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Monoamine Oxidase Inhibitors: Clinical Review

SUMMARY

Monoamine oxidase inhibitors (MAOIs) are effective antidepressant agents. They are increasingly and effectively used in a number of other psychiatric and non-psychiatric medical syndromes. Their potential for serious toxicity (i.e., hypertensive reaction) is far less than original reports suggest, and newer reversible substrate-specific MAOIs may offer even less toxicity. The author reviews the pharmacology, mechanism of action, clinical indications, and dosing strategies of MAOIs. The common MAOI side-effects (hypotension, weight gain, sexual dysfunction, insomnia, daytime sedation, myoclonus, and hypertensive episodes) are described and management techniques suggested. Recent clinical developments involving MAOIs are outlined. (*Can Fam Physician* 1990; 36:1151–1155.)

RÉSUMÉ

Les inhibiteurs de la monoamine-oxydase sont efficaces comme antidépresseurs. On les utilise de plus en plus efficacement dans un certain nombre d'autres syndromes médicaux tant psychiatriques que non psychiatriques. Leur potentiel toxique (i.e. réaction hypertensive) semble moindre que ne le laissaient supposer les rapports originaux, et de nouveaux substrats spécifiques aux IMAO semblent présenter encore moins de toxicité. L'auteur révise la pharmacologie, le mécanisme d'action, les indications cliniques et les stratégies permettant des posologies appropriées aux IMAO. On en décrit les effets secondaires les plus fréquents (hypotension, gain pondéral, dysfonction sexuelle, insomnie, sédation diurne, myoclonie et épisodes hypertensifs) et on en propose le traitement approprié. On y décrit également les développements cliniques récents entourant les IMAO.

Key words: antidepressants, family medicine, monoamine oxidase inhibitors, mood disorders, pharmacologic agents, psychiatry

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MONOAMINE OXIDASE inhibitors have been marketed as antidepressants for 30 years,[1] yet are used infrequently. There is now a renewed clinical interest in MAOIs because of a number of factors.

1. More critical reviews of earlier studies, coupled with recent research on MAOI efficacy, suggest that they are effective antidepressants.
2. Monoamine oxidase inhibitors could have a broader range of activity than just depressive syndromes, which could then extend their use in the medical community.
3. There is a growing awareness that these drugs are less toxic than previous reports suggest.
4. Newer, more specific and perhaps less toxic MAOIs may further increase their safety and spectrum of activity.

With these factors in mind, this clinically oriented review is intended to evaluate new developments and to reacquaint physicians with MAOIs.

Efficacy

Early studies, which suggested that MAOIs are less effective than tricyclic antidepressants,[2] were not methodologically sound and have been critiqued.[3] Recent trials with tranylcypromine (Parnate), phenelzine (Nardil), and isocarboxazid (Marplan) provide evidence that these drugs are superior to placebo and equivalent or superior to tricyclics in depressed patients.[4–6] All recent studies indicate that MAOIs are effective in a variety of depressive states, although depression with associated features of anxiety, somatization, and hypochondriasis (the so-called atypical depressions) seem particularly responsive.[3,7–9]

In addition to their use in major depression, MAOIs have been used successfully in a variety of other disorders,

including panic attacks, panic disorders and agoraphobia,[8,10] obsessive-compulsive disorder,[11] social phobia,[12] post-traumatic stress syndrome, bulimia,[13] attention deficit disorders,[14] chronic pain syndrome,[15] narcolepsy, Parkinson's disease, and migraine headaches.[16]

Pharmacology

Brain monoamine oxidase is located presynaptically and oxidatively deaminates a wide variety of monoamines, including the putative monoamine neurotransmitters (noradrenaline, dopamine, serotonin) and a variety of monoamines found in foodstuffs (tyramine, phenelethylamine).[16]

In the 1950s, iproniazid, a drug tested for its antituberculous activity, was found to have mood-elevating properties.[17] Later, it was discovered this effect was from the MAOI properties of the drug, and research into less toxic MAOIs began. Currently available MAOIs in the United States and Canada are phenelzine, tranylcypromine, and isocarboxazid. Phenelzine and isocarboxazid are hydrazine compounds; tranylcypromine is not.

