The Role of Monoamine Oxidase Inhibitors in Depression Treatment Guidelines

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Monoamine oxidase inhibitors (MAOIs) have proven efficacy for treating depression and for decades have been a preferred treatment for patients with atypical depression, high levels of anxiety, anergic bipolar depression, and treatment-resistant depression. However, MAOIs are infrequently used due to safety and tolerability concerns and the need for dietary restrictions. Current guidelines, which are reviewed here, recommend MAOIs as third-, fourth-, or fifth-line treatments due to these concerns. However, a transdermal formulation of selegiline limits the need for dietary restrictions and has fewer side effects than many more widely used antidepressants. The availability of a safer and more tolerable formulation gives clinicians another option in their armamentarium for treating depression.

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MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase inhibitors (MAOIs) were developed in the 1950s after iproniazid, a medication introduced for treatment for tuberculosis, was observed to have mood-elevating effects. Eventually, it was discovered that iproniazid inhibited monoamine oxidase (MAO), an enzyme located in the membranes of mitochondria that inactivates neuronal dopamine, serotonin, and norepinephrine. By inhibiting MAO in the brain, iproniazid increased the synaptic availability of these monoamines.[1] Although iproniazid was eventually removed from the market due to toxicity, other MAOIs were developed and have been used as antidepressants for decades. Now, however, MAOIs are prescribed infrequently, due in part to concerns over potential serious dietary and drug-drug interactions directly associated with their mechanism of action.[2] Many clinicians are unfamiliar with the mechanism of action, adverse effects, and efficacy of these medications. While depression treatment guidelines no longer recommend MAOIs as first-line agents, they do suggest the use of these drugs in certain situations.

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Mechanism of Action of MAOIs

Monoamine oxidase is found in the brain, gut, liver, and other tissues. Two isomers of MAO enzymes have been identified, each with different substrate affinities: MAO-A is found primarily in the intestine and in brain regions with serotonin, norepinephrine, dopamine, and tyramine substrates, whereas MAO-B is concentrated in platelets as well as in brain regions that are rich in dopaminergic neurons. Monoamine oxidase inhibitors can be either nonselective (inhibiting both isomers) or selective for either isomer, but it is thought that inhibition of MAO-A is necessary for an antidepressant effect to occur.[3]

The MAOIs available in the United States are the nonselective medications phenelzine, tranylcypromine, and isocarboxazid and the selective MAOI selegiline. Oral selegiline is selective for MAO-B at doses of less than 20 mg/d and is used as an adjunct medication for treating Parkinson's disease at 10 mg/d. Oral selegiline loses its MAO selectivity at the higher doses needed for antidepressant effect.[3,4]

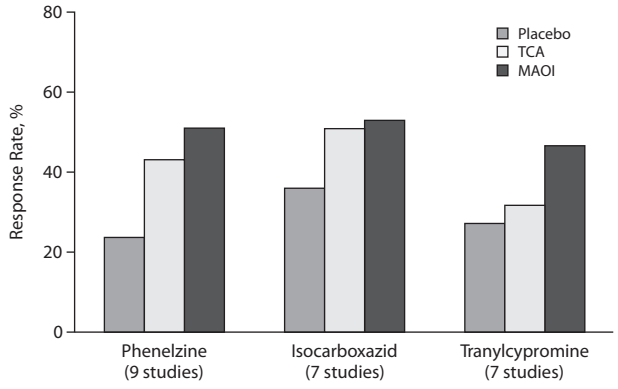
All of these medications have irreversible action, meaning that they permanently bind to MAO for the life of the enzyme (ie, 14–28 days).[4] A minimum of 7 to 14 days is needed for new enzyme to be generated and MAO activity to return.

Moclobemide, which is a reversible inhibitor of MAO-A (ie, high concentrations of dietary tyramine can displace the drug from the MAO enzyme) is not available in the United States, although it is widely available throughout much of the rest of the world. Evidence suggests that, while moclobemide is an efficacious antidepressant, it may not be as effective (at the therapeutic doses that are typically used) as the older, nonselective, MAOIs.[4]

MAOI Adverse Effects

Early side effects most commonly reported for oral MAOIs include insomnia, sedation, orthostatic hypotension, dizziness, and nausea.[5] Side effects occurring later include weight gain, edema, muscle pain, myoclonus, paresthesia, and sexual dysfunction. However, the most serious potential

Figure 1. Tricyclic Antidepressants (TCAs) Versus Monoamine Oxidase Inhibitors (MAOIs) in a Meta-Analysis of 23 Outpatient Studies[a]



[a]Data from Thase et al[3]; figure adapted with permission from Rapaport.[12]

side effects of MAOIs are hypertensive crisis and serotonin syndrome.

