Irreversible Monoamine Oxidase Inhibitors Revisited

October 08, 2012 | **Major Depressive Disorder** [1], **Bipolar Disorder** [2], **Mood Disorders** [3], **Psychopharmacology** [4]
By Kenneth J. Bender, PharmD, MA [5] and Scott E. Walker, MScPhm [6]

Given the likelihood that insufficient numbers of patients will be available for a randomized controlled trial of MAOIs in refractory depression or atypical depression, we must still rely on consensus guidelines and expert opinion.

As with many psychiatric drugs, the discovery of irreversible MAOIs was serendipitous. While being used as an antitubercular agent in the 1950s, iproniazid—a derivative of the hydrazine compound isocarboxazid—was observed to have significant antidepressant properties. Almost at the same time as the discovery of TCAs such as amitriptyline and imipramine (which were also discovered by chance), MAOIs began to be widely used as the first effective antidepressants.

In 1957, Nathan Kline, MD, one of the pioneers of psychopharmacology, published the first report on the neuropsychiatric experiences with iproniazid, referring to it as a “psychic energizer.” Within a year of the original report by Kline, more than 400,000 patients with depression had received iproniazid. This development led to the discovery of other, more potent MAOIs and more effective antidepressants, including phenelzine, isocarboxazid, and the nonhydrazine derivative tranylcypromine.

The vast majority of MAOI prescriptions were for tranylcypromine and phenelzine, which largely remain the MAOIs of choice today. Thus, MAOIs became the first class of antidepressants that became widely used in the early 1960s. In the 1960s and 1970s, combination drugs that included antidepressants and neuroleptic agents became popular. One such example was Parstelin, a combination of tranylcypromine and trifluoperazine.

The success of MAOIs in the late 1950s and early 1960s suddenly changed when iproniazid was removed from the US market because of concerns regarding hepatotoxicity. MAOIs were quickly replaced by the TCAs in the 1960s. López-Muoz and Alamo [1] suggest that the withdrawal of these drugs because of hepatotoxicity and jaundice may have been an overreaction. They also highlight the dramatic effect that an “antidepressant” drug had on the general attitude toward depression.

The fact that a medication that altered brain monoamines could treat a psychiatric illness such as depression suggested that the mechanism of action may be a chemical imbalance and not a predominantly psychological reaction. Even though ECT had been known to have a potent antidepressant effect, it was not until a pharmacological antidepressant was discovered that the fundamental concept of a neurobiological cause for depression was crystallized.

**Pharmacology**

The enzyme monoamine oxidase exists as 2 subtypes, MAO-A and MAO-B. MAO-A metabolizes serotonin and norepinephrine (NE), the monoamines most closely linked to depression. MAO-B preferentially metabolizes dopamine and trace amines, including phenethylamine. Tyramine is metabolized by both MAO-A and MAO-B. Inhibition of MAO-B is not effective as an antidepressant because there is no direct effect on either serotonin or NE metabolism. Brain MAO-A must be inhibited for an antidepressant effect to occur. The ratio of MAO-A to MAO-B varies throughout the body. In the human brain, the ratio of MAO-A to MAO-B is 25% to 75%, whereas in the liver, the ratio is 50% to 50%. The ratio is 80% to 20% in the intestine, and in the peripheral adrenergic neurons, the ratio is 90% to 10%.²

MAOIs act by inhibiting the activity of MAO and preventing the breakdown of monoamine neurotransmitters (serotonin and NE), thereby increasing their availability. Inhibition may be reversible or irreversible. When an MAOI covalently binds to the enzyme, it is irreversibly inhibited and the enzyme is permanently deactivated.³ Enzyme activity cannot be restored until the body replaces the enzyme through new enzyme synthesis. Restoration of full activity can take up to 2 weeks. Tranylcypromine and phenelzine, the most commonly prescribed MAOIs, are nonselective, irreversible inhibitors of isoforms MAO-A and MAO-B. Tranylcypromine was originally developed as an amphetamine analogue and thus also has some amphetamine-like effects. The pharmacokinetics of both drugs are very different. Caddy and colleagues [4] observed that
phenelzine has a half-life of 2 hours. Weber-Grandke and colleagues observed that tranylcypromine exists as both a + enantiomer, with a half-life of 0.75 hours, and a – enantiomer, with a half-life of 1.5 hours. Nevertheless, since activity occurs through irreversible inhibition of MAO, the pharmacokinetcis of the concentration of these drugs appears to have little relationship to effect.