Two forms of brain monoamine oxidase are now recognized, and they are classified as type A or type B, according to substrate specificity. Monoamine A acts upon the following substrates: serotonin, epinephrine, norepinephrine, normetanephrine, octopamine, tyramine, and dopamine. Monoamine B selects benzylamines, phenelethylamine, N-methylhistamine, tyramine, and dopamine. All currently marketed MAOIs are non-selective with respect to A or B substrates, but newer MAOIs currently under investigation are A- or B-specific. Selective monoamine oxidase A inhibitors are superior antidepressants compared with selective monoamine oxidase B inhibitors.[18]

All clinically available MAOIs are irreversible in their binding to monoamine oxidase. Enzyme resynthesis, which has been estimated to occur with a half-life of 10 to 12 days in the brain, accounts for the long duration of action after discontinuation of the drug. Some newer MAOIs do not form covalent bonds (i.e., competitive inhibitors) with the enzyme and may be reversible.[16,19]

Mechanism of Action

While MAOIs exert their pharmacologic effect by inhibiting the deamination of biogenic amines, it is unknown whether this directly results in their antidepressant effect as originally hypothesized.

The antidepressant effects are known to be less likely to occur when peripheral monoamine oxidase inhibition is less than 75%.[20] Comments concerning how MAOIs work in depression (or other psychiatric syndromes) must be considered speculative. Recent theories postulate that the accumulation of monoamine neurotransmitters due to monoamine oxidase inhibition leads to either pre- or post-synaptic receptor changes that result in their psychoactive effects.[21,22]

Clinical Use

Before starting a patient on MAOI therapy, the following questions should be answered.

1. Does the patient have a disorder that will respond to MAOI treatment? Evidence suggests that patients with a major depressive disorder, and especially depressive states associated with anxiety, panic attacks, or agoraphobia, will respond to an MAOI. If the patient warrants antidepressant therapy, consider MAOIs. They may be the treatment of choice for patients who do not respond to tricyclic agents or for patients who are intolerant of tricyclic antidepressants. Symptoms of atypical depression, including anxiety, somatization, hypersomnia, hyperphagia, and lethargy, may respond preferentially to MAOIs.
2. Will the patient comply with diet and drug restrictions? The willingness of the patient to follow strict dietary control (Chart 1) should be determined. Often meal preparation depends on other family members; any MAOI dietary discussions must include the preparer of family meals. Involvement by family members will also improve the patient's drug and dietary compliance.
3. Are there any potential advantages to selecting an MAOI for some patients? Patients with cardiac problems, especially conduction defects, which require caution with tricyclic agents, could be treated with MAOIs. Patients with hypertension may benefit from the blood pressure–lowering side-effect of the MAOIs. Monoamine oxidase inhibitors have fewer anticholinergic side-effects, such as urinary retention, making these drugs a consideration in geriatric depression.
4. Are there patients in whom MAOIs should be avoided? Patients with pre-existing hypotension may be difficult to manage on MAOIs. Patients with substance or alcohol abuse or who cannot responsibly comply with dietary restrictions should not receive MAOIs. Recent work suggests that patients receiving fluoxetine should discontinue this drug for five weeks before initiating MAOI treatment.[23]

Dosing

After deciding to use an MAOI, the patient should be instructed to observe the food, drink, and drug restrictions for at least 24 hours before starting the first dose and for two weeks after stopping the last dose (Chart 1). Doses less than

Chart 1
Instructions for Patients Taking Monoamine Oxidase Inhibitors

Foods to avoid

- Cheese (cottage cheese, ricotta, and cream cheese are permitted). Beware of pizza, fondues, many Italian dishes, and salad dressings
- Red wine and sherry
- Smoked or pickled fish (especially herring, lox, anchovies, and caviar)
- Dry sausage (pepperoni, salami, bologna, summer sausage)
- Aged meats (chicken or beef pâté, corned beef
- Fava or broad bean pods
- Yeast vitamin supplements (brewer's yeast)
- Meat extracts (Bovril, marmite, soup cubes, and soups with meat extracts)

In general, avoid all foods that may be slightly off, fermented, aged, or leftovers.

