MAO INHIBITORS: LOOKING TO THE FUTURE

MAO inhibitors (MAOIs) were the first group of antidepressants developed; however, they are not used as much as other antidepressant classes for the treatment of depression. With the prevalence of depression and the level of difficulty in treating some patients, exploration into novel applications for existing therapies is under way. This article of CLIPs reviews the past, present and potential future of MAOIs. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


The History of MAOIs

- Iproniazid, originally an antituberculosis agent, was found to have antidepressant properties and marketed as the first MAOI; side effects were unknown at the time and iproniazid was removed from the market due to hepatotoxicity.
- In the mid-1960s, tranylcypromine (another MAOI) was reported to cause tyramine-induced hypertensive crisis, especially when patients reported eating cheese or drinking a draft beer prior to the reaction occurrence. These events precipitated the FDA establishment of dietary restrictions to reduce the occurrence of future events.
- Today, MAOIs are considered third- or fourth-line agents for treatment due to potential drug-drug interactions, intolerable adverse events and difficult dietary restrictions that must be followed.
- Research indicates that the medical establishment has abandoned use of MAOI agents and that contemporary psychiatrists have little clinical experience with MAOIs. The current estimated prescription rates in Canada for MAOIs are approximately 1.4% per 100,000 patients.

MAO types and MAOIs

- Monoamine oxidase (MAO) is a critical enzyme that is responsible for catabolism of endogenous monoamines (i.e., epinephrine, serotonin, and dopamine) and exogenous monoamines (i.e., tyramine). Inhibition of the MAO enzyme renders therapeutic application for psychiatric and neurologic disorders.
- MAO-A is located mostly in the intestinal tract and liver, while subtype MAO-B is predominantly located in brain and liver tissues. MAO-A is the most prevalent subtype in the intestinal tract (80%) and preferentially metabolizes serotonin and norepinephrine. MAO-A is most commonly associated with tyramine-related adverse effects due to its prevalence in the gastrointestinal tract.
- The nonselective MAOIs available in the US include phenelzine, isocarboxazid and tranylcypromine.
- Selegiline is the only selective MAOI available in the U.S. and is selective for MAO-B. Selegiline becomes a non-selective MAOI when doses exceed 20mg/day, which are necessary to see antidepressant effects, but not anti-parkinsonian effects.
- All of these agents are nonreversible antagonists that permanently bind to the enzyme active site.
- Potentially safer and less-effective reversible MAO-A inhibitors have been developed but are not available in the US.

Concerns about MAOIs

- The oral MAOIs are associated with many adverse effects, including orthostatic hypotension, dizziness, insomnia and nausea; phenelzine is strongly associated with sedation.
- Adverse effects can be managed by decelerating dosage titration, giving smaller doses more often, or increasing fluid intake.
- Weight gain, muscle pain, sexual dysfunction and paresthesias are adverse effects that are associated with prolonged MAOI therapy. Paresthesias are commonly treated with pyridoxine supplements.
- Serotonin syndrome, a potentially fatal condition, has been reported with MAO therapy alone.

CONTINUED NEXT PAGE
• Signs and symptoms of serotonin syndrome include changes in mental status, restlessness and hyperactivity of the autonomic system. These symptoms are alleviated by removing the causative drug therapy in addition to supportive care.

• When transitioning therapy from other antidepressants to MAOIs it is important to ensure that the most recently received antidepressant agent is completely eliminated to reduce risk for serotonin syndrome. Typically a waiting period of 5 elimination half-lives is appropriate:
  o For most agents including the selegiline patch an appropriate period 14 days.
  o Fluoxetine requires wash-out period of 35 days.

• Common drug-drug and drug-food interactions associated with MAOIs are tabulated below:

<table>
<thead>
<tr>
<th>Drugs or foods to avoid due to interactions*</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>linezolid, meperidine, MAOIs, mirtazapine, SNRIs, SSRIs, St. John’s wort, TCAs, tramadol, non-subcutaneous dosage forms of triptans.</td>
<td>Serotonin Syndrome</td>
</tr>
<tr>
<td>Pseudoephedrine, phenylephrine, other vasoconstrictors</td>
<td>Hypertensive crisis</td>
</tr>
<tr>
<td>Aged cheeses or meats, soy-based products, fava beans, draft beer, wine (&gt;2 servings per day), concentrated yeast extracts, spoiled meat, sauerkraut, banana peels</td>
<td>Tyramine-induced hypertensive crisis.</td>
</tr>
</tbody>
</table>

*SNRI=serotonin norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant

• Patients receiving MAOIs should be encouraged to wear a medical alert bracelet to notify healthcare providers in the case of incapacitation during an emergency event.

Efficacy of MAOIs in clinical practice and place in primary care

• MAOIs are utilized for the treatment of major depressive disorder (MDD) with atypical features or if other treatment options have failed. Other clinical applications for MAOIs include Parkinson’s disease, bulimia, anorexia nervosa and anxiety disorders.

• Trials indicate that therapeutic doses of MAOIs offer similar clinical benefit compared to other antidepressant agents for treatment of MDD.

• MAOIs have demonstrated superiori in randomized trials versus TCAs for the treatment of atypical depression.

• Study results indicate that TCAs may be less effective than MAOIs in treating anergic bipolar depression but future trials are needed to investigate the function of antidepressants in this patient type.

New horizons for MAOIs?

• Emsam (selegiline transdermal) was approved by the FDA in 2006 for the treatment of major depressive disorder and may be an option for select patients who desire ease of use and offers the potential for less risk of drug-related interactions associated with MAOI therapy.

• Emsam is available in varying doses: 6mg/24 hours, 9mg/24 hours, 12mg/24 hours with the lowest available dose regimen not requiring the patient to follow MAOI dietary restrictions.

• Because selegiline is not absorbed in the gut, this dosage form is less likely to cause tyramine-induced hypertensive crisis, but it is still recommended that patients receiving higher doses (9mg or 12mg) observe MAOI dietary restrictions.

• Several placebo-controlled, pre-approval studies for Emsam at a 6mg/24 hour dose demonstrated a 12-month relapse rate of 16.8% for major depressive symptoms plus high tolerability and adherence rates (84.2%).

• Emsam is an expensive therapy compared to other antidepressant agents currently available (30-day supply of 6mg/24hour Emsam patches= $700) and may be difficult for many patients to obtain without prior approval.

Conclusion

• MAOIs are underused. There is renewed interest in this drug class as drug development technologies allow for optimization of drug effects and minimization of adverse events. The introduction of the selegiline transdermal system is an important first step in identifying new clinical applications for MAOIs.

• Current guidelines place MAO inhibitors as third- or fourth-line agents in the primary care setting. Recommendation of MAOIs for widespread use in patients with depression is not warranted at this time.

• Future advances and pending introduction of newer and more selective MAOI formulations may improve the variety of available treatment options for clinicians to utilize for depressive disorders.

Prepared by: Khushboo Shah, Pharm.D. Candidate Reviewed by: Peter J. Hughes, Pharm.D.