Monoamine oxidase inhibitors and tricyclic antidepressants for MDD

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Ms. B, age 45, has a history of major depressive disorder (MDD) and migraines. She is admitted after presenting with anhedonia, hopelessness, and hypersomnia. These symptoms have become more severe over the last few weeks. Ms. B describes a past suicide attempt via overdose on doxylamine for which she required treatment in the intensive care unit. The only activity she enjoys is her weekly girls' night, during which she drinks a few glasses of wine. Ms. B's current medications are dextromethorphan/bupropion 45/105 mg twice daily and aripiprazole 5 mg/d, which she has taken for 3 months. She states she has "been on every antidepressant there is."

When clinicians review Ms. B's medication history, it is clear she has had adequate trials of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), intranasal esketamine, multiple augmentation strategies, and electroconvulsive therapy (ECT). Ms. B seeks an alternative medication to improve her depressive symptoms.

Treatment-resistant depression (TRD) is commonly defined as depression that has not responded to ≥2 adequate trials of an antidepressant.[1] Some guidelines recommend monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) as second- or even third-line options for MDD,[2] while others recommend reserving them for patients with insufficient responses to alternative treatment modalities.[3,4] Although MAOIs and TCAs have been available since the 1950s, prescribing these medications has become less prevalent due to safety concerns, the availability of other pharmacologic options, and a lack of clinical training and comfort.[5,6] Most research notes that MAOIs are superior for treating atypical depression while TCAs are more effective for melancholic depression.[2-4] In a review of 20 studies, Thase et al[7] found that 50% of TCA nonresponders benefited from an MAOI. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, monotherapy with the MAOI tranylcypromine was associated with a lower remission rate than the TCA nortriptyline; many argue the dose of tranylcypromine was suboptimal, and few participants completed an adequate trial in

When considering prescribing an MAOI or TCA, look at patient-specific factors and the medication's unique properties

Practice Points

- When switching from a serotonergic agent to a monoamine oxidase inhibitor, **ensure that at least 5 half-lives have passed before administering the next dose.**
- Educate patients on the **realities of a tyramine-restricted diet** in accordance with current literature.
- Secondary amine tricyclic antidepressants (TCAs) **have fewer adverse effects in comparison to tertiary amines.**
- **Consider additional indications of TCAs** to guide treatment for major depressive disorder.

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Table 1

Monoamine oxidase inhibitors FDA-approved for major depressive disorder

Medication	Chemical structure	Half-life (h)	Starting dose	Target dose
Phenelzine	Hydrazine	11.6	15 mg 3 times daily	60 to 90 mg/d (twice or 3 times daily)
Isocarboxazid	Hydrazine	2.5	10 mg twice a day	40 to 60 mg/d (up to 4 times daily)
Tranylcypromine	Nonhydrazine	2.5	10 to 30 mg/d (twice or 3 times daily)	30 to 60 mg/d (twice or 3 times daily)
Selegiline[a]	Nonhydrazine	20	6 mg/24 h	6 to 12 mg/24 h

[a]Transdermal formulation only

Source: References 5,12-17

Clinical Point

A recent meta-analysis found MAOIs and TCAs are 'competitive' with SSRIs based on efficacy and tolerability

Table 2

Food and beverages guidelines for a tyramine-restricted diet[a]

Category	Unacceptable	Acceptable
Dairy	Aged and matured cheeses	Processed cheeses, mozzarella, ricotta cheese, cottage cheese, yogurt
Fish, poultry, meat	Aged and fermented fish or meat (ie, dry sausages)	Fresh fish, poultry, and meat (including processed meats)
Fruits and vegetables	Fava bean pods, banana peel	All other fruits (including bananas) and vegetables
Beverages	Tap beer or beer that has not been pasteurized	Bottle and canned beer, red and white wine in reasonable servings
Miscellaneous	Sauerkraut, fermented soy sauce	Tofu in reasonable serving sizes, commercial soy sauce

[a]For a more extensive list, see the AAPP MAOI Pharmacist Toolkit (https://aapp.org/guideline/maoi), p 12-14, or reference 26

Source: References 5,13-18,25-28

the last level.[8,9] A more recent study by Kim et al[10] found MAOIs to be "generally more effective" than TCAs for TRD, particularly in patients with fewer antidepressant trials; however, this was a small retrospective exploratory trial. A network meta-analysis found both classes to be "competitive" with SSRIs based on efficacy and tolerability, which leads to the question of whether these medications should be considered earlier in therapy.[11] Considering patient-specific factors and particular medication properties is an effective strategy when prescribing an MAOI or TCA.

