Why Aren't MAOIs Used More Often?

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While I have spent most of my last 45 years in psychiatry working in an academic setting and doing clinical research, I have always had an active practice focused on major affective disorders, especially treatment-resistant or treatment-refractory cases. It is my impression that monoamine oxidase inhibitors (MAOIs) are currently underutilized in the clinical practice of psychiatry. Very few of the treatment-resistant patients that I see have received a serious trial of MAOI therapy.

It is clear that MAOI antidepressants (isocarboxazid, phenelzine, tranylcypromine, and oral selegiline) carry serious potential risks such as hypertensive crisis with stroke, and serotonin syndrome—with the possibility of hyperpyrexia, convulsions, and death—that usually result from medication and food interactions. Also, significant side effects may occur, such as orthostatic hypotension, as well as bilateral ankle edema and sexual dysfunction.

Given this, why would anyone want to take these medications? Many patients suffering lives of chronic depression are unresponsive to newer antidepressants, tricyclics, and in some cases electroconvulsive therapy (ECT). (Although I would want to make sure that a full dose of clomipramine was first tried.) Many of these patients, in my experience, can reach remission or close to it when given a course of MAOI therapy. By a course of MAOI therapy, I mean at least 6 weeks at the maximally tolerated dose, allowing for dose adjustment and management of side effects, particularly orthostatic hypotension.

To put these risks in perspective, in reviewing my own experience in over 40 years of practice, I have had 1 case of hypertension (190/100) with headache that was induced by diet and was managed in my office by several 50-mg doses of thioridazine samples (the patient refused to go to the emergency room and came to my office). One case of hypertension (180/100) was noted 50 minutes after an initial dose of 5 mg of dextroamphetamine was administered to a patient receiving 80 mg of tranylcypromine. The increase in blood pressure was transient and did not require treatment.

I also had a death occur from an acute cardiac arrhythmia in an 80-year-old man who had had a full therapeutic response to tranylcypromine, 60 mg. The patient responded after the failure of 2 therapeutic trials of tricyclics with lithium, thyroid, and amphetamine augmentation as well as 2 full courses of ECT. His acute cardiac death was found unrelated to the medication (I was, however, relieved to have required a written double consent because of the patient's age). Another patient, an elderly man who also failed to recover with ECT but responded to high-dose isocarboxazid, fell and broke his hip. He recovered and maintained his response. Orthostatic hypotension and significant lower leg edema have occurred in other patients of mine, but in most cases these side effects are manageable and have not prevented successful treatment.

The point is that some patients have few treatment options left and are condemned to a life of misery. They are at increased risk for suicide when they realize that they are trapped in their current state of daily dysfunction, loss of pleasure, and, in some cases, torture from comorbid anxiety.

Because of the potential for serious adverse events, one must select appropriate candidates for treatment in terms of severity of illness and prior failure of other treatments. To help the patient make an informed decision and to minimize the risk of lawsuits, all possible adverse outcomes should be reviewed with the patient and the significant other (double consent). This is recorded in the chart, together with explicit documentation that warnings were clearly given concerning potential dietary and drug interactions (and that the patient or significant other is capable of understanding these warnings). Yes, there is increased risk; yes, it takes work and patience—but there is a good chance of resurrecting a life devastated by depression or even saving a life. I have found that explaining risks fully to patients rarely discourages them if the risks are explained in the context of my past experience of positive outcomes to patients who have been selected on the basis of the severity of their condition and a history of nonresponse to a full enough range of prior treatments.

While I certainly don't advocate for the use of MAOI antidepressants in patients who have not first had a trial of available medications, combinations, and augmentations, as well as a trial of ECT if indicated, I see a significant number of patients who are treated with one selective serotonin reuptake inhibitor (SSRI) after another without response and who are chronically disabled but have never had a trial of an MAOI.

I am presently in the preliminary stages of looking at data from 47 patients who received MAOI treatment, exclusive of the selegiline patch, who entered a recurrent depression treatment study sponsored by the National Institute of Mental Health. Patients received sequential treatment with medications up to 18 months to achieve remission. Data are available from the active treatment phase as well as from the Antidepressant Treatment History Form,[1] which documents prior treatments in terms of drug, dosage, and duration of treatment. At this stage, not all of the treatment data are extracted, but it appears that close to half of the patients treated with either phenelzine or tranylcypromine remitted even after an average of 5 prior treatment failures. When we have completed the analysis, these data will be reported in full.

Upon reviewing my practice over the past 5 years (a university practice, the equivalent of about a half-time private practice), I was able to find 7 patients who required MAOIs, 6 of whom achieved remission, 3 with augmentation with stimulants. The bipolar patients were taking atypical antipsychotics for mood stabilization. Of this group, 2 had failed to respond to a full course of ECT. Two of the patients with bipolar depression responded to MAOIs after having failed to respond to lamotrigine, atypicals alone, and SSRIs with augmentation. One patient with a comorbid personality disorder with borderline features has been on treatment with a combination of tranylcypromine, dextroamphetamine, and an atypical antipsychotic and has been able to function as a physician over the past 5 years with several short-lived interpersonal crises along the way. Two patients relapsed on one MAOI, but responded to another and then maintained their response for over 1 year. Another patient who suffered from recurrent panic attacks in addition to major depression was able to survive significant legal stress and function over the past 5 years with alprazolam added to a continuing dose of isocarboxazid. The seventh patient failed to respond to 2 courses of ECT and 2 different trials of MAOI, but did respond to 300 mg/day of clomipramine and has stayed in remission with the addition of vagus nerve stimulation. Therefore, 6 of 7 patients with severe treatment-resistant or treatment-refractory depression achieved sustained remission for 6 months to 5 years. All of them had failed an exhaustive series of SSRIs and bupropion, as well as trials of tricyclic antidepressants. It is true that half of these patients also benefited from augmentation of their MAOIs with stimulants,[2] but they had not responded

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to these augmentation efforts when they were taking other antidepressants.

The use of MAOI medications should not be a casual decision—the cases I reviewed above were a highly selected minority who had few options left when MAOI treatment was initiated. Before initiating an MAOI, I ask myself: If this patient is unlucky enough to have a serious adverse reaction as the result of the MAOI, can I honestly say that the MAOI was fully indicated? I want to be sure that other medications less likely to be harmful (e.g., clomipramine) have been tried before recommending an MAOI.

My own preference is to avoid phenelzine because of increased anticholinergic-like effects, increased rates of leg edema, and sexual side effects, unless the patient suffers from severe comorbid anxiety or panic attacks for which it seems most effective. I will select tranylcypromine in patients who are sensitive to weight gain and for whom cost is an issue (there is a generic version). Isocarboxazid is my first choice if none of the special considerations mentioned above apply, since in my experience, it is usually easiest for the patient to tolerate. In case of an incomplete response, I may, after obtaining double consent, augment with methylphenidate or dextroamphetamine.[2]

We are all waiting for the promise of pharmacogenetic, neurochemical, and brain imaging research and designer medication development to bring us new, more effective treatments for our patients who do not respond to presently available treatments. We must also more fully realize that the addition of specific psychotherapies may be necessary to bring many of our treatment-resistant depressed patients closer to remission.

For the present time, until a savior has arrived, we should fully use the weapons we have in our battle with depression. As difficult as their use can be, the MAOI medications can be lifesaving and life-resurrecting for patients with treatment-resistant or refractory depression. Patients should have the opportunity of therapeutic trials of MAOIs if they are willing to accept the fully disclosed risks of taking them.

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