoms began shortly after the TCA chlorimipramine was added to a failed MAOI regimen.

CONCLUSION

MAOIs are among the most efficacious and least used antidepressant agents. A review of the literature shows that MAOIs are effective for the treatment of major depression with melancholic features, major depression with atypical features, psychotic depression, bipolar depression, dysthymic disorder, double depression, and treatment-resistant depression. When used with caution, MAOIs are safe and well tolerated.

However, most psychiatrists do not prescribe MAOIs for fear of precipitating a hypertensive event resulting from dietary indiscretion. A recent survey found that nearly 27% of psychiatrists have not prescribed a MAOI within the past 3 years, and at least 12% have never prescribed a MAOI. Only 2% of treating psychiatrists consistently use MAOIs in their practice. Nevertheless, despite their shortcomings, MAOIs usually provide the best efficacy and often represent the final common arbiter for patients with depression refractory to all other treatments. New research efforts with these medications hold promise for a new generation of safe and highly effective antidepressants.

REFERENCES

25. Nolen WA, van de Putte JJ, Dijken WA, et al. Treatment strategy in depression: I. Non-tricyclic and selective reup...


57. de Montigny C, Courtoyer G, Morissette R, Langlois R, Caille G. Lithium carbonate addition in tricyclic antidepressant-resistant unipolar depression: correlations with the neurobiologic actions of tricyclic antidepressant drugs and lithium ion on the serotonin system. *Arch Gen Psychiatry*. 1983;40:1327-1334.


64. Amsterdam JD, Gracia-Espana F, Rosensweig M. Clomipramine augmentation in treatment-resistant depression. Depress Anxiety. 1997;5:84-90.
68. Pare CMB. Potentiation of monoamine oxidase inhibitors by tryptophan. Lancet. 1963;2:527-528.
77. Amsterdam JD, Bodkin JA. Transdermal selegiline in major depression: a placebo-controlled trial. Presented at the NCDEU 40th Annual Meeting; May 30-June 2, 2000; Boca Raton, FL.

2002 NARSAD Young Investigator Award

NARSAD announces award opportunities up to $30,000/year for up to two years (maximum of $60,000) open to advanced postdoctoral fellows or assistant professors (or equivalent) either to extend their research fellowship training or to begin careers as independent research faculty. Basic and/or clinical investigators are supported, but research must be relevant to schizophrenia, major affective disorders, or other serious mental illnesses.

Guidelines and accompanying face sheet are available for download on June 1, 2001, at www.narsad.org. Application submission deadline for 2002 is July 25, 2001. Contact Audra Moran, 516-829-5576 (phone), amoran@narsad.org (e-mail answered daily).