Monoamine oxidase inhibitors

Four MAOIs are FDA-approved for treating MDD (***Table 1***[5,12-17]): phenelzine, isocarboxazid, tranylcypromine, and selegiline. These medications irreversibly inhibit MAO, which exists as isomers A and B. MAO-A primarily metabolizes serotonin and norepinephrine, which is largely responsible for these medications' antidepressant effects. Both isomers equally metabolize dopamine.[5,12,18] It is best to avoid using MAOIs in patients with cerebrovascular disease, hepatic disease, or pheochromocytoma. Patients with active substance use disorders (particularly

	Renal dose adjustment	Hepatic dose adjustment
	Contraindicated in severe renal impairment	Contraindicated in hepatic impairment
	Caution in mild-to-moderate renal impairment, contraindicated in severe renal impairment	Contraindicated in hepatic impairment
	No recommendations provided	No recommendations provided
	No recommendations provided	No recommendations provided

sympathomimetics and hallucinogens) are at an increased risk for hypertensive crises and serotonin syndrome, respectively. The most common adverse effects are orthostatic hypotension (despite more well-known concerns regarding hypertension), alterations in sleep patterns (insomnia or hypersomnia, depending on the agent), gastrointestinal issues, and anticholinergic adverse effects such as dry mouth and constipation.[13,19-21]

In one review and meta-analysis, phenelzine displayed the highest efficacy across all MAOIs.[11] It likely requires high doses to achieve adequate MAO inhibition.[11] A metabolite of phenelzine inhibits gamma-aminobutyric acid transaminase and may be helpful for patients with comorbid anxiety disorders or MDD with anxious distress.[18,21] Additional considerations include phenelzine's propensity for orthostasis (with rapid titrations and higher doses), sedation, weight gain, sexual dysfunction, and a rare adverse effect of vitamin B6 deficiency.[5,13,14,20-22]

Use of isocarboxazid in clinical practice is rare. Its adverse effects are similar to those of phenelzine but isocarboxazid is less studied. Tranylcypromine has a similar chemical structure to amphetamine. It can be stimulating at higher doses, potentially benefitting patients with comorbid attention-deficit/hyperactivity disorder (ADHD) or significant apathy.[13,23] Selegiline's distinct quality is its availability as a transdermal patch, which may be useful for patients who struggle to take oral medications. At low doses (6 mg/24 h), the selegiline transdermal patch allows patients to disregard a dietary tyramine restriction because it avoids first-pass metabolism. It inhibits both MAO isomers in the brain but is only selective for MAO-B once concentrations are distributed to the liver. Higher doses require a tyramine-restricted diet because there is still some MAO-A inhibition in the gut. Selegiline is also stimulating because it is converted to amphetamine and methamphetamine.[5,12,13,17,19,24]

Despite promising results from the use of MAOIs, physicians and patients may be reluctant to use these medications due to perceived limitations. One prominent barrier is the infamous "cheese reaction." Tyramine, an amino acid found in certain food and beverages (***Table 2***,[5,13-18,25-28] ***page 36***), is broken down by MAO-A in the gut. When this enzyme is inhibited, higher concentrations of tyramine reach systemic circulation. Tyramine's release of norepinephrine (which now cannot be broken down) can lead to a hypertensive crisis. Consequently, a tyramine-restricted diet is recommended for patients taking an MAOI. However, the common notion that cheese, wine, and beer must be avoided is false, because most of the dietary restrictions developed following the discovery of MAOIs are antiquated.[5,12,25-28] Patients who take an MAOI only need to slightly adjust their diet, as outlined in ***Table 2***.[5,13-18,25-28] A reasonable serving size of most foods and beverages containing tyramine is unlikely to elicit this "pressor" response. Of the 4 MAOIs FDA-approved for MDD, tranylcypromine appears to be the most sensitive to tyramine.[21] Transient postdose hypertension (regardless of tyramine) may occur after taking an MAOI.[29] Encourage patients to monitor their blood pressure.

Additional hurdles include the required washout period from serotonergic medications and interactions with sympathomimetics. MAOIs pose the highest risk of

Clinical Point

Patients receiving an MAOI need to only slightly adjust their diet, focusing on a reasonable serving size of items containing tyramine

