DRUG REVIEW

Tranylcypromine: Its Pharmacology, Safety, and Efficacy

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Tranylcypromine is a monoamine oxidase inhibitor that should be considered in patients with refractory depressive symptoms, particularly those with ECT-resistance or atypical features. This article reviews tranylcypromine's pharmacology, interactions, efficacy, and side effects.

Monoamine oxidase inhibitors (MAOIs) are efficacious drugs for the treatment of depression (1). After the advent of MAOIs in the early 1950s, their use fell in the decades that followed because of concerns over adverse effects (2). Misconceptions regarding the safety profile, efficacy, and tolerability of MAOIs played a sizable role in the shift in perception of these drugs (3). This review will focus on tranylcypromine, particularly its pharmacology, efficacy, and side effects.

REVIEW OF PHARMACOLOGY

Based on their biochemical structure, MAOIs can be subclassified into hydrazine (phenelzine and isocarboxazid) and nonhydrazine (tranylcypromine and selegiline) compounds. All nonselective MAOIs act via irreversible inhibition of monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B), enzymes responsible for the catabolism of various neurotransmitters (Table 1). At higher doses, tranylcypromine also acts as a norepinephrine reuptake inhibitor and weak dopamine releaser. This means that tranylcypromine itself may attenuate tyramine reactions, because tyramine reuptake occurs via the norepinephrine transporter (4). Tranylcypromine has a half-life of 2 hours and inhibits CYP2A6 at standard doses (5) (Table 1).

CLINICAL EFFICACY

A recent meta-analysis of predominantly double-blind randomized trials demonstrated that tranylcypromine has efficacy superior to placebo and comparable to other psychotropics (namely other MAOIs and tricyclic antidepressants [TCAs]) (6). The authors noted, however, that randomized controlled trials have not been done comparing tranylcypromine to agents "introduced after 1985, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, mirtazapine, trazodone, bupropion or agomelatine."

Treatment-Resistant Depression

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study was a four-step, multicenter randomized trial of antidepressant efficacy for depressed outpatients. All patients were first treated with citalopram, with nonremitters advancing to other treatments. The low response rate to tranylcypromine in STAR*D has been cited as evidence for its lack of efficacy. Some have argued that by having tranylcypromine in the final step, the prevalence of "biologically responsive" depression and, hence, the likelihood of treatment response would be low among the final sample (7). In other words, the generalizability of this finding is limited because tranylcypromine may theoretically have shown superior response rates had it been included earlier in the study design.

Further, the dose of tranylcypromine needed for difficult-to-treat populations may be significantly higher than the doses used in STAR*D (mean of 36.9 mg/day) (6). A recent study of 28 patients with treatment-resistant depression found that 25% of patients remitted with standard doses and 21% remitted with higher doses (mean of 56 and 105 mg/day, respectively) (8). Notably, several remitters had previously failed bilateral ECT, indicating that tranylcypromine may be an option before ECT or after ECT has failed. Another important finding is that the number of prior treatment failures was not statistically correlated with response to pharmacotherapy with tranylcypromine.

Atypical Depression

Atypical depression is a subtype of depression characterized by mood reactivity, interpersonal rejection sensitivity, leaden paralysis, increased appetite, and hypersomnia. There is evidence that individuals with atypical depression may have high activity of MAO, which may explain the unique efficiency of MAOIs for this subclass (9). Currently, three controlled trials have displayed superior efficacy of tranylcypromine over either placebo or imipramine for atypical depression (6).

TABLE 1. Monoamine oxidase inhibitor (MAOI) isoforms: tissue localization and substrates[a]

Enzyme	Distribution		Substrate			
Isoform	Brain	Gut	5-HT	NE	DA	Tyr
MAO-A	Yes	Yes	Yes	Yes	Yes	Yes
MAO-B	Yes				Yes	

[a] 5-HT, serotonin; NE, norepinephrine; DA, dopamine; Tyr, tyramine.

STARTING PATIENTS ON TRANYLCYPROMINE

For drugs that are serotonin reuptake inhibitors, a washout, or medication-free, period of five half-lives is required to prevent serotonin toxicity. For most drugs that inhibit serotonin reuptake this equates to approximately 1–2 weeks, but drugs with longer half-lives require more time (e.g., approximately 5 weeks for fluoxetine). When starting tranylcypromine, a complete washout of all psychiatric drugs is usually recommended. However, experts may choose to bridge with or continue certain medications when appropriate. The usual starting dose is 10–20 mg/day up to a Food and Drug Administration (FDA)-approved range of 30 to 60 mg/day in divided doses (1). Although the upper limit of the FDA-approved dosage range of tranylcypromine is 60 mg/day, studies have examined the use of higher doses in patients with treatment-resistant depression.

AUGMENTATION STRATEGIES

Drug Interactions

Before considering augmentation of tranylcypromine with another agent or vice versa, it is important to understand potentially life-threatening pharmacodynamic interactions. Serotonin toxicity can occur with coadministration of tranylcypromine with serotonin reuptake inhibitors (e.g., SSRIs, serotonin–norepinephrine reuptake inhibitors, clomipramine, imipramine, and ziprasidone). Psychiatric drugs that lack serotonin reuptake inhibition can be coadministered with tranylcypromine safely (4). Other drugs to advise patients to avoid are those with adrenergic activity, such as decongestants (e.g., phenylephrine or pseudoephedrine), which may cause synergistic blood pressure elevation with tranylcypromine (5). As a rule, patients should be counseled to always consult their provider before starting a new drug, because some may secondarily inhibit serotonin reuptake (e.g., certain antihistamines, such as chlorpheniramine, or narcotic analgesics, such as tramadol) (4).