Hypertensive crisis. In addition to metabolizing serotonin and norepinephrine, MAO-A also metabolizes dietary tyramine in the gut and liver, thus restricting the uptake of tyramine into the circulatory system during digestion. When an MAOI is used, high levels of tyramine can enter the blood stream, which, in turn, can lead to the release of norepinephrine, causing a rapid increase in blood pressure. Patients may experience hypertensive crisis, which can result in a stroke or even death due to cerebral hemorrhage. Therefore, patients taking MAOIs are required to follow dietary restrictions that limit tyramine intake. Primarily, patients should avoid aged cheeses; aged or cured meats or any meat, poultry, or fish that could potentially be spoiled; broad bean (fava) pods; Marmite (concentrated yeast extract); sauerkraut; soy sauce, tofu, and soybean condiments; and tap beer.[6] Although not particularly onerous, these dietary restrictions have been perceived by patients and many clinicians as difficult to manage and have contributed to the limited use of MAOIs.

One way to decrease the risk of tyramine reactions is to use the reversible MAO-A inhibitor moclobemide, which is much less likely to cause hypertensive crisis than an irreversible MAOI. However, this option is not readily available to clinicians practicing in the United States. A non-oral medication delivery system (eg, sublingual, parenteral, and transdermal), which minimizes the inhibition of MAO-A in the intestine and liver by "skipping" first-pass metabolism, is another way to reduce risk. The US Food and Drug Administration (FDA) has approved a transdermal formulation of selegiline that allows the drug to be absorbed into the blood stream, thereby targeting central nervous system MAO while minimizing exposure of the gastrointestinal tract to the drug.[7] Dietary restrictions are not required at the minimum effective dose of the selegiline patch (6 mg/24 h) but are still required at higher doses due to insufficient safety data. The transdermal formulation delivers sustained plasma concentrations with minimal peak-trough fluctuations,

For Clinical Use

- Consider prescribing an MAOI for patients with depression who have had 2 or more unsuccessful trials of SSRIs or other newer antidepressants.
- Guidelines generally reserve MAOIs as third- or fourth-line treatments due to concerns over safety and tolerability, but newer formulations can lessen the risks.
- When prescribing MAOIs, educate patients about necessary dietary restrictions and the potential for hypertensive crisis and serotonin syndrome due to drug interactions.

allows for lower doses of medication than oral delivery, and, except for application site reactions, has a tolerability profile similar to that of placebo (including low potential for weight gain and sexual side effects).[8] Application site reactions can be minimized by advising patients to rotate the patch site daily, to clean the patch sites with warm soapy water after each application, and to avoid applying patches to areas of skin that are hairy, shaved, or subject to sweating or rubbing against garments.

Drug interactions. Serious drug-drug interactions are possible with all of the MAOIs, including transdermal selegiline. The risk of hypertensive crisis is thought to be increased by using MAOIs with adrenergic medications, including amphetamines, sympathomimetic vasoconstrictive agents, and over-the-counter decongestants.[9] The rare but potentially lethal serotonin syndrome has also been reported as a result of the interaction between MAOIs and drugs with strong serotonergic effects (eg, other antidepressants, synthetic opioids, and some migraine medications).[10] Contraindicated medications should not be taken for 1 to 2 weeks prior to instituting MAOI treatment (with the exception of fluoxetine, which requires a washout of 5 weeks due to its long half-life), or for 2 weeks after ceasing MAOI treatment.[11] Patients should also be educated about the risk of drug-drug interactions and instructed to let their other doctors know that they are taking an MAOI.