Table 3

Tricyclic antidepressants for major depressive disorder

Medication	Neurotransmitter reuptake inhibition	Starting dose (mg/d)	Target dose (mg/d)	Metabolism	Half-life (h)	Therapeutic level (ng/mL)
Tertiary						
Amitriptyline (metabolite: nortriptyline)	5HT > NE	25 to 50	100 to 300	CYP1A2, 3A4, 2C19, 2D6	10 to 28	80 to 200
Clomipramine (metabolite: norclomipramine)	5HT > NE	25 to 50	100 to 250	CYP1A2, 3A4, 2C19, 2D6	16 to 60	230 to 450
Doxepin (metabolite: N-desmethyldoxepin)	5HT = NE	25 to 50	100 to 300	CYP1A2, 2C19, 2D6	15 to 20	30 to 150
Imipramine (metabolite: desipramine)	5HT > NE	25 to 50	100 to 300	CYP1A2, 3A4, 2C19, 2D6	11 to 25	175 to 300
Trimipramine (metabolite: des-methyltrimipramine)	5HT > NE	25 to 50	75 to 300	CYP1A2, 3A4, 2C19, 2D6	7 to 40	150 to 300
Secondary						
Amoxapine	NE > 5HT; DA	100 to 150	200 to 300	CYP2D6	8	NA
Desipramine	NE > 5HT	25 to 50	100 to 300		15 to 18	50 to 300
Nortriptyline	NE > 5HT	25 to 50	50 to 150		18 to 44	70 to 170
Proptriptyline	NE > 5HT	10 to 20	20 to 60		54 to 92	NA

5HT: serotonin; CYP: cytochrome P450; DA: dopamine; NA: not available; NE: norepinephrine

Source: References 36-51

serotonin syndrome; however, this usually occurs if given concomitantly with other serotonergic agents. The standard recommendation is a 14-day washout period from SSRIs (5 weeks for fluoxetine and 3 weeks for vortioxetine), SNRIs, mirtazapine, and other antidepressants. It can be distressing for patients to be without medication during that period. Because some antidepressants have much shorter half-lives, waiting 5 half-lives (typically 5 to 7 days) for the discontinued medication to be excreted is feasible if patients are closely monitored.[5,12,13,25,27,30] There are rare instances where a TCA may be combined with an MAOI (typically initiated within 1 to 2 days of each other), but never clomipramine or imipramine due to their potent serotonin reuptake inhibition.[31] If switching to an alternative MAOI, waiting 7 to 14 days is recommended to allow adequate time for the inhibited enzyme to regenerate.[14-17,32] Taking medications that increase dopamine and norepinephrine (eg, stimulants or oral over-the-counter decongestants) with an MAOI is typically not recommended due to the risk of hypertensive crisis.[25,27] In severe TRD or comorbid ADHD, successful simultaneous use of methylphenidate or amphetamine—typically at low doses—with close blood pressure monitoring has been reported.[33] There have also been positive cases of the use of modafinil in combination with an MAOI; however, this should be done with caution.[34,35] Clinicians must use clinical judgment when considering a combination of medications that pose a higher risk.

Table 4

Common uses for tricyclic antidepressants

	MDD	OCD	Insomnia	Panic disorder	Neuropathic pain	Migraine prophylaxis
Amitriptyline	X				X	X
Clomipramine	X	X		X		
Doxepin	X (capsules)		X (tablets)			
Imipramine	X			X	X	
Trimipramine	X					
Amoxapine	X					
Desipramine	X			X	X	
Nortriptyline	X				X	X
Protriptyline	X					

MDD: major depressive disorder; OCD: obsessive-compulsive disorder

Source: References 38-46,49,56-61

Tricyclic antidepressants

TCAs work differently than MAOIs to increase monoamines. They inhibit presynaptic serotonin and norepinephrine transporters in the CNS to increase levels of these chemicals in the synaptic cleft. While all TCAs inhibit these transporters, they do so at varying levels (***Table 3***,[36-51] ***page 38***). Based on their chemical structure, TCAs can be categorized into secondary and tertiary amines. Tertiary amines are metabolized via demethylation into their derivatives (***Table 3***[36-51]). Patients who have recently suffered a myocardial infarction (MI) should avoid tertiary amines. TCAs can reduce heart rate variability, which is already decreased after an MI, thus presenting the potential for cardiac arrhythmias. TCAs should also be avoided in patients with cardiac conduction abnormalities.[38-46,52] Patients with a prior baseline cardiac conduction defect, such as a bundle branch block, are at higher risk for further cardiac abnormalities. In those with a preexisting first-degree heart block, TCAs can still be used, but electrocardiogram monitoring is recommended.[52,53] TCAs have also been reported to decrease the seizure threshold.[38-46] They can be used with caution in patients who have a history of epilepsy or head trauma, or with concomitant medications that lower the seizure threshold.[38-46]

Table 5

Impact of medications on tricyclic antidepressant levels

Increase TCA levels	Decrease TCA levels
Bupropion	Carbamazepine
Duloxetine	St. John's wort
Mirtazapine	Barbiturates
Fluoxetine	Phenytoin
Haloperidol	
Paroxetine	
Valproic acid	
Quinidine	

TCA: tricyclic antidepressant

Source: References 38-46

Overdose risk is a concern with TCAs because ingestion of 10 to 20 mg/kg can lead to significant toxicity.[54] This is due to their blockage of voltage-gated sodium channels found in the CNS and heart, which contributes to overdose symptoms such as a widened QRS complex and seizures. Symptoms usually develop within 2 hours but may be delayed up to 6 hours.[55] Patients with a history of overdose must be carefully assessed before initiating a TCA.