Do not use cold decongestants, hayfever, or sinus remedies (i.e., Dristan, Sudafed, Sinutab, Contac C, Coricidin "D," Neo-synephrine nose drops, Novahistine) containing pseudoephedrine, phenylephedrine, and phenylpropanolamine. Be sure to tell your physician, surgeon, and dentist you are taking this medication. Other medications to avoid are antihypertensive agents (methyldopa, guanethidine, reserpine), narcotics (meperidine), sympathomimetics (dopamine, metaraminol), anesthetic drugs, and insulin. Do not use diet pills (amphetamines) or stimulants (methylphenidate, cocaine, methylenedioxyamphetamine [MDA]).

Go to the nearest emergency medical facility if you experience a sudden throbbing headache associated with high blood pressure, nausea, or vomiting. You may wish to carry a wallet card listing the necessary medical precautions and wear a medic-alert bracelet.

45 mg of phenelzine or 30 mg of tranylcypromine or isocarboxazid are rarely effective. Physicians should avoid prescribing inadequate doses because they expose the patient to drug side-effects without providing any benefit. Monoamine oxidase inhibitors usually take a minimum of three weeks and often as long as six weeks to obtain significant therapeutic benefit, but side-effects begin much earlier.

A suitable starting regimen is phenelzine, 15 mg (or tranylcypromine or isocarboxazid, 10 mg), on the first morning. This dose can be increased by one tablet every 24 to 72 hours until the minimum therapeutic dose is reached. Divided morning and noon dose times are best tolerated by most patients.

Tranylcypromine, the non-hydrazine, is associated with more hypertensive reactions, but less sexual dysfunction or urinary retention. The hydrazines, phenelzine and isocarboxazid, produce fewer hypertensive crises, but slightly more postural hypotension, weight gain, sexual dysfunction, and urinary retention.[24]

Therapeutic dose ranges typically are:

- phenelzine, 45 to 90 mg/day;
- tranylcypromine, 30 to 60 mg/day; and
- isocarboxazid, 30 to 60 mg/day.

The average course of treatment would be approximately six months. When the drug is discontinued, one should reduce the dose by a 10- or 15-mg tablet every one to three weeks until it has been discontinued. Some patients with frequent recurrent depressions have used the medication for long periods with minimal side-effects.

Side-Effects

One reason MAOIs have been underprescribed is because of physician concern about drug side-effects. Serious side-effects with MAOIs are extremely rare (Chart 2), and the common, non–life-threatening, "nuisance" side-effects can be either effectively managed or tolerated by patients without drug discontinuation.

Hypertensive Reactions

Mechanism. Hypertensive reactions (the so-called cheese reaction) are the most frequently mentioned side-effects due to the seriousness of the problem, although they are uncommon.[25] The mechanism of this reaction is that tyramine, a pressor amine found in certain foods, is not metabolized due to monoamine oxidase inhibition. It then circulates peripherally, where it can displace the increased stores of norepinephrine, resulting in precipitous increases in blood pressure. Tyramine, which is found in fermented, decaying, and over-ripe foods, is particularly at fault. Other offending agents are over-the-counter decongestants. When careful dietary and drug restrictions are followed, MAOIs are unlikely to cause this type of reaction (Chart 1).[26]

The hypertensive crisis is characterized by the sudden onset of a severe throbbing headache. It is often associated with flushing, sweating, blurred vision, nausea, palpitations, chest pain, and shortness of breath. Symptoms typically occur within minutes of ingestion of the suspected foodstuff.

Management. Treatment in the past has focused on α-adrenergic blockade with such drugs as phentolamine and chlorpromazine. These widely quoted recommendations are not in keeping with the agents now used in managing hypertensive emergencies. Calcium channel blockers, such as nifedipine, may be the treatment of choice in the management of hypertensive patients treated with MAOIs.[27] Nifedipine has an onset of action in less than five minutes, peaks in 20 minutes, and lasts three to five hours. After oral administration, the onset of action is approximately 20 minutes, with peak effect in 45 minutes. The dosage is 10 to 20 mg, and the drug is readily available in most emergency rooms. Side-effects, including hypotensive overshoot and reflex tachycardia, are unusual.

