In lecturing to medical students, residents, and psychiatrists during the past several years, we have encountered widespread hesitancy in the use of MAOIs and even TCAs, mainly because of concerns about their safety but also because of doubts about their effectiveness compared with newer alternatives. Thus, it is timely to review the literature on the efficacy and safety of TCAs and MAOIs, with a view to maintaining an appropriate place for these 2 drug classes in the pharmacotherapy of depression.

An SSRI antidepressant is the initial choice for standard treatment of major depression, and often another SSRI antidepressant is the second choice if the first is ineffective. The overwhelming majority of antidepressant prescriptions in the United States are for SSRIs. They are considered safer and better tolerated than the antidepressant medications that preceded them, including monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs).

Yet, a pivotal recent study that measured the rate and degree of clinical response to SSRI therapy in 2876 typical outpatients in conventional "real-world" treatment settings, found a 47% response rate (defined as 50% or more improvement), and a 28% remission rate (conventionally defined as a 17-item Hamilton Depression Rating Scale Score of 7 or less). Although remission rate was not commonly reported in early antidepressant trials and so direct comparisons cannot be made with the early literature, this is a markedly lower rate of response than had been consistently observed with TCAs and in a subgroup of outpatients with MAOIs.

Various explanations have been offered for the decreasing response rates to antidepressants reported in clinical trials over time. These include changes in placebo response, study settings (inpatient vs outpatient), and populations studied (more treatment-refractory persons presenting for studies). Whatever the role of the comparative efficacy of older versus newer antidepressants may be, a review of the recent literature clearly indicates that a large percentage of patients will not respond, have only partial response, or lose an initial response to the newer antidepressants. Thus, it is important to be familiar with, and comfortable using, all classes of antidepressant medications.

Tricyclic antidepressants

The prototype TCA is imipramine, the antidepressant activity stumbled on in the late 1950s in the search for new phenothiazine antipsychotics, which resemble imipramine on the molecular level. The second TCA to be found effective was amitriptyline. Subsequently, the active metabolites of each of these, desipramine and nortriptyline, were marketed and found to be somewhat better tolerated than their parent compounds. Several other TCAs were also introduced, including clomipramine; doxepin; trimipramine; protriptyline; and the closely related tetracyclic compounds, maprotiline and amoxapine.

TCAs were the precursors of the current SSRIs and the serotonin-norepinephrine reuptake inhibitors (SNRIs). They share the basic mechanism of action of inhibition of reuptake of monoamine neurotransmitters from the synaptic cleft. They vary across a spectrum of relative affinity for serotonin and norepinephrine reuptake sites (Table 1), with clomipramine showing the most selective affinity for the serotonin reuptake site, desipramine the most potency at the norepinephrine reuptake site, and maprotiline the most selectivity for the norepinephrine reuptake site. It is notable that the major metabolite of clomipramine, desmethylclomipramine, is also an SNRI, giving clomipramine a combined serotonergic-noradrenergic effect clinically.

Apart from serotonin and norepinephrine reuptake blockade, TCAs share varying degrees of direct receptor antagonist activity (Table 2), which is considered responsible for their side effects, although
it has been speculated that this activity may contribute to their therapeutic effects as well. In addition to blocking adrenergic, histaminergic, and cholinergic receptors, these drugs all show quinidine-like effects on cardiac conduction, which contribute to their potentially lethal toxicity when taken in overdose.

**TCA efficacy**

Placebo-controlled studies have consistently found TCAs to be highly effective in treating major depression. In a 1969 review of all studies published in English with sufficient data to be analyzed, the prototype TCA, imipramine, was shown to be superior to placebo by a large margin. In patients treated with imipramine, the percentage of those who were moderately improved or better was 70% versus 39% for placebo. Early clinical trials characterized TCAs as most effective in endogenous depression, a diagnosis similar to the current DSM-IV subtype of depression with melancholic features. This form of depression manifests as a marked loss of pleasure or interest with insomnia, weight loss, and guilt. These studies compared endogenous depression with reactive and neurotic depression subtypes. Neither subtype has current-day equivalents, but they can perhaps best be considered forms of nonmelancholic depression. A consistent observation has been that severe depression showed the most reliable response to tricyclics.

Since the introduction of the SSRIs, it has been repeatedly observed that severely depressed inpatients, usually those with melancholia, show a more robust response to TCAs than to SSRIs. The first studies to demonstrate this were by the Danish University Antidepressant Group, which published 2 widely cited studies showing the superiority of the TCA clomipramine to 2 SSRIs, citalopram and paroxetine, in hospitalized patients who had depression. Subsequent studies replicated the finding that TCAs are superior to SSRIs in specific populations.

Akhoundzadeh and colleagues reported that nortriptyline was more effective than fluoxetine for the treatment of moderate to severe depression. Roose and colleagues demonstrated the superiority of nortriptyline over fluoxetine in elderly hospitalized patients with melancholic depression with comorbid heart disease. Joyce and colleagues found melancholia more responsive to nortriptyline than fluoxetine treatment in older men, but the opposite was true in younger women. Increased benefits have been demonstrated by Robinson and colleagues with nortriptyline compared with fluoxetine in patients with poststroke depression. Interestingly, in a study designed to rate patients' perceived benefit from treatment, patients reported older medications and electroconvulsive therapy (ECT) to be more helpful than the newer antidepressants. The authors also reported that ECT and older antidepressant treatments were more strongly correlated with acute recovery.