Efficacy of MAOIs

The efficacy of oral MAOIs for treating major depressive disorder (MDD) has been compared with that of placebo and of tricyclic antidepressants (TCAs). For inpatients, MAOIs are more effective than placebo but not as effective as TCAs.[3] However, MAOIs are more effective than TCAs in outpatients with atypical depression (Figure 1),[3,12] which is generally characterized by persistent vegetative symptoms (overeating/weight gain, hypersomnia, and leaden paralysis) coupled with sensitivity to rejection.[1,13] Prior to the introduction of the newer-generation antidepressants, the MAOIs were the primary pharmacotherapy option for patients who had not responded to TCAs, including those with depression with comorbid panic attacks or phobias and anergic bipolar depression.[3,13] The transdermal formulation of selegiline is

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significantly better than placebo in improving depressive symptoms and preventing relapse, but data comparing the patch with other antidepressants or for those with atypical depression are lacking.[2]

MAOIs AND DEPRESSION TREATMENT GUIDELINES

Due to the dietary restrictions and potential drug interactions associated with these medications, MAOIs are usually recommended as third-, fourth-, or fifth-line treatments in current depression treatment guidelines. However, the treatment recommendations do differ among the guidelines.

American Psychiatric Association

The American Psychiatric Association (APA) published an updated Practice Guideline for treating patients with MDD in 2010. The APA Practice Guidelines[11] recommend considering an antidepressant medication or psychotherapy as an initial treatment choice for patients with mild to moderate MDD, but they state that patients with severe MDD should definitely be provided antidepressant treatment. As evidence suggests that most antidepressants are comparable in efficacy, the Practice Guideline advises that the choice of an initial antidepressant for a patient should be based on other factors, such as the medication's anticipated side effects and the patient's sensitivity to those side effects. Other medication-related factors include properties such as the medication's cost, half-life, effect on cytochrome P450 enzymes, and interactions with other drugs. Patient-related factors that can influence the choice of antidepressant include patient preference and prior response to medication.

The Practice Guideline recommends that most patients should receive one of the newer antidepressants (ie, selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], mirtazapine, or bupropion) due to their safety and tolerability profiles. However, when choosing among these antidepressants, individual patient factors should still be taken into consideration. For instance, the patient may have a comorbid diagnosis that responds better to one antidepressant than another, or he or she may have a somatic symptom that can be improved by one class of antidepressants but not another. In addition, even medications within the same class may have differing side effect profiles.

Because of the risk of serious side effects due to drug or food interactions, the APA guidelines generally limit the use of nonselective MAOIs to patients who have not responded to other treatments. The guidelines note the particular efficacy of MAOIs for patients with atypical depression. Of course, if a patient has previously had treatment success with an MAOI and would like to restart the same type of therapy, then his or her wishes can be accommodated. If prescribing an MAOI is appropriate, the Practice Guideline advises clinicians to start at a low dose and titrate up to the usual daily dosage (Table 1).[11,14]

Whichever antidepressant is selected, patients should be regularly monitored for side effects. Should intolerable side effects occur, clinicians can try lowering the dose of the antidepressant or can switch the patient to a different medication with a lower propensity for that side effect.

The goal of the acute treatment phase is to induce remission of symptoms and return the patient fully to his or her baseline level of functioning. To achieve this goal, patients should be monitored regularly to assess treatment response, and their treatment regimens should be adjusted as necessary. The APA guidelines endorse the use of measurement-based tools to assess response and side effects. Patients should have received 4 to 8 weeks of an antidepressant at an adequate dose before the clinician determines that they are only partially responsive or nonresponsive to that treatment. The medication should be optimized such that the patient receives the maximum recommended dosage, unless intolerable side effects occur. For patients with inadequate response, clinicians should reassess the diagnosis and comorbid diagnoses and reevaluate the medication's side effects, the patient's psychosocial factors, and treatment adherence. Medication factors contributing to nonresponse should be assessed (eg, pharmacodynamic properties or pharmacokinetics).

Once a treatment adjustment has been made, continued inadequate response after 4 to 8 more weeks of treatment requires another careful review of the treatment plan. Strategies to try include augmenting the medication with psychotherapy or another agent and switching to another (non-MAOI) antidepressant.

Augmentation with another antidepressant generally utilizes an antidepressant from a different pharmacologic class, other than an MAOI (due to the potential for serotonin syndrome). Other, nonantidepressant medications that may also be used for augmentation include lithium, thyroid hormone, and atypical antipsychotics. When switching medications, patients may change to another medication within the same class or switch to another class. The APA guidelines note that it might be helpful for patients who do not respond to trials of SSRIs to try an SNRI. Switching to a nonselective MAOI after an appropriate washout period is an option for those patients who can follow the necessary dietary and medication restrictions. Switching to transdermal selegiline, which has no dietary restrictions at the minimum dosage, is also an option.