continued

Clinical Point

A washout period is required when switching a patient from a serotonergic medication to an MAOI

Clinical Point

TCAs can reduce heart rate variability, thus presenting the potential for cardiac arrhythmias

Related Resources

- Meyer JM. A concise guide to monoamine oxidase inhibitors. Current Psychiatry. 2017;16(12):14-16,18-23,47,A.
- Espejo GD. Treating major depressive disorder after limited response to an initial agent. Current Psychiatry. 2021;20(10):51-53. doi:10.12788/cp.0178
- American Association of Psychiatric Pharmacists (AAPP) MAOI Pharmacist Toolkit. https://aapp.org/guideline/maoi

Drug Brand Names

Amitriptyline • Elavil
Amphetamine • Adzenys, Dyanavel
Aripiprazole • Abilify
Clomipramine • Anafranil
Desipramine • Norpramin
Dextromethorphan/bupropion • Auvelity
Doxepin • Sinequan, Adapin
Esketamine • Spravato
Fluoxetine • Prozac
Imipramine • Tofranil
Isocarboxazid • Marplan
Methamphetamine • Desoxyn
Mirtazapine • Remeron
Modafinil • Provigil
Nortriptyline • Pamelor
Phenelzine • Nardil
Protriptyline • Vivactil
Selegiline • Emsam
Tranylcypromine • Parnate
Trimipramine • Surmontil
Vortioxetine • Trintellix

Prescribing a limited supply of these medications may be valuable. The use of TCAs has often been limited due to their adverse effects, most of which are associated with their respective affinities for alpha 1, muscarinic 1, and histamine 1 receptors. Inhibition of the alpha 1 receptor is associated with hypotension, muscarinic 1 with anticholinergic adverse effects, and histamine 1 with sedation and weight gain. Tertiary amines have a higher affinity for these receptors compared to secondary amines, leading to a more significant adverse effect profile.[36,50] Among TCAs, amitriptyline is the most likely to cause hypotension, whereas desipramine and nortriptyline are least likely. Amitriptyline and clomipramine are most likely to cause anticholinergic adverse effects, whereas desipramine and nortriptyline are the least likely. Amitriptyline, doxepin, and imipramine have the highest propensity for QTc prolongation.[36]

Beyond treating MDD, TCAs have shown benefits for treating other disease states (***Table 4***,[38-46,49,56-61] ***page 39***). These differing indications may help psychiatrists determine the best TCA to prescribe for a given patient. Amitriptyline is the most studied TCA for MDD; however, nortriptyline is typically preferred due to its favorable tolerability profile.[4,62] Nortriptyline also has data supporting its use in ECT to prevent relapse.[63] Amitriptyline and nortriptyline have shown benefits in patients with neuropathic pain and for migraine prophylaxis.[56-60] Although frequently used for MDD, clomipramine is not FDA-approved for this indication, but is for obsessive-compulsive disorder.[39] Doxepin is FDA-approved for insomnia at lower doses and for MDD at higher doses.[40] Therefore, it may benefit patients with sleep difficulties secondary to depression. Desipramine has been used off-label to treat ADHD in children and has shown some benefits in adults.[64-66] Protriptyline, trimipramine, and amoxapine are infrequently used in clinical practice.

A unique feature of TCAs is the ability to monitor serum concentrations (***Table 3***[36-51]). Guidelines recommend therapeutic drug monitoring (TDM) with amitriptyline, clomipramine, imipramine, and nortriptyline for routine use. TDM is still recommended for doxepin, desipramine, and trimipramine, but its utility is largely for treatment failure or resistance.[37] These plasma levels can be altered based on coadministered medications (***Table 5***,[38-46] ***page 39***) and should be closely monitored. Physicians should obtain a trough level after at least 5 half-lives and before the next dose is due, and use TDM as indicated to optimize dosing.

CASE CONTINUED

Ms. B's outpatient psychiatrist provides collateral information about her medical history and confirms her long-standing MDD with multiple medication trials, though she has never received an MAOI or TCA. Ms. B is adamant she does not want a medication-free period between treatments and refuses to adjust her diet, despite being educated on the few changes necessary. She has no contraindications for TCAs and may benefit from a TCA for her comorbid migraines. The care team expresses concern for TCA overdose to Ms. B and her family. Ms. B's sister reassures the team they will have someone monitor

and dispense her medications at home. They decide to discontinue her current psychiatric regimen, and Ms. B is started on nortriptyline 50 mg/d at night, with plans to titrate based on tolerability.

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continued

Clinical Point

Some TCAs may be beneficial for patients with OCD, insomnia, panic disorder, neuropathic pain, or migraines

Clinical Point

Therapeutic drug monitoring is recommended for amitriptyline, clomipramine, imipramine, and nortriptyline

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