9 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Essential Concepts

- Monoamine oxidase inhibitors (MAOIs) are the most effective class of antidepressants.
- MAOIs are associated with risks of hypertensive crisis and serious drug interactions with serotonin reuptake inhibitors (SRIs) and opiate derivatives.
- About 10% of depressed persons probably deserve a trial of MAOIs.
- A new MAOI patch, using selegiline, provides a somewhat safer alternative with few medical risks at the lower end of the therapeutic dose range.
- Tricyclic antidepressants (TCAs) should be tried in almost all refractory unipolar depressed patients.
- Nortriptyline is the most effective, tolerable first-line TCA.

MONOAMINE OXIDASE INHIBITORS

MAOIs generally are considered the most effective class of antidepressant medications. Unfortunately, they pose the greatest risk in terms of frequency of potentially serious medical side effects, and their use has fallen off in recent years.

The standard MAOIs are tranylcypromine (Parnate) and phenelzine (Nardil). These agents are irreversible inhibitors of the two main types (A and B) of the monoamine oxidase enzyme. This enzyme breaks down monoamines, that is, norepinephrine, serotonin, and dopamine. MAO-A is the main enzyme responsible for metabolism of all types of monoamines, whereas MAO-B appears to be more specific to dopamine metabolism. In addition to the standard irreversible MAOIs that affect both MAO-A and MAO-B, it is relevant that there is an MAOI that is specific to MAO-B—selegiline (Deprenyl). This medication has a different profile of side effects owing to this difference in mechanism. A related class of medications, the

TABLE 9.1. Monoamine Oxidase Inhibitors

Drug	*Effective Dose (mg/day)*	*Comments*
Tranylcypromine (Parnate)	20–60	Amphetamine-like, more tolerable than phenelzine
Phenelzine (Nardil)	15–45	Sedating, weight gain
Selegiline (Deprenyl)	5–30	Selective at lower doses, probably best tolerability
Selegiline patch (Em-Sam)	6–12	Bypasses gastrointestinal metabolism, removing or reducing risk of hypertensive crisis, no diet needed at lower doses
Moclobemide	150–500	Reversible, no diet needed, not available in United States

reversible inhibitors of monoamine oxidase (RIMAs), inhibits both MAO-A and MAO-B, but does so reversibly and possesses a different side-effect profile. Moclobemide, the prototype RIMA, is not available in the United States but is in wide use in Canada, Europe, and other nations.

Basic rules of thumb regarding this class are as follows (Table 9.1): Phenelzine tends to be sedating, whereas tranylcypromine tends to be stimulating. Both these agents can cause weight gain, hypertensive crisis, and potentially serious drug interactions. Hypertensive crisis occurs with the ingestion of tyramine, which is similar chemically to tyrosine, the precursor to norepinephrine and dopamine. Tyramine is catabolized by MAO; thus excessive amounts of tyramine can remain in the body when MAO is inhibited. This tyramine can lead to increased blood pressure through its effects on increased activity of the sympathetic nervous system. Blood pressure can rise to dangerous levels, leading to stroke and possibly death. Foods associated with the tyramine reaction are aged cheeses, wine, and certain beans (Table 9.2).

MAOI use involves the paradoxical situation of being appropriate for severe refractory depression, but only in those persons who are not extremely impulsive, noncompliant, cognitively impaired, or otherwise unable to negotiate this complicated diet. Further, while patients need to be severely depressed, they

TABLE 9.2. Diet Advice to Avoid Tyramine Reaction with MAOIs

Avoid completely: All matured or aged cheese, all aged/cured meat, fava beans, all tap beers or red wine, sauerkraut, soy sauce, other soy condiments, Marmite concentrated yeast extract

May be safe in moderation: Cottage cheese, cream cheese, fresh milk products, fresh meats, vodka, gin, white wine, canned or bottled beer (no more than one alcoholic beverage per day), brewer's yeast, soy milk

should not be extremely suicidal owing to these risks. Such patients do exist. In fact, most depressed patients (even those who are severely depressed) are not suicidal, impulsive, irritable, or markedly impaired cognitively. Good therapeutic alliance is also an important feature of MAOI use because the clinician needs to trust that the patient will use these agents responsibly.

There are many drug interactions associated with MAOIs (Table 9.3), the two most serious being the combination with SRIs and the combination with opioid derivates such as meperidine (Demerol). Both combinations have proven fatal and are absolutely contraindicated. In both cases, it appears that serotonin syndrome ensues with autonomic instability, fever, myoclonus, flushing, sweating, and abnormal laboratory tests. Another major risk is hypertensive crisis, which can occur with stimulant agents such as phentermine, a common ingredient in over-the-counter cold remedies.