Meta-analyses of the efficacy of TCAs compared with other antidepressants have tended to find TCAs somewhat more effective than SSRIs. However, because of heterogeneity of study designs and outcome measures, it is difficult to draw firm conclusions based on the meta-analyses currently available.

One study looked at the effect of a placebo-controlled crossover to the alternative treatment between an SSRI and a TCA in cases of clinical nonresponse to an initial 6-week trial of paroxetine versus imipramine. It was found that 73% of paroxetine nonresponders recovered while taking imipramine, while only 50% of imipramine nonresponders recovered when treated with paroxetine. Interestingly, in the 1-year follow-up maintenance study, including initial responders and crossover responders, 26% of those who had recovered with paroxetine relapsed, while no patients who had recovered with imipramine relapsed.

A much larger multicenter crossover study of treatment-resistant chronic depression found that imipramine was slightly less effective than sertraline as a second treatment (55% vs 63%), although completer analysis did not demonstrate a significant difference. In the STAR*D study, after failing to achieve remission from 2 previous courses of treatment for the index episode of illness, the first being 14 weeks of treatment with 40 mg of citalopram daily, 20% of patients were able to achieve remission by taking nortriptyline while only 12% achieved remission when treated with mirtazapine.

Finally, there is a small database of literature that examined the risks and benefits of combining SSRIs with TCAs, which we have reviewed elsewhere. Although there are metabolic interactions to be careful of, and the published numbers are still quite small, when practiced with care, the combination has been demonstrated to be highly effective.

**Adverse effects of TCAs**

The main reasons for the massive shift from TCAs, which formerly dominated the pharmacotherapy of depression, to SSRIs and SNRIs are the adverse effect burden of TCAs and their lethality in overdose. An overdose with a TCA is more than 5 times as likely as an overdose with an SSRI to
result in death.\(^{32}\)

Treatment strategies for adverse effects of TCAs have been discussed elsewhere; in general, they can be managed satisfactorily.\(^{33}\) Risk of overdose is another matter, and in frankly suicidal patients it is often wisest to avoid medications from this class. When it is judged that TCAs are the most appropriate treatment despite potential overdose risk, prescribing a 1-week supply of the medication at a time may be a wise precaution. An alternative effective solution, when available, is to have someone responsible hold and administer the medication.

Because patients with major depression often need to receive medical treatment for comorbid medical conditions, it is important to be aware of pharmacokinetic and pharmacodynamic interactions. Since high serum levels of a TCA can cause multiple problems, it is important to be aware of any interactions that may increase the level of the TCA. Therapeutic levels are available for TCAs, making monitoring for drug interactions quite easy. Levels drawn before the addition of another drug can be compared with levels a few days after the addition for increased TCA levels and after a couple of weeks for decreased TCA levels. The major pharmacokinetic drug interactions are listed in Table 3. Pharmacodynamic interactions can often be easily predicted based on known effects of medications. For example, taking an antihistamine with an antidepressant that is antihistaminic would result in increased sedation, dry mouth, and constipation.

Monoamine oxidase inhibitors

Before TCAs were stumbled on, MAOIs were already established as the first effective modern pharmacotherapy for major depression.\(^{34}\) They had been discovered as the result of an accident. An antituberculosis agent introduced at the beginning of the 1950s was an MAOI, and tuberculosis patients with depression were observed to rise from their gloom while receiving the new drug, iproniazid.\(^{34}\) Within a few years, a number of MAOI antidepressants had been approved for marketing in the United States, including 3 that are still available: phenelzine, isocarboxazid, and tranylcypromine. Later, the European MAOI, selegiline, was approved in the United States, initially as an antiparkinsonian treatment. Selegiline is currently the only transdermal antidepressant available in the United States. This form of medication offers various advantages, providing relative safety from dietary interactions and permitting treatment of patients who are unable to take oral medication or who may not adequately absorb medications from their GI tract.

The mechanism of action of MAOIs illuminated the biological basis of depressive illnesses. The function of monoamine oxidase in the brain is to metabolize monoamines. The monoamines considered to have a role in depressions are serotonin, norepinephrine, and dopamine. Monoamine oxidase type A is found in monoaminergic presynaptic nerve terminals. Inhibition of its activity causes monoamines to build up in the presynaptic neurons, and monoaminergic neurotransmission is enhanced. It is notable that unlike TCAs, SSRIs, or SNRIs, the MAOI antidepressants increase brain levels of dopamine as well as norepinephrine and serotonin, which may contribute to their differing effect in certain clinical settings.