Chart 2
Side-Effects of Monoamine Oxidase Inhibitors

Most frequent side-effects
Orthostatic hypotension with dizziness
Weight gain, edema
Sexual dysfunction
Other side-effects
Insomnia
Daytime sedation
Myoclonus
Uncommon but serious toxicities
Hypertensive crises
Drug interactions with the MAOI-CNS syndrome

Orthostatic Hypotension

Mechanism. Orthostatic hypotension is the most common MAOI side-effect. The hypotension associated with MAOIs usually occurs three to four weeks after treatment initiation and is thought to be related to the inhibition of the normal breakdown of tyramine. This excess tyramine undergoes β-hydroxylation to form a "false neurotransmitter," which is stored in nerve terminals. This transmitter has little adrenergic activity, resulting in decreased sympathetic outflow.[28]

Management. It is essential to inform the patient and to be aware of the possibility of hypotension, as it is easy to forget about a potential problem occurring so late in treatment. Dizziness, weakness, faintness, or light-headedness upon standing are typical symptoms. Reassurance with instructions to rise slowly from a lying or sitting position to a standing position may be all that is required. Mild symptoms frequently resolve over time.

If the problem continues, contributing factors, such as dieting, a low-salt diet, dehydration, diuretics, antihypertensive drugs, and hypothyroidism, should be corrected. The next procedure might be to alter the schedule of medications by prescribing a divided dose or all medication at bedtime, or if possible, lowering the dose slightly.

Elastic support stockings are effective, but limited in use because of the expense, inconvenience of having them fitted, and refusal by most male patients to wear them. Others suggest that drinking tea or coffee throughout the day may be helpful. When all of these measures are insufficient, volume expanders, such as salt tablets or fludrocortisone (Florinef), have proven helpful.[29] The dose of salt tablets is 600 to 1800 mg twice a day, or fludrocortisone in dosages less than 0.5 mg/day. The use of salt or mineralocorticoids is, of course, contra-indicated in several concomitant medical disorders. In an otherwise healthy young depressive, this may relieve the problem.[28]

Sexual Dysfunction

Mechanism. Sexual dysfunction, quite separate from the decreased libido associated with depression, can occur with MAOIs. Orgasmic and ejaculatory capacity are more often affected than arousal.[30] Possible mechanisms by which antidepressants affect sexual

function include anticholinergic activity, changes in adrenergic tone, or changes in CNS serotonin levels.

Management. The most important point in the management of sexual dysfunction is to inquire about it. Patients may discontinue treatment due to sexual difficulties (perhaps without telling their physician). Some patients will be reassured if they understand what problems can be expected and that these side-effects may fade over time. It is important to reassure patients that these changes are reversible. Some suggest that tranylcypromine produces less anorgasmia and impotence than phenelzine.[24,31]

Other methods of treatment include bethanechol (Duvoid, Urecholine), a cholinergic drug, and cyproheptadine, a serotonin antagonist. Starting with doses of bethanechol, 10 mg t.i.d., and increasing by 30 mg every day to 100 mg/day, may resolve the problem in a short time.[32] Cyproheptadine in dosages of 4, 8, or 12 mg b.i.d. can produce normal sexual responsiveness. Some patients have found that, instead of regular doses, they need only to take the cyproheptadine one to two hours before intercourse.[33]

Weight Gain and Peripheral Edema

Mechanism. Weight gain is a common side-effect of many antidepressant treatments, and it is unclear which mechanisms are involved. It may be due to an increase in appetite, fluid retention, histamine blockade, changes in glucose metabolism, or hypothalamic dysfunction.[34]

Management. Dietary considerations to reduce carbohydrates and fat intake with regular exercise should be encouraged. Edema can be treated with diuretics and careful monitoring of electrolytes. In some cases, switching from phenelzine to tranylcypromine can help reduce weight gain, but often there is no suitable treatment.

Hypomania

Mechanism. Hypomania is often described as a side-effect of tricyclic antidepressants and MAOIs, although it is not clear that the incidence of this reaction is greater than what one would expect from the natural history of the illness. The overall incidence of hypomania in unipolar patients is approximately 10% for patients treated with tricyclic antidepressants and MAOIs, but is much higher for bipolar patients (up to 60%).[31] The onset of hypomania occurs anywhere from two to 28 weeks after initiation of treatment.