TIP

Serotonin syndrome occurs with the combination of MAOIs and SRIs. Serotonin syndrome is similar to neuroleptic malignant syndrome (i.e., high fever, autonomic instability, high mortality rate), but the two conditions differ clinically on muscular manifestations; myoclonus occurs with serotonin syndrome, and severe rigidity occurs with neuroleptic malignant syndrome.

TABLE 9.3. Dangerous Drug Interactions with MAOIs

Hypertensive crisis: L-DOPA, other MAOIs, phentermine (in over-the-counter cold remedies)

Serotonin syndrome: Meperidine, SRIs, possibly TCAs

Morphine is associated with hypotension. Codeine is somewhat safer, although not definitively safe.

Standard MAOIs have been proven to be the most effective antidepressant medications in existence. They have proven effective in patients nonresponsive to other classes (such as TCAs and SRIs), in the most difficult kinds of depression (such as melancholia), and in bipolar depression. Thus, short of electroconvulsive therapy (ECT), MAOIs are probably the most powerful weapons in the clinician's arsenal for treating severe depression.

Even if one recognizes the major benefits of these agents, the risks seem to weigh heavily in the other direction. I have a personal approach to this problem that I find useful and pragmatic. I start my refractory depressed patients on selegiline as the first MAOI trial, following later with tranylcypromine or phenelzine. I take this approach because selegiline is a selective MAO-B inhibitor, selective for dopamine metabolism. Since the noradrenergic system is not involved, there is no significant risk of hypertensive crisis or drug interactions at low doses of selegiline (5 mg per day to 10 mg per day). Although these low doses are indicated for the treatment of Parkinson's disease, some persons also will experience antidepressant efficacy. If so, they have the benefit of response to an MAOI without most of the risks. Unfortunately, most persons require higher doses of selegiline for antidepressant efficacy (20 mg per day to 30 mg per day), and these doses irreversibly block both MAO-A and MAO-B. However, even with this standard MAOI mechanism, selegiline appears to have a somewhat lower risk of hypertensive crisis with tyramine ingestion than do phenelzine or tranylcypromine and may be the safest MAOI available. The major disadvantage to its use is that it is less studied in treating depression than the other agents, although there are a few double-blind, controlled studies supporting selegiline's use in depression. A new seligiline patch has been developed that bypasses gastrointestinal metabolism, thus reducing the risk of hypertensive crisis. It is given once daily at doses of 6, 9, or 12 mg per day (all shown more effective than placebo in acute unipolar depression). The patch does not require any special dietary considerations at 6 mg per day, although at higher doses the usual restrictions are necessary. It appears that the selegiline patch blocks both MAO-A and MAO-B in the brain but mainly MAO-B in the gastrointestinal tract, resulting in the lowered risk of hypertensive crisis. Nonetheless, even at the higher doses, the risk of hypertensive crisis should be lower than with oral MAOI medications.

CLINICAL VIGNETTE

The patient is a 53-year-old man who has been diagnosed with treatment-refractory chronic depression. He has been treated for 17 years and has received full therapeutic trials at adequate doses and durations of fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, nortriptyline, venlafaxine, and mirtazapine. He has not been able to tolerate trials of nefazodone and bupropion for more than 1 month owing to marked side effects. The consulting physician recommends an MAOI trial. His treating clinician and the patient are wary about the use of a diet because the patient has been chronically suicidal for over 10 years. However, with the support and encouragement of his spouse, the patient agrees to a trial of selegiline. Treatment at 5 mg per day has no effect, and the dose is increased to 10 mg per day after 2 weeks. The patient does not need to be on a special diet yet. He reports no side effects and no benefit after 6 weeks. The dose is then increased to 15 mg per day, and the special MAOI diet is begun. He still has no benefit, although he is somewhat less anxious than usual and mildly sedated. At 20 mg per day (week 12), he begins to report mild improvement in depressed mood. At 25 mg per day, his wife reports that he is more active around the house and more interested in social activities. His appetite, which was low, is gradually increasing. At 30 mg per day, he reports improvement in his mood to a greater extent than he has ever experienced, although he is still depressed about a third of the time and not as active or interested in activities as he had been before the onset of his illness. He is no longer suicidal.

TRICYCLIC ANTIDEPRESSANTS

TCAs were once the bread and butter of antidepressant treatment (Table 9.4). In the United States, however, TCAs are used less and less frequently, and now, most of the graduates of psychiatric residencies are quite unfamiliar with how to prescribe TCAs.

