MAO Inhibitors: Is Concomitant Use Safe or Too Risky?

September 15, 2017 | Psychopharmacology [1], Depression [2]
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MAOIs deserve special consideration in the treatment of refractory depression. Here’s a case in point.

A Case Study in Treatment-Refractory Depression

Monoamine oxidase inhibitors (MAOIs) have a long and storied history as some of the earliest antidepressants created. The efficacy of these medications led to the development of the monoamine hypothesis of depression and the development of subsequent antidepressant medications. Despite their known efficacy, MAOIs have fallen out of favor in clinical practice, giving way to newer agents with more favorable adverse-effect profiles and improved tolerability. However, the contemporary psychiatrist would be remiss to disregard these medications as archaic or dangerous.

Depression is both common and challenging to treat. Most patients with MDD require more than one medication trial to obtain remission. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study highlighted the difficulty in treating depression to remission. \(^1\) Findings from this study indicate that only 67% of patients achieved remission after aggressive treatment through up to 4 levels of switching or adding medications and psychotherapy. Savvy clinicians would be well served to incorporate MAOIs into their arsenals for managing treatment-refractory depression.

To highlight the difficulty in treating refractory depression, consider the following Case Vignette.

CASE VIGNETTE

A 66-year-old married, retired architect was treated at a large academic hospital and outpatient clinic for recurrent, severe, major depressive episodes. The depression was characterized by anxious distress, hypersomnia, mood reactivity and, when severe, delusions of poverty. He was treated with several SSRIs and SNRIs without improvement, even when in combination with atypical antipsychotics.

He had some improvement with a course of ECT following a severe suicide attempt. Tranylcypromine was started after the course of ECT, which produced significant improvement in symptoms after titration to 70 mg daily in divided doses. Recurrence of depression was successfully treated with the addition of 100 mg of nortriptyline, and he remained in remission for many years. He resisted maintenance treatment with ECT because of lasting cognitive deficits.

The concept of atypical depression, characterized by mood reactivity, hyperphagia, hypersomnia, leaden paralysis, and rejection sensitivity, is an important consideration in this case. MAOIs were shown superior to tricyclic antidepressants (TCAs) in treating these patients. \(^2,3\) One double-blind crossover study of nonmelancholic, treatment-resistant depression revealed 67% of patients who failed treatment with imipramine had symptom remission with phenelzine. \(^4\) Moreover, phenelzine and tranylcypromine were found to be superior to TCAs in the treatment of outpatients with atypical depression. \(^5\)

The consistency of these findings is remarkable because it is uncommon for studies of antidepressant efficacy to demonstrate comparative superiority of one medication over another. The utility of MAOIs extends beyond treatment of MDD. Primary anxiety disorders, particularly social anxiety disorder, have consistently responded to MAOIs—a finding that is supported by a meta-analysis. \(^6\)

Adverse effects

The possibility of serious dietary and drug interactions, and the development of newer agents with better tolerability and safety, have caused MAOIs to fall out of favor. The American Psychiatric Association guidelines recommend that their use be limited to patients who have not responded to other agents. \(^7\) However, these guidelines also highlight the utility of MAOIs in treating atypical depression.
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Published on Psychiatric Times
(http://www.psychiatrictimes.com)

While it is true that serotonin syndrome and hypertensive crises are potential serious adverse effects, the incidence of these events is rare when high-risk medication combinations are avoided. The dietary restrictions have been progressively liberalized over time. In fact, a review of the literature does not show any deaths reported due to hypertensive crisis from MAOIs used as monotherapy. Some of the most common adverse effects, including orthostatic hypotension, dizziness, insomnia, nausea, and weight gain, are often successfully mitigated by slow initial titration, divided dosing, and increased fluid intake.

