*The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column gave informed consent for the publication of the column.*

## Use of MAOIs in severe treatment-resistant depression: back to the old school

**Jacob Cookey, MD, MSc**

A man in his 60s with longstanding major depressive disorder was stabilized for more than 30 years on phenelzine, which is a nonselective monoamine oxidase inhibitor (MAOI). Unfortunately, his medication had to be discontinued because of a global shortage of phenelzine.[1] Within 3 weeks, his depressive symptoms began to gradually relapse, and he experienced severe anxious distress. He had quit smoking 14 years earlier (50 pack/yr smoking history), and he did not drink alcohol or use cannabis or any illicit drugs. He had comorbid chronic obstructive pulmonary disease, but otherwise had a noncontributory medical history.

The patient's family physician attempted several medication trials during the ensuing months. Vortioxetine (serotonin reuptake inhibitor and modulator) was titrated to 20 mg/d for 6 weeks without benefit. He was then switched to escitalopram (selective serotonin reuptake inhibitor; SSRI) 10 mg/d; however, this medication was discontinued within 1 week because of overall symptom exacerbation. Sertraline (SSRI) was then titrated up to 200 mg/d for a period of 8 weeks, with no benefit and was therefore also discontinued.

A trial of moclobomide (a reversible MAOI; RIMA) was then attempted, titrating to 600 mg/d. Within 3–4 weeks, there was some clinical improvement. However, because of persistent depressive and anxiety symptoms this trial was also discontinued.

The patient was then connected with our service, at which point we decided to try tranylcypromine (MAOI). However, just before starting this trial, the patient was briefly hospitalized for intensifying suicidal ideation. By the time he was discharged from hospital the following week, phenelzine supplies had been restored so we decided to restart phenelzine 15 mg twice daily. After 1 week, the dosage was increased to 30 mg twice daily (his previous maintenance dose). Within 3 weeks, both the patient and his wife reported a noticeable difference. At 6 weeks, he had only mild depressive symptoms. At 8 weeks, his symptoms had completely resolved, with no identifiable residual symptoms.

Our patient's case demonstrates a uniquely positive clinical effect for phenelzine. Nonselective MAOIs, such as phenelzine, are thought to work by increasing the availability of the monoamines: serotonin, norepinephrine and dopamine. This is in contrast with most other antidepressants, which target only 1 or 2 of the monoamines.[2] Also, the limited efficacy of moclobomide in this case illustrates that RIMAs, despite being better tolerated, do not seem to have the same efficacy as nonselective MAOIs.[3]

Notably, the first MAOI, iproniazid, was discovered serendipitously when it was observed to have an antidepressant effect when used in the treatment of tuberculosis in the early 1950s.[4] Since then, data have shown MAOIs to have significant clinical benefits in the treatment of depression (particularly atypical and treatment-resistant cases) as well as in the treatment of anxiety disorders and perhaps even posttraumatic stress disorder.[5–7] It is believed that anxiolytic actions of phenelzine are mediated, at least in part, by increasing γ-aminobutyric acid (GABA) levels in the brain.[8] The most recent Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines consider phenelzine a third-line option for the treatment of depression, with additional recommendations to consider its use for depression with atypical features (with evidence of superiority over tricyclic antidepressants).[9]

Despite their potential benefits, MAOIs are only rarely used, mainly because of their adverse effect profiles. Perhaps one of the primary fears a clinician may have is the potential for hypertensive crisis (now termed either hypertensive urgency or emergency). This can occur if a patient treated with an MAOI ingests too much tyramine (a biogenic amine found in some foods) or if other compounds are ingested, such as sympathomimetics, some of which can be found in over-the-counter cold/flu preparations. While this hypertensive reaction remains a significant concern, it is likely that safe daily tyramine doses are higher than previously believed (closer to 30–50 mg/d with meals rather than 6–10 mg/d).[2,10] Furthermore, the likelihood of death or end organ damage is quite rare (approximately 0.001% due to hypertensive crisis by some early estimates) and may even be comparable to morbidity and mortality related to SSRIs causing increased gastrointestinal bleeding (estimated number needed to harm of 1000).[10]

The other more important safety issue to consider is serotonin syndrome, particularly if combined with SSRIs, tricyclic antidepressants, amphetamines or opioids.[5,11] Serotonin syndrome is a lethal but rare condition that can be easily avoided with proper monitoring and education to ensure patients avoid coingestion of serotonergic compounds while taking MAOIs. It is also important to bear in mind the 2 week washout period when switching between MAOIs and serotonergic medications (5 weeks if switching from fluoxetine, an SSRI, to an MAOI).[11]

While these rare but severe complications can occur, clinicians should keep in mind the potential benefits of MAOIs, as there may be subpopulations with clinically resistant depression that could greatly benefit from

their use. Patient education with liberal use of handouts and regular clinical monitoring can allow the safe and effective use of this class of medications.

Our patient's case demonstrates how MAOIs remain an important option to consider in modern-day psychiatric practice. It would be prudent for psychiatric training programs to include both theoretical and practical instruction on the use of MAOIs. In some cases, an "old-school" approach may be the best approach.

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