MAO inhibition will persist long after the drug has been eliminated from the body. Shortly after the introduction of MAOIs into clinical practice in the early 1960s, the very serious adverse effect of hypertensive crisis was observed. The hypertensive crisis was initially described as a “cheese effect.” It is now known that this effect is caused by and proportional to the amount of tyramine ingested. Tyramine is a potent releaser of NE. When MAO activity is normal, the NE released by oral tyramine can be metabolized, including metabolism by MAO-A in the gut wall. However, when MAO is inhibited, the amount of NE released can elevate blood pressure. The average person can ingest about 400 mg of tyramine before excessive stimulation of adrenergic receptors occurs and blood pressure rises.

Because MAOIs inhibit MAO-A and MAO-B, if an MAOI such as tranylcypromine or phenelzine is administered before tyramine ingestion, tyramine sensitivity is dramatically increased. Ingesting foods high in tyramine can cause a pressor response in a patient with MAO-A and MAO-B inhibition, which is an increase in systolic blood pressure of 30 mm Hg or more. Tyramine that escapes into the systemic circulation is delivered to noradrenergic sympathetic neurons, where it causes the release of NE. Since MAO-A is inhibited, NE release results in a rise in blood pressure. In patients who have received either tranylcypromine or phenelzine, the amount of tyramine that can safely be ingested is likely less than 8 mg.

The tyramine-cheese reaction, hypertensive crises, and MAOI diets
The amino acid tyrosine (from the Greek word for cheese, tyros) was isolated from cheese as early as 1846. By 1911, it was known that tyramine (derived from tyrosine) had the potential to increase blood pressure. However, it was a series of case reports in the 1960s that described hypertensive crises associated with MAOIs that brought the MAOI-cheese relationship to the forefront and contributed to the rapid decline in MAOI use at a time of increasing medicolegal sensitivity. This also led to the development of detailed dietary restrictions that were not always evidence-based. An international survey conducted in the early 1980s found that as many as 70 restricted food items had appeared on various MAOI diets. Shulman and colleagues went on to conduct a series of systematic and carefully conducted tyramine analyses that in conjunction with a literature review of case reports led to a dramatically simpler MAOI diet (Table). This diet attempts to find a balance between patient safety and compliance—only a few food items are restricted, such as aged cheeses and meats, draft beer, concentrated yeast extract (marmite), sauerkraut, and soy sauces.

Current practice
The use of MAOIs has declined since the 1960s. Health care data from 1997 through 2007 were used in a population-based observational cohort study to determine prescribing trends and safety profiles of MAOIs in older adults. Only 348 new continuous users of irreversible MAOIs were identified over the 10-year period. The yearly incidence rate of MAOI prescriptions (new users for whom no MAOIs had been prescribed in the previous year) decreased from 3.1 per 100,000 in 1997 to 1.4 per 100,000 in 2006, while prevalence (among individuals in Ontario for whom MAOIs were prescribed) decreased from 400 in 1997 to 216 in 2006. During 2002, antidepressants as a whole were being prescribed at an increasing rate (10,900 per 100,000 of older adults). In stark contrast, during the same year, prescriptions for MAOIs were down to 21.3 per 100,000. In other words, only 1 of 500 prescriptions for antidepressants for older adults was for an MAOI. As expected, MAOIs were being used primarily for those older adults who had a high rate of prior use of other antidepressants and ECT.

While the use of MAOIs as first-line treatment has declined dramatically, these agents have remained in the clinical armamentarium for refractory depression and atypical depression. Winbiscus and colleagues reviewed the evidence for the use of MAOIs in atypical depression. This subtype of depression is defined by mood reactivity and 2 of the following symptoms: weight gain or hyperphagia, increased sleep, subjective feeling of leaden paralysis, and a personality trait of rejection hypersensitivity. It has been estimated that 30% of patients with unipolar depression may meet criteria for atypical depression.