Patients who reach remission during acute treatment should continue on the same antidepressant for 4 to 9 months at the same dose to reduce the risk of relapse. Maintenance treatment should then be considered for patients with 3 or more prior episodes of depression, with chronic MDD, or with risk factors for recurrence such as residual symptoms, the presence of psychosocial stressors, early age at onset, and a family history of mood disorders. The maintenance phase should continue the antidepressant medication used during the acute and continuation phase that produced remission. If treatment is discontinued, the antidepressant should be tapered over the course of several weeks.

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Table 1. Suggested Starting, Titration, Initial Target, and Maximum Daily Doses for Selected Antidepressants for Depression as Tabulated in the Practice Guidelines of the APA, TMAP, and WFSBP[a,b]

Drug	Starting Dose, mg/d	Titration, mg/d[c]	Initial Target Dose, mg/d	Maximum Daily Dose, mg/d
SSRIs[d]				
Citalopram	20	10 every 2 weeks	20–40[j]	60[j]
Escitalopram	10	10 every 2 weeks	10–20	20
Fluoxetine	20	10–20 every 4 weeks	20–40	60–80
Fluvoxamine	50	50–100 every 2 weeks	100–200	300
Paroxetine	20	10–20 every 2 weeks	20–40	50–60
Sertraline	50	50–100 every 2 weeks	50–150	200
SNRIs[e]				
Duloxetine	30–60	30 at 1–2 weeks	60	120
Milnacipran	50–100	Day 1: 12.5, days 2–3: 25, days 4–7: 50, and after day 7: 100	100	200
Venlafaxine	37.5–75	37.5–75 every week	75–150	225–375
Other Antidepressants[f]				
Agomelatine[g]	25	…	25	50
Bupropion	150–200	150 at 3–7 days	300	300; 300–400 (SR); 450 (XL)
Mianserin[g]	30	…	60	120
Mirtazapine	15	15 every 1–2 weeks	15–30	45
Nefazodone	50–100	…	150–300	300–600
Reboxetine[g]	4–8	…	8	12
Setiptiline[g]	3	…	3	6
Tianeptine[g]	37.5	…	37.5	37.5
Trazodone	50–100	…	75–200	300–600
Viloxazine[g]	100	…	200	500
TCAs and TeCAs[h]				
Amitriptyline	25–75	25–50 every week	100–150	300
Amoxapine	50	…	100	400
Clomipramine	25–50	Gradually increased to 100 over first 2 weeks	100	250
Desipramine	25–75	25–50 every week	100–200	300
Dibenzepine[g]	120–180	…	240	720
Doslepine[g]	75	…	75	150
Doxepin	25–75	25–50 every week	75–150	300
Imipramine	5–100	25–50 every week	100	300
Lofepramine[g]	70	…	140	210
Maprotiline	25–50	…	100–150	225
Nortriptyline	25–50	25 every week	50–75	150–200
Protriptyline	10	…	15–20	60
Trimipramine	25–50	…	100	300
MAOIs[i]				
Isocarboxazid	10–20	…	30–60	30–60
Moclobemide[g]	150	…	300	600
Phenelzine	15–45	15 every 2–3 weeks	15–60	90
Selegiline transdermal	6	3 at intervals no less than every 2 weeks	6	6–12
Tranylcypromine	10–30	10 every 2–3 weeks	20–40	60

[a]Adapted with permission from Nutt et al.[14]

[b]Note that the starting, initial target, and maximum daily doses are based on US and European recommendations. These doses may need to be appropriately adjusted as tolerated and for other populations.

[c]Refer to the manufacturer's recommended dosage administration.

[d]SSRIs may have drug-drug interactions with carbamazepine, clozapine, cyclosporine, grapefruit, hydantoins, linezolid, MAOIs, methadone, NSAIDs, phenothiazines, pimozide, ropivacaine, St John's wort, sympathomimetics, tacrine, theophyllines, thioridazine, tizanidine, tramadol, triptans, and TCAs.

[e]SNRIs may have drug-drug interactions with alcohol, linezolid, MAOIs, St John's wort, sympathomimetics, thioridazine, tramadol, and triptans.

[f]Other antidepressants may have drug-drug interactions with alcohol, carbamazepine, cyclosporine, linezolid, MAOIs, ritonavir, SNRIs, SSRIs, St John's wort, TCAs, and tramadol.

[g]This drug is not approved for the treatment of depression in the United States.