**MAOI efficacy**

A few years after the introduction of MAOIs, when TCAs became available as well, medical literature began to emerge about the differential indications for these 2 classes of antidepressant medication. TCAs were found to be most effective in severe depression, especially with melancholic features. MAOIs, on the other hand, were more effective in less severe, chronic depression with prominent anxiety, without melancholic features, and often in the presence of reversed vegetative symptoms.\(^{35,36}\) It was noted early on that although TCAs worked in a larger percentage of depressed patients, the degree of improvement was markedly more dramatic in those for whom MAOIs were effective.\(^{37}\)

In the early 1960s it was realized that MAOIs had a rare but potentially severe hypertensive interaction with foods with high tyramine content (mainly aged or spoiled high protein foods, aged cheeses being the first identified). This had been the cause of a number of cerebrovascular accidents before the interaction was identified. The reason for this interaction is that the human GI system contains monoamine oxidase that metabolizes dietary tyramine before it reaches the circulatory system. Tyramine is a naturally occurring pressor amine that arises from bacterial fermentation of the amino acid tyrosine found in edible proteins. Use of an MAOI will deactivate the gut monoamine oxidase, increasing systemic absorption of tyramine and resulting in an increased pressor response. Once it was established that dietary restriction of tyramine intake made these medications safe to use, they returned to limited use, but their popularity was never restored.

Investigators have shown that MAOIs, in particular tranylcypromine, are more effective than imipramine in anergic and bipolar depression.\(^{38-41}\) In several comparative trials, the Columbia University group has demonstrated unequivocal superiority of phenelzine to imipramine, and both to
Placebo, in rigorously defined atypical depression.\textsuperscript{42,43} Their definition of atypical features has since come to be included in \textit{DSM-IV}. This is a clinical picture characterized by the absence of melancholia, in which there is a capacity to become “cheered up,” often dramatically, but an accompanying morbid tendency to be devastated by interpersonal rejection. Associated vegetative symptoms are reversed from the picture seen in melancholia, with prominent oversleeping and overeating. Marked anergia is commonly found.

McGrath and colleagues\textsuperscript{44} designed a study to assess whether SSRIs would have an advantage over TCAs comparable to that of MAOIs. Interestingly, the trial revealed that fluoxetine and imipramine were of essentially identical efficacy in atypical depression. Based on previous studies demonstrating imipramine’s inferiority to MAOIs, the authors concluded that fluoxetine was inferior to phenelzine in treating atypical depression.\textsuperscript{44} Other studies have shown efficacy of MAOIs in generic treatment-resistant depressive illness.\textsuperscript{45-47} These and other results have been compelling enough for the American Psychiatric Association’s treatment recommendations for major depression to now include 2 specific indications for the use of MAOIs: atypical depression and treatment-resistant depression.\textsuperscript{48}

**MAOI diet**

Despite the demonstrated areas of superior efficacy, use of MAOIs continues to be limited by the perception of their relatively high risk. However, this common perception is somewhat deceptive. Safety from the dietary tyramine interaction can be achieved by excluding a limited list of foods from the patient's diet. Typically, tyramine content of less than 6 mg in a meal is considered safe.\textsuperscript{49} Based on recent data, the original restrictive MAOI diet has been modified to allow many foods originally thought to be unsafe (Table 4). Alternatively, if the drug is administered parenterally, as with a recently marketed form of transdermal selegiline, sufficient GI monoamine oxidase activity persists that dietary restrictions are unnecessary, except in cases where high doses are required.\textsuperscript{50}

**MAOI drug interactions and adverse effects**

Other safety issues with MAOIs include a range of drug-drug interactions that can be dangerous (Table 5). Outcomes of drug interactions with MAOIs can be life-threatening (hypertensive crisis, serotonin syndrome). It is important to be aware of MAOI drug interactions and to educate your patients. A MedicAlert bracelet or necklace can be useful in emergency situations when the patient is unable to explain that he or she is taking an MAOI. While some drugs such as TCAs and stimulants are known to potentially cause serious drug interactions, they have occasionally been used safely with MAOIs for severe and treatment-resistant depression.\textsuperscript{51}

Other adverse effects of MAOIs are listed in Table 6. Strategies to manage these are presented elsewhere.\textsuperscript{33,51}

**Conclusions**

Despite their being somewhat cumbersome relative to SSRIs in the treatment of depressive illness, it is clear that TCAs have an important role, especially in treating severe depression and depression with melancholic features.

As with TCAs, there continue to be clinical circumstances in which MAOIs are the optimal treatment, despite the complexity of their use compared with SSRIs and other more recently developed antidepressants. Specifically, a clinician should consider MAOIs when a patient presents with atypical depressive features, including oversleeping, overeating, and markedly low energy; and when a patient proves unresponsive to other antidepressant medications. The threshold for considering the use of an MAOI should be significantly lowered by the recent availability of a member of the MAOI class that does not require special dietary precautions at usual doses and has a relatively mild side effect profile, even when compared with other recently introduced antidepressant drugs.\textsuperscript{52,53}

**References:**


46. Amsterdam JD, Shults J. MAOI efficacy and safety in advanced stage treatment-resistant depression. J Affect Disord. 2005;89:183-188.
50. EMSAM prescribing information. Tampa, Fla: Somerset Pharmaceuticals; 2006.

Source URL: http://www.psychiatrictimes.com/articles/not-obsolete-continuing-roles-tcas-and-maois