Management. The initial treatment of hypomania is dose reduction. If this treatment is unsuccessful, the drug could be discontinued or lithium added.

Insomnia

Mechanism. Insomnia is commonly reported with MAOIs, especially if most of the dose is given in the evening. Monoamine oxidase inhibitors interfere with and suppress rapid eye movement sleep. Rapid eye movement rebound associated with vivid dreams is observed about 10 days after withdrawal of MAOIs.

Management. Attempts should be made to modify the dose schedule so that most of the drug is given in the early part of the day. Dose reductions, if feasible, may alleviate the problem. Recent reports suggest that the more sedative antidepressant trazodone, prescribed in low bedtime doses, can alleviate MAOI-induced insomnia.[35]

Myoclonus, Paresthesias

Mechanism. Monoamine oxidase drugs produce neuromuscular effects that range from muscle tension and twitches to myoclonic jerks. They more commonly occur during rest, sleep onset, and sleep. These effects occur after at least two weeks of treatment and appear to be dose related. Proposed mechanisms include an increased serotonergic tone and central disinhibition.[36] One study suggests that numbness, paresthesias, and "electric shock" sensations are caused by pyridoxine deficiency.[37] This condition usually develops over six to eight weeks of treatment.

Management. Myoclonic jerks may respond to a simple decrease in the dosage of MAOIs. Pyridoxine, in doses of 150 to 300 mg/day, is inexpensive, is benign, and may be helpful for paresthesias and "electric shock" sensations.

Daytime Sedation

Mechanism. Fatigue and daytime drowsiness occur in some patients. Although the exact mechanism is unknown, speculation includes a hypoglycemic type of reaction.

Management. Modification of the dosage schedule or reduction in the dose may alleviate the problem. For some patients this side-effect fades over time.

Additional Side-Effects

Uncommonly reported adverse reactions from MAOIs include skin rashes, photosensitivity, leukopenia, lupus-like syndrome, mouth sores, inappropriate antidiuretic syndrome, altered prolactin secretion, and hepatotoxicity.

New Developments

MAOIs and Tricyclic Antidepressants

Recent studies and reviews indicate that combined treatments are safe and effective in patients unresponsive to either class of drug alone and may be useful for refractory depressions.[38] Both drugs should be started together or the MAOI gradually added to the tricyclic in low doses. Tricyclic antidepressants should not be added without a seven-day washout period if a patient is already receiving an MAOI. Interactions have caused hyperthermia, agitation, delerium, convulsions, and coma. It is recommended that clomipramine not be the tricyclic used in this combination. Further, this combination should be undertaken only with the supervision or direction of a skilled psychopharmacologist.

MAOIs and Lithium and Other Drugs

Monoamine oxidase inhibitors have been safely combined with lithium, neuroleptics, and benzodiazepines. Methylphenidate and amphetamine should be avoided because they increase the risk of hypertension. Some research indicates that the addition of lithium in patients who do not respond to MAOIs may convert these patients to drug responders.[39]

Selective MAOIs

The selective irreversible MAOI-A clorgyline (not available in Canada) is an effective antidepressant,[40] although it offers no particular advantages over non-selective agents. The selective irreversible MAOI-B deprenyl appears to have benefit in conditions with dopamine deficits, such as Parkinson's disease.[41]

The selective reversible MAOI-A compounds (meclobemide, brofaromine) have antidepressant activity[42] and are in phase II and III trials in Canada today. Their reversibility results in little tyramine potentiation[43] and little reported risk of hypertensive episodes.

This, in theory, could make them safer and easier to use.

Conclusion

There is substantial evidence that MAOIs are effective antidepressant drugs. When proper dietary precautions are followed, the risk of hypertensive crises is low, making these drugs safer than previously thought. One is often able to manage other side-effects with a variety of interventions. Monoamine oxidase inhibitors may be particularly useful in patients who cannot tolerate the anticholinergic side-effects of tricyclic agents and in an increasing number of psychiatric and non-psychiatric disorders. ■

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