[h]TCAs may have drug-drug interactions with carbamazepine, cimetidine, clonidine, fluoxetine, guanethidine, linezolid, MAOIs, paroxetine, procainamide, quinidine, quinolones, rifabutin, rifampin, St John's wort, sympathomimetics, valproate, and ziprasidone.

[i]MAOIs may have drug-drug interactions with atomoxetine, bupropion, carbamazepine, dextromethorphan, insulins, levodopa, linezolid, meperidine, SNRIs, SSRIs, St John's wort, sulfonylureas, sympathomimetics, TCAs, tramadol, triptans, and tyramine foods.

[j]Because of possible risk of cardiac arrhythmias, the US Food and Drug Administration now recommends doses no higher than 20 mg/d for elderly patients or patients with heart disease and no higher than 40 mg/d for healthy adults.

Symbol: … = not provided.

Abbreviations: APA = American Psychiatric Association, MAOI = monoamine oxidase inhibitor, NSAID = nonsteroidal anti-inflammatory drug, SNRI = serotonin-norepinephrine reuptake inhibitor, SR = sustained release, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, TeCA = tetracyclic antidepressant, TMAP = Texas Medication Algorithm Project, XL = extended release, WFSBP = World Federation of Societies of Biological Psychiatry.

British Association for Psychopharmacology

The British Association for Psychopharmacology (BAP) issued a revised guideline for treating depressive disorders with antidepressants in 2008.[15] The BAP guideline recognizes that many patients with depression will be treated by primary care physicians rather than specialists in psychiatry, but it advises general practitioners to refer patients to psychiatric specialists if they perceive that the patient is at risk for suicide, harm to others, or severe self-neglect; has psychotic symptoms; or has a history or likelihood of bipolar disorder. General practitioners should also consult with or refer to a psychiatrist when the patient has had 2 or more antidepressant trials that have resulted in either insufficient response or nonresponse.

In the acute phase, treatment choice in the BAP guidelines is driven by the duration and severity of the patient's depression. Antidepressants are a first-line treatment for moderate to severe major depression in adults, which is defined by the BAP as Hamilton Depression Rating Scale (HDRS) scores above 17, and for subthreshold depression lasting at least 2 years. For mild major depression, antidepressants should be considered if the depressive episode lasts for more than 2 to 3 months or if the patient has a history of moderate to severe recurrent depression. For subthreshold depression in adults, antidepressants are not a first-line option unless the depressive episode has lasted for more than 2 to 3 months or the patient has a history of moderate to severe recurrent depression. Antidepressants are not recommended as a first-line treatment option for children and adolescents with major depression but may be considered if other treatment options have failed or if the patient has a history of moderate to severe recurrent depression.

First-line antidepressant choices include SSRIs, which have the most evidence for safety and tolerability, and other newer antidepressants such as the SNRIs. Patient preference, comorbid psychiatric or medical diagnoses, previous treatment response, medication side effect profile, and possible drug interactions should all be considered when choosing an antidepressant.

Next-step options should be initiated if the patient shows no improvement after at least 4 weeks of adequate treatment (including adequate dosing and patient adherence to the treatment). The patient should be reassessed after 6 to 8 weeks. Next-step options include increasing the dose of the first antidepressant, switching to another antidepressant, or augmenting the initial medication.

Should patients not reach remission with first-line treatments, TCAs and MAOIs should be tried. The guidelines warn that abrupt switching, which appears safe and well tolerated for most antidepressants, should not occur with SSRIs (especially fluoxetine) and MAOIs due to the risk of serotonin syndrome. In addition, the initiation of MAOIs is limited by the guideline to physicians with expertise in treating mood disorders. The guideline also notes that evidence indicates that MAOIs are more effective than TCAs for atypical depression but that not enough evidence exists to compare MAOIs with newer antidepressants. A family history of differential response to a TCA or an MAOI is also a factor in choosing between the 2 classes when switching.

Once the patient reaches remission, the BAP guideline recommends continuing treatment with the same medication at the same dose to help prevent relapse. Treatment should continue for at least 6 to 9 months for patients with a lower risk of relapse (eg, patients who remitted from their first episode), for 1 year after full remission for those with an increased risk of relapse, and for 2 years or longer for those with the highest risk (eg, patients with more than 5 lifetime episodes).