**Combination therapy**

Limited data exist regarding the use of MAOIs in combination with other psychotropic agents. The combination is generally considered contraindicated because of the risk of serotonin syndrome. Off-label combination use may be helpful in the management of treatment-refractory depression; however, caution is recommended. The combination of an MAOI and a TCA is generally safe and well tolerated; orthostatic hypotension is the most common adverse effect. Despite a lack of significant tolerability concerns reported in clinical trials or case reports, most studies did not demonstrate improved efficacy with the combination compared with monotherapy. In fact, one study of 135 outpatients with mild or moderate depression demonstrated trimipramine (a TCA) was superior when compared with an MAOI (phenelzine or isocarboxazid) and the combination of trimipramine plus an MAOI. Another randomized controlled trial of bilateral ECT and the combination of low doses of phenelzine and amitriptyline showed higher remission rates with ECT. Although these studies did not reveal significant improvements in efficacy with combination therapy, they serve to further highlight the tolerability of MAOIs when used in combination with TCAs. The efficacy and safety of MAOIs have been shown with bupropion, trazodone, and stimulants; however, these therapies are not approved for combination use by the FDA. Despite the theoretical risk of hypertensive crisis, 2 reports documented patients who tolerated tranylcypromine in combination with bupropion (dosed to 300 mg/d and 450 mg/d) to produce sustained remission. Except for one patient who did not adhere to dietary restriction, there were no instances of hypertensive crises in 32 patients treated with a combination of MAOIs and stimulants for refractory depression.

In the event of a hypertensive crisis, signaled by the onset of a severe, occipital headache after a meal or medication ingestion, early and successful management has been reported with administration of a 10-mg nifedipine tablet (calcium channel blocker). A small case study reported that all 29 patients who utilized this “bite and swallow” treatment had rapid relief of symptoms. Treatment with oral medication would not be recommended in severe cases because of the delay in onset compared with parenteral medications.

With regard to management of other potential adverse effects associated with MAOIs, in cases of orthostatic hypotension, concomitant use of stimulant medications can offset this otherwise prohibitive adverse effect for some patients. Finally, low doses of trazodone for insomnia can be used safely with MAOIs, although the combination should be used judiciously to avoid worsening of orthostatic hypotension, lightheadedness, and sedation.

**Efficacy and safety**

One retrospective case series of 29 adult patients at a large academic medical center examined the tolerability and efficacy of MAOIs in combination with other antidepressants and stimulants. Among the agents used were trazodone, TCAs, bupropion, SSRIs, and mirtazapine. In total, 21% of patients experienced clinical improvement without adverse effects, 24% had no clinical improvement, and 45% had some adverse effects that necessitated discontinuation of one or both agents. No serious adverse effects were reported; hypotension, constipation, fatigue, dry mouth, and dizziness were most common. The use of SSRIs and SNRIs should be avoided with an MAOI because of the risk of serious adverse effects and even death. The combination has a high risk of serotonin syndrome, and deaths have been reported when taken at therapeutic doses. These safety concerns have resulted in the general recommendation of discontinuing an SSRI or SNRI for 2 weeks before starting an MAOI. A similar 2-week period should also be observed in transitioning from an MAOI to an SSRI or SNRI because of the irreversible inhibition of monoamine oxidase. An exception is fluoxetine, which should be discontinued for 5 weeks before starting an MAOI because of the long half-life of its active
metabolite. Like SSRIs and SNRIs, clomipramine (a TCA) should be avoided in combination with an MAOI because of its prominent serotonergic reuptake inhibition and higher risk of serotonin syndrome.

**Conclusion**

Returning to the Case Vignette, the decision to prescribe tranylcypromine was based on the previous failed trials of multiple antidepressants, severity of symptoms, presence of atypical features, and patient willingness to adhere to drug and dietary restrictions. Although studies do not suggest consistent improvement with combination treatment, this patient achieved and maintained symptom remission with the addition of nortriptyline. Because of concerns about tolerability as he aged, doses were tapered and the TCA was discontinued, which ultimately precipitated a recurrent depressive episode. In the months thereafter, nortriptyline and tranylcypromine were gradually returned to previous doses, and depressive symptoms remitted. It should be noted that if this combination is to be used, it is advised that the TCA is started first or at the same time as the MAOI, with slow titration to allow for careful monitoring.

While not recommended as first-line agents, MAOIs deserve special consideration in the treatment of refractory depression. Data suggest that a subset of depressed patients with atypical features and social anxiety may be particularly responsive to treatment with an MAOI. Unfortunately, there is limited information regarding the use of these medications in refractory depression or with other augmenting antidepressants, and further research is unlikely.

Studies have consistently shown that judicious use of MAOIs with other psychotropic agents—namely TCAs, trazodone, bupropion, mirtazapine, and stimulants—is well tolerated and safe, despite general consensus to the contrary. The use of MAOIs warrants careful patient selection and discussions about safety but should be a consideration in patients who continue to suffer from severe depression.

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**Disclosures:**

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**References:**


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