Antidepressants and Mood Stabilizers

TCAs (excluding clomipramine and imipramine) can be safely added to tranylcypromine, although tolerability may be limited by their anticholinergic and anti-alpha side effects (10). Notably, a recent retrospective cohort study found that ECT nonresponders (N=25) treated with tranylcypromine and amitriptyline did not have a recurrent major depressive episode during follow-up (mean of 9.37 years) (11).

Studies have also examined supplementation with bupropion, trazodone, and lithium. Case studies on bupropion augmentation have found it to be effective, without reports of blood pressure elevation (12, 13). Studies examining trazodone supplementation for insomnia have found low doses to be both safe and effective (10). Lithium has been used to augment partial response or for mood stabilization in bipolar depression without reported complications (14).

Stimulants

Stimulants may be carefully administered by experts with slow titration and close blood pressure monitoring (5). The major risks of stimulant augmentation include blood pressure elevations and drug-induced psychosis (however, the latter was reported in an aforementioned study that supplemented high-dose tranylcypromine with doses of dextroamphetamine as high as 15 mg b.i.d.) (8).

ADVERSE EFFECTS

As a class, MAOIs display variation in their side-effect profiles. Hydrazine MAOIs are associated with weight gain and sexual dysfunction that may limit their tolerability. Phenelzine and isocarboxazid have been associated with pyridoxine deficiency or hepatotoxicity. In contrast, tranylcypromine is not frequently associated with weight gain or sexual dysfunction. Commonly reported side effects of tranylcypromine include dry mouth, insomnia, and overexcitement; however, these may attenuate or disappear with continued use (15, 16) (Table 2).

Effects on Blood Pressure

The most frequently cited side effect of tranylcypromine is dizziness as related to its orthostatic effects (6). Slow titration, divided dosing, and dose adjustments may be needed for patients sensitive to orthostasis caused by tranylcypromine (17). Less commonly, patients may experience a transient increase in blood pressure approximately 1–2 hours after dosing that may cause symptomatic discomfort. Coadministration of amlodipine or divided dosing can mitigate this side effect (propranolol can be used in place of amlodipine as well) (8). Predose and post-dose blood pressure measurements are useful for patients on tranylcypromine, given its variable effects on blood pressure.

Tyramine Reaction

Tyramine is an amino acid found in select food products, particularly those that are fermented or spoiled (4). MAOIs inhibit tyramine breakdown due to incidental inhibition of MAO in the gastrointestinal tract. When unmetabolized tyramine enters nerve terminals, it triggers the release of norepinephrine, which can cause dangerous blood pressure elevations (5). Tyramine levels were histori-

TABLE 2. Adverse effects of irreversible nonselective monoamine oxidase inhibitors

Drug	Side effect	Comments
Nonhydrazine		
Tranylcypromine	Orthostasis, dizziness, dry mouth, insomnia	Inhibits tyramine catabolism, associated with transient post-dose hypertension
Hydrazine		
Phenelzine	Orthostasis, dizziness, weight gain, sexual dysfunction, edema, sedation	Inhibits tyramine catabolism, has been associated with hepatotoxicity, potential risk for pyridoxine (B6) deficiency, CYP 2C19 and 2B6 inhibition
Isocarboxazid	Orthostasis, dizziness, weight gain, sexual dysfunction, edema	Inhibits tyramine catabolism, potential risk for hepatotoxicity, potential risk for pyridoxine (B6) deficiency

cally a limitation to the use of MAOIs; however, advances in food storage and hygiene have led to significantly lower concentrations of tyramine (4). Nonetheless, patients should still limit or avoid certain products known to carry high levels of tyramine.

Blood pressure elevations related to tyramine ingestion are usually mild and self-limiting, unless a substantial quantity of tyramine has been consumed (18). Experts generally do not recommend self-management with antihypertensives (1, 4). Although sometimes prescribed, sublingual nifedipine in particular carries significant risks (e.g., cerebral hypoperfusion) that may outweigh the risks of transient hypertension in milder cases of tyramine ingestion (1). Benzodiazepines are likely a safer temporizing measure and may be considered for emergency use; however, symptomatic patients with significant blood pressure elevations or signs of end-organ damage still require emergency medical attention (4).

CONCLUSIONS

Tranylcypromine is an efficacious antidepressant medication that may be considered earlier in the course of treatment for patients who have failed first- and second-line options based on a number of considerations (e.g., ability to adhere to diet, severity and duration of illness, and presence or absence of atypical features). In particular, patients who have failed trials of multiple medication classes or ECT may stand to benefit greatly from treatment with tranylcypromine. Given the high risk of suicide and continued loss of quality-adjusted life years among patients with treatment-resistant depression, providers should be mindful of the potential utility of tranylcypromine in providing relief to this population.

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KEY POINTS/CLINICAL PEARLS

- Tranylcypromine can be effective in severe depression, even when ECT has failed.
- In contrast to hydrazine MAOIs, tranylcypromine is not associated with significant weight gain, sexual side effects, hepatotoxicity, or pharmacokinetic interactions.
- For patients treated with tranylcypromine, ambulatory blood pressure monitoring is useful for postural hypotension, post-dose hypertension, or tyramine reactions. The risks of sublingual nifedipine may outweigh the risks of hypertension from ingestion of tyramine. The pressor response is self-limiting and can be managed more conservatively with benzodiazepines, if needed.
- Concomitant administration of tranylcypromine with any drug that exhibits serotonin reuptake inhibition is strictly contraindicated. Caution is warranted before administration of any drug or anesthetic with MAOIs, as certain drugs may secondarily inhibit serotonin reuptake. Prior to starting tranylcypromine, a washout of a minimum of five half-lives of a serotonin reuptake inhibitor drug is required to prevent serotonin toxicity.

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