I think that this is unfortunate because a number of studies strongly suggest that TCAs are more effective than SRIs in the treatment of melancholia and refractory depression. I believe that a refractory unipolar depressed patient has not received adequate treatment if he or she fails to receive at least one trial of a TCA. It is common today for a unipolar depressed patient to receive multiple trials of new antidepressants, often over years, and yet never receive a single trial of a TCA. This reluctance often comes from the clinician rather than the patient.

TABLE 9.4. Common TCAs

Drug	*Amine class*	*Comments*
Imipramine	Tertiary	Oldest of the class
Amitryptyline	Tertiary	Very sedating
Desipramine	Secondary	Often too stimulating, most noradrenergic drug available
Nortriptyline	Secondary	Most tolerable
Clomipramine	Tertiary	Most serotonergic, useful in obsessive-compulsive disorder
Doxepin	Tertiary	Most antihistaminic, extreme sedation

In my experience, a few simple rules suffice to become comfortable with prescribing TCAs (Table 9.5). First, as background, it is important to distinguish between tertiary and secondary amines. Tertiary amines are agents such as amitriptyline and imipramine, and secondary amines are agents such as their metabolites nortriptyline and desipramine, respectively. Tertiary amines block the reuptake of serotonin and norepinephrine, whereas secondary amines are more selective for norepinephrine reuptake. The tertiary amines also block multiple other receptor systems, leading to a host of other side effects (Table 9.6), whereas the secondary

TABLE 9.5. General Rules for TCA Treatment

1. Tertiary amines (such as amitriptyline) are metabolized to secondary amines (such as nortriptyline).
2. Secondary amines are more specific to norepinephrine reuptake and are more tolerable.
3. All TCAs need to be dosed to 200 to 300 mg/day for full efficacy, with the exception of nortriptyline.
4. Nortriptyline is the only TCA with a definitive therapeutic blood level, 50 to 150 ng/dL.
5. Nortriptyline is the most effective, tolerable TCA and usually the best first-line agent.

TABLE 9.6. Common Receptor Blockade Effects of Tertiary TCAs

1. Anticholinergic effects: dry mouth, constipation
2. Antiadrenergic effects: sedation, sexual dysfunction, orthostatic hypotension
3. Antihistaminic effects: weight gain, sedation

amines do so to a lesser degree. Thus, as a rule, the secondary amines are more tolerable, although occasionally there may be increased efficacy with a tertiary amine.

In general, then, in using TCAs, it is wise to begin with a secondary amine, using a tertiary amine as a last resort. In practice, tertiary amines are tolerated infrequently in full antidepressant doses for refractory depression because all TCAs except nortriptyline generally require a dose of 200 to 300 mg per day for optimal efficacy. Nortriptyline is the only TCA with a definitive blood level (50 to 150 ng/mL, with 100 ng/mL being ideal). Usually, the same numbered dose produces this blood level (100 mg per day of nortriptyline tends to yield a blood level of 100 ng/mL). A patient thus can be dosed more readily and rapidly to an effective amount with nortriptyline than with any other TCA. Since it is also a secondary amine, I tend to prefer nortriptyline as the most effective and tolerable TCA.

TIP

Of all TCAs, nortriptyline is the best tolerated and most easily dosed.

All TCAs have quinidine-like effects on cardiac muscle, which can cause or exacerbate conduction defects, resulting in prolongation of the QT interval. In extreme cases, this can result in torsades de pointes and ventricular tachycardia, which often is fatal. This effect is dose-related, hence the potential fatal risk of overdose with TCAs. As a general rule, a 2-week or more prescription of a TCA poses a risk of fatality in overdose.

Some clinicians seem to think that low doses of TCAs for nondepressive indications are less harmful. One continues to see low-dose tertiary TCAs, such as amitriptyline (Elavil) or doxepin (Sinequan), prescribed for insomnia. However, this use of TCAs is inappropriate. Many safe treatments for

insomnia exist (e.g., trazodone). There is no benefit to using a TCA for a sedating effect. This use is harmful because even at low doses, some potential for cardiac arrhythmia exists, especially in the elderly and those with underlying cardiac disease. Even a small exposure to such risk, when unnecessary, is too much exposure. Also, a low dose of TCAs for insomnia is often the fourth or fifth drug in a polypharmacy cocktail; in almost all cases, the patient experiences sedation or some other side effect shared between TCAs and other agents in the mix. In general, the low-dose TCA can be omitted altogether without any risk to the patient.

I emphasize the need to remain open to the use of TCAs in refractory unipolar depression, especially full doses and levels of secondary amines such as nortriptyline, but I highly discourage the use of low-dose tertiary TCAs for nondepressive indications such as insomnia.