The largest study of atypical depression was undertaken by Quitkin and colleagues. Phenelzine was shown to be superior to the TCA amitriptyline for atypical depression in more than 400 patients. Using a meta-analysis, Henkel and associates found a mean effect size of 0.45 in favor of MAOIs over placebo and a more modest effect size of 0.27 in favor of MAOIs over TCAs, similar to the...
results of Quitkin and colleagues. The widely cited STAR*D (Sequenced Treatment Alternatives to Relieve Depression) naturalistic study conducted in the US provided for a sequence of therapeutic options depending on response. The primary outcome measure in this study was remission, defined as a score of less than 7 on the Hamilton Depression Rating Scale. The secondary outcome was response defined by a 50% reduction on the Quick Inventory of Depressive Symptomatology (QUIDS). Of the 4 levels of treatment in the study, level 4 included a switch to the MAOI tranylcypromine or to a combination of 2 antidepressants, mirtazapine and venlafaxine. Response and remission rates were found to be nonsignificantly greater in the antidepressant combination group than in the tranylcypromine group. The remission rate for the combined antidepressants was 14%, while it was only 7% for tranylcypromine. The response rate for the combination of antidepressants was 24% compared with only 12% for tranylcypromine. There were significantly fewer trial dropouts in the antidepressant combination group than in the tranylcypromine group. In the 21 patients with atypical depression, there was no significant difference in response rates between the two groups. The mean dose for tranylcypromine was 36.9 mg and the mean dose for the antidepressant combination was 210.3/95.2 mg. All in all, this was a disappointing outcome for MAOIs. However, a comment by Wingo and Ghaemi highlights the fact that of the patients randomized to the tranylcypromine group, 41% had entered the study because of previous medication intolerance in other STAR*D trials, while only 22% of patients who were randomized to the combination antidepressant group had a similar medication intolerance. This could very well account for the increased dropout rate for tranylcypromine and the relatively poor response.

Professor Phillip Cowan, a prominent psychopharmacologist from the University of Oxford, reports his personal favorable experience with the use of tranylcypromine. Although the wait is well worth it, he notes the practical problem of using an MAOI in refractory depression—the need for a prolonged washout period to avoid possible serotonin syndrome. The wait is 2 weeks when switching from an SSRI and 5 weeks when switching from fluoxetine. This interim period requires close follow-up with symptomatic management only.

### Recent guidelines and recommendations

Two recent articles report on recommendations for an algorithm-guided treatment for depression, similar to that in the STAR*D trial. Spijker and Nolen compared a Dutch algorithm for the treatment of depression with 4 other guidelines, including those from the Texas Medication Algorithm Project (TMAP), the Canadian Network for Mood and Anxiety Treatments (CANMAT), the Royal Australian and New Zealand College of Psychiatrists (RANZCP), and the STAR*D study. The RANZCP guideline does not mention MAOIs at all. However, the Dutch algorithm recommends tranylcypromine as a step-4 treatment and as a step-2 treatment for atypical depression. TMAP and CANMAT guidelines recommend MAOIs as an option in step 3.

A German study used a 10-step algorithm that involves antidepressant monotherapy, lithium augmentation, combined lithium and MAOI therapy, and finally ECT. Steps 7 and 8 of the algorithm comprise MAOI combined with lithium. In this single-center prospective study, algorithm-guided therapy was demonstrated to produce significantly better outcomes and less frequent medication changes than treatment as usual.

This algorithm uses lithium augmentation followed by lithium monotherapy. If this is unsuccessful, the next step includes the use of an MAOI (tranylcypromine) at 20 mg/d in combination with lithium. If that fails, then 40 mg/d of tranylcypromine combined with lithium is used. The researchers suggest that a better response may have been achieved with a higher dosage of tranylcypromine than the maximum 40 mg/d recommended in this algorithm. This is similar to the concerns for the STAR*D trial in which a mean dose of 36.9 mg of tranylcypromine was used. A recent article by Fawcett reflects the personal opinion of another experienced and well-respected psychopharmacologist. Because of limited numbers of patients available for clinical trials, guidance
Irreversible Monoamine Oxidase Inhibitors Revisited
Published on Psychiatric Times
(http://www.psychiatrictimes.com)