Canadian Network for Mood and Anxiety Treatments

In 2009, the Canadian Network for Mood and Anxiety Treatments (CANMAT) released revisions to the 2001 MDD treatment guideline produced in a collaboration between CANMAT and the Canadian Psychiatric Association.[16] The CANMAT guidelines support SSRIs, SNRIs, and other newer agents as first-line medications due to their proven efficacy and because their safety and tolerability profiles are better than those of TCAs and the nonselective MAOIs. Although not widely used in Canada, moclobemide is included as a first-line antidepressant because it is a reversible inhibitor of MAO-A.

Second-line recommendations include TCAs and the serotonin reuptake inhibitor trazodone. The guidelines acknowledge that the atypical antipsychotic quetiapine has sufficient evidence as an efficacious antidepressant as a monotherapy, but consider it to be a second-line recommendation due to its tolerability profile and the lack of comparative data with newer antidepressants. Because transdermal selegiline has a better tolerability profile than older MAOIs, it is a second-line recommendation. The older, irreversible MAOIs are third-line recommendations.

Because evidence does not support unequivocal differences in efficacy or overall tolerability among the first-line antidepressants, the choice of an initial antidepressant should be based on type of expected side effects, patient preference, simplicity of use, and cost. Additional factors that may affect antidepressant choice include age and sex of the patient, severity and diagnostic subtype of depression, comorbid disorders, past response, and the potential for drug interactions. Per CANMAT guidelines, adverse effect profiles differ among the agents, and individual sensitivities to side effects should be considered when choosing medications.

The CANMAT guideline has an algorithm, based primarily on expert opinion, to show a sequential approach for nonresponse.[16] Using the definition of clinical response as a 50% or greater reduction on a depression rating scale, CANMAT recommends that patients with at least 20% improvement after 4 to 6 weeks should continue the treatment trial for another 2 to 4 weeks before changes are made. Those who show less than 20% improvement after 2 weeks of antidepressant use should have a change made, such as the dose of the antidepressant increased, and then be reassessed. If there is still no improvement, the patient's

diagnostic and therapeutic issues should be reevaluated; validated rating scales to measure response and side effects can be helpful. Strategies for managing nonresponse to an initial antidepressant trial include switching to another first-line agent or adding another agent to the initial medication.

National Institute for Health and Clinical Excellence

The National Institute for Health and Clinical Excellence (NICE)[17] updated its guideline (for primary care and specialty providers) on treating depression in 2009. NICE does not recommend antidepressant treatment for subthreshold depressive symptoms or for persons with mild depression except in special circumstances (eg, a history of moderate or severe depression, subthreshold depressive symptoms lasting at least 2 years). Patients with moderate or severe depression should be treated with a combination of antidepressants and either cognitive-behavioral therapy or interpersonal therapy.

Patients should initially receive generic SSRIs because of their favorable risk-benefit ratios. However, the tolerability profiles of SSRIs do differ and should be considered when choosing a medication for an individual patient. If an antidepressant other than an SSRI is prescribed, clinicians should be aware of the safety and tolerability profile of that medication; nonreversible MAOIs should be prescribed only by specialists in mental health. The NICE guideline does not endorse changing initial treatment strategies based on depressive subtype (eg, atypical or seasonal depression) or personal characteristics such as sex or ethnicity.

Patients who start antidepressant therapy should be monitored regularly, ie, after the first 2 weeks of treatment, every 2 to 4 weeks thereafter for the next 3 months, and then at longer intervals if the patient is responding. If after 2 to 4 weeks the patient has not responded to the medication, first verify the patient's adherence to treatment. Clinicians should increase contact frequency with the patient and can consider increasing the dose of the antidepressant or switching to another medication. If after 4 weeks the patient has experienced some improvement but response is inadequate, continue treatment for 2 to 4 more weeks, but consider switching if there are side effects or if the patient would prefer to change antidepressants. The initial switch should be to a different SSRI or other newer-generation antidepressant with a good tolerability profile, while subsequent switches might be to an antidepressant of a different pharmacologic class (eg, an SNRI) or to an antidepressant that is less well-tolerated (eg, a TCA or an MAOI). Appropriate washout periods are advised. Augmentation can also be used if a psychiatrist is consulted.

To reduce the risk of relapse, patients should be encouraged to continue pharmacotherapy for at least 6 months after reaching remission. Patients who have risk factors for relapse, such as residual symptoms or multiple previous episodes, should continue treatment for at least 2 years.

Other Treatment Guidelines

Both the Texas Medication Algorithm Project[18] (TMAP) and the World Federation of Societies of Biological Psychiatry[19] (WFSBP) acknowledge that the efficacy of MAOIs is comparable to that of other antidepressant classes and is superior to that of TCAs for atypical depression. However, due to safety and tolerability concerns, neither guideline recommends MAOIs as first-line treatment.

The TMAP panel created a treatment algorithm based on visits (critical decision points) at weeks 2, 4, 6, 9, and 12.[18] The algorithm recommends SSRIs, SNRIs, bupropion, and mirtazapine as first-line treatments. As these antidepressants are considered comparable in efficacy by the TMAP panel, choosing a medication for an individual patient should be based on patient preference, comorbidities, side effect profiles, and the potential for drug interactions.

Patients should be assessed at each visit for response based on the 16-item Quick Inventory of Depressive Symptomatology (QIDS) (a score of ≥ 9 is considered nonresponse, and a score of 6–8 is considered partial response). Monoamine oxidase inhibitors, TCAs, and combination therapies are introduced after at least 2 failed trials of newer antidepressants. In the panel's consensus opinion, MAOIs and TCAs should be considered before combination treatments, although patient preference and tolerability influence this decision.

The WFSBP guideline states that no unequivocal evidence shows that one class of antidepressant is more efficacious than another, although minor differences might exist for clinical subtypes. The WFSBP guideline advises the initial use of newer antidepressants (eg, SSRIs, mirtazapine, nefazodone, reboxetine, and venlafaxine) as they are better tolerated than older medications. Acute-phase medication trials should last at least 6 weeks, but 8 to 10 weeks may be needed to fully assess symptom reduction.

The WFSBP guidelines suggest using rating scales to measure patient response, based on the following criteria: nonresponse equals a 25% or less decrease in baseline symptom severity, whereas partial response is a 26% to 49% decrease in baseline symptom severity. Response is a 50% or greater improvement from baseline, and remission is the absence of symptoms. If a patient does not respond adequately to the initial antidepressant, the clinician should first optimize the dosage of the medication and evaluate for nonadherence, continuing psychosocial stressors, comorbidities, and pharmacokinetic and pharmacogenetic factors that could affect response. Treatment strategies then include switching to an antidepressant from a different class, switching to a different antidepressant within the same class, combining 2 antidepressants from different classes, augmenting the antidepressant with a nonantidepressant agent, and combining the initial antidepressant with psychotherapy.

The continuation phase should last for at least 6 months after the patient reaches remission, with the goal of preventing early relapse, eliminating residual symptoms, and restoring the patient to his or her prior level of functioning.

SUMMARY

Although MAOIs have demonstrated efficacy for treating depression, particularly atypical depression, treatment

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guidelines do not recommend them as first-line pharmacotherapy due to safety and tolerability issues, such as the potential to cause hypertensive crises and serotonin syndrome. For these reasons, current guidelines recommend using MAOIs no sooner than third-stage treatment, although some guidelines recommend considering using MAOIs sooner for atypical depression. However, newer formulations of these agents, such as the selegiline patch, limit some of the risks associated with older MAOIs. Reversible MAOIs and the transdermal delivery system can also lessen the need for dietary restrictions, which many patients find difficult to adhere to and clinicians perceive as difficult to manage. When switching to MAOI treatment, washout recommendations must be followed.

Drug names: atomoxetine (Strattera and others), bupropion (Wellbutrin, Aplenzin, and others), carbamazepine (Carbatrol, Equetro, and others), cimetidine (Tagamet and others), citalopram (Celexa and others), clomipramine (Anafranil and others), clonidine (Catapres, Duraclon, and others), clozapine (Clozaril, FazaClo, and others), cyclosporine (Gengraf, Neoral, and others), desipramine (Norpramin and others), doxepin (Zonalon and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), isocarboxazid (Marplan), linezolid (Zyvox), lithium (Lithobid and others), meperidine (Demerol and others), methadone (Methadose and others), milnacipran (Savella), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil and others), pimozide (Orap), protriptyline (Vivactil and others), quetiapine (Seroquel), rifabutin (Mycobutin), rifampin (Rifadin and others), ritonavir (Norvir), ropivacaine (Naropin), selegiline oral formulation (Eldepryl, Zelapar, and others), selegiline transdermal system (EMSAM), sertraline (Zoloft and others), theophylline (Elixophyllin, Theocron, and others), tizanidine (Zanaflex and others), tramadol (Ryzolt, Ultram, and others), tranylcypromine (Parnate and others), trazodone (Oleptro and others), trimipramine (Surmontil and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

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