is often dependent on the personal experience of opinion leaders. In his experience, many patients with treatment-resistant depression may reach remission when given a course of MAOI treatment. Fawcett considers a full course of treatment to be at least 6 weeks at the maximum tolerated dose. He also comments on the relative safety of MAOIs. In over 40 years, he had only 1 case of hypertension with headache induced by diet, which was managed in the office with thioridazine. Fawcett highlights the nature of treatment-refractory depression and the misery to which it condemns its victims. While acknowledging some increased risk, he feels that there is still a good chance of “resurrecting a life devastated by depression or even saving a life.” He discusses 7 patients from his personal practice with recalcitrant depression who were treated with MAOIs—6 of the patients had symptom remission. Three of the 6 patients were given additional augmentation with stimulants. Fawcett provides sage advice: “Before initiating an MAOI, I ask myself, ‘if this patient is unlucky enough to have a serious adverse reaction as a result of the MAOI, can I honestly say that the MAOI was fully indicated?’” In retrospect, he found the answer to be a resounding “yes.”

Summary
Opinion leaders and several international consensus guidelines include MAOIs in the armamentarium of treatment-refractory depression and atypical depression. As such, we feel—like Fawcett—that the current low rate of MAOI prescriptions is not consistent with current recommendations. The safety profile of MAOIs seems to have improved significantly, based on a population-based cohort study of older adults; there were no episodes specific for a hypertensive crisis or serotonin syndrome identified in that study.11

Given the likelihood that insufficient numbers of patients will be available for a randomized controlled trial of MAOIs in refractory depression or atypical depression, we must still rely on consensus guidelines and expert opinion. The proportion of patients who may potentially benefit from MAOIs is substantial. The atypical depression subtype of mood disorder may represent 15% to 29% of all patients with MDD.20

Findings from STAR*D suggest that a third of patients with MDD meet criteria for stage 2 treatment-refractory depression. Potentially, MAOIs could be used in a much larger proportion of patients with mood disorder than is currently the case. Revised dietary recommendations in combination with psychoeducation regarding the need to avoid concomitant exposure to serotonergic and sympathomimetic agents should provide a reasonable balance of risk and benefit in the use of irreversible MAOIs. Because they are not promoted by any major pharmaceutical company and because of their checkered history, we are at risk for seeing this class of drugs with the potential to benefit a significant subset of patients with mood disorder relegated to obscurity.

Editor’s Note: Our Category 1 CME articles are on a brief hiatus. In the meantime, we invite you to test yourself: read the article, take the posttest on the next page, and then check the answer key on the last page of this article for the correct answers.

1. Which of the following was the first MAOI—referred to as a “psychic energizer”?

A. Tranylcypromine
B. Iproniazid
C. Phenelzine
D. Selegiline

2. Once ECT was shown to be effective for treating depression, the neurobiological cause for depression was crystallized.

A. True
B. False

3. As a metabolizer of serotonin and norepinephrine, which of the following is most clearly linked to depression?

A. MAO-A
B. MAO-B

4. Which of the following is true of an irreversible MAOI?

A. The binding of the MAOI to the enzyme is temporary
B. It inhibits the activity of monoamine oxidase
C. Depending on the MAOI, the half-life of the drug plays an important role in efficacy

5. When MAO is inhibited, tyramine will release _______________; excessive amounts will consequently raise blood pressure.
A. Dopamine  
B. Serotonin  
C. Epinephrine  
D. Norepinephrine  

6. Which of the following is safe on a low-tyramine diet?  
A. Red wine  
B. Beer on tap  
C. Salami  
D. Sauerkraut  

7. MAOIs have remained in the armamentarium as a first-line treatment for which of the following?  
A. Unipolar depression  
B. Atypical depression  
C. Bipolar depression  

8. Patients with refractory depression treated with tranylcypromine should start the restricted diet 1 day before taking the medication and continue the diet for 2 weeks after stopping the medication.  
A. True  
B. False  

**Answer key to the Mine Your Mind posttest:**  
1. B; Iproniazid  
2. B; False  
3. A; MAO  
4. B; It inhibits the activity of monoamine oxidase  
5. D; Norepinephrine  
6. A; Red wine  
7. B; Atypical depression  
8. A; True  

**References:**  
References  
8. Blackwell B, Mabbitt LA. Tyramine in cheese related to hypertensive crises after


Source URL:
http://www.psychiatrictimes.com/printpdf/irreversible-monoamine-oxidase-inhibitors-revisited/page/0/2

Links: