

MAOI Antidepressants:

A History Being Rewritten

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*The one great duty we owe to history
is to rewrite it.*

—Oscar Wilde

This invited commentary has been prepared by members of the International MAOI Expert Group (www.imaoi.org). The historical use of classic monoamine oxidase inhibitors (MAOIs) is overviewed, with consideration given to their efficacy and safety before we underscore the importance of reassessing their place in current treatment algorithms.

Were they to be discovered today, MAOIs would probably be described as a major advance in psychiatric treatment—yet they are rarely used in current practice. Their regrettable marginalization is a testament to the enduring influence of their complicated early history and misconceptions of safety and the marketing of newer agents positioned as of equivalent or even superior effectiveness.

Introduced in the 1950s as the first pharmacologic treatments for depression, initial clinical reports of MAOIs documented impressive remission rates in severely depressed patients, including nonresponders to electroconvulsive therapy (ECT).¹ When MAOIs first became commercially available, clinical observations reinforced the findings that the nonselective and irreversible MAOIs that are still in use—tranylcypromine, phenelzine, isocarboxazid (and more recently transdermal selegiline)—were highly effective agents for depressive disorders, especially for the melancholic and atypical

variants,² and for some anxiety disorders.³

Nonetheless, by the end of the 1970s, prescription rates for the MAOIs began to fall as a reflection of two factors. First, ongoing fears concerning the “cheese reaction” (tyramine-induced hypertension) and interactions with other drugs⁴ (addressed below). Second, influential but methodologically flawed trials that employed insufficient doses (eg,^{5,6}), thus eroding physician confidence in MAOI efficacy. When tricyclic antidepressants and, later, the selective serotonin-reuptake inhibitors entered the market, they were heavily marketed as safer than MAOIs, easier to use and equally effective, while MAOIs were increasingly characterized as “dangerous” and outdated and thus became widely regarded as treatments of last resort—if prescribed at all.

The intervening decades have clarified the pharmacology underlying interaction risks with MAOIs. Serotonin toxicity, misleadingly labeled as “serotonin syndrome,” is now understood to be a predictable and dose-dependent toxidrome.⁷ It occurs only when an MAOI is combined with a potent serotonin reuptake inhibitor or serotonin releaser.⁸ When adequate drug washout intervals (5 half-lives of the relevant agent)⁹ are respected, and contraindicated combinations are avoided, there is no risk of serotonin toxicity.

Similarly, tyramine-induced hypertension is no longer the unpredictable hazard it once seemed. Contemporary tyramine assays have shown that the implementation of modern food production and

processing standards have greatly lowered tyramine levels compared to those measured in the 1960s. We also have better evidence to reliably guide dietary advice. As a result, the risk of adverse sequelae of transient hypertension is both less severe and less significant than previously believed.¹⁰

Consequently, current pharmacologic appraisal places MAOIs firmly within acceptable risk parameters for routine psychiatric practice,⁹ particularly in the context of the significant morbidity and mortality associated with inadequately treated and otherwise refractory depressive illnesses.

Despite these advances, worldwide use of MAOIs continues its precipitous decline, owing to several factors. Pharmaceutical companies focus on promoting the “new,” often more expensive drugs under patent rather than the “old” generic antidepressants, leading to the decreased manufacturing of MAOIs. In some countries, insurers or health care agencies add prior-authorization hurdles, or allow national formularies to omit MAOIs, leading physician training programs to provide little educational exposure to the competent use of MAOIs—all factors perpetuating a self-reinforcing cycle of loss of interest and use.

A significant consequence is that patients with severe, treatment-resistant depression may receive ECT or multiple rounds of comparatively ineffective newer drugs without ever being offered the option of an MAOI—a drug class with more than 60 years of proven efficacy.

Regrettably, recent advances in MAOI research have not yet permeated

psychiatric teaching and practice adequately, so that their side effects remain misunderstood or overstated. For example, orthostatic hypotension is dose-related, common, and transient; insomnia can be managed with gradual dose escalation and add-on pharmacotherapy and may abate over time; weight gain is a notable issue with hydrazine MAOIs but typically absent with tranylcypromine (or transdermal selegiline).⁹ Expert consensus confirms that, under contemporary dietary guidance, serious hypertensive events are now so rare as to be virtually absent.¹⁰ For the sake of our patients, it is imperative that modern knowledge prevails over historical misinformation and outdated beliefs. Updated interaction monitoring software that correctly flags (un)safe combinations would be a useful aid in this endeavor.

Fortunately, the unique efficacy of MAOIs is regularly reinforced in specialist affective disorder services, where patients with long illnesses and multiple failed treatment attempts commonly improve in a few weeks on an MAOI. We need to disseminate these messages of hope and facilitate their greater translation into routine care.

However, because MAOIs entered the pharmacopeia prior to the current randomized controlled trial (RCT)-focused paradigm to evaluate drug efficacy, another notable barrier to their use at present is an overreliance on evidence hierarchies that assign uniquely superior status to RCTs. Because organizing new drug trials is commercially implausible for off-patent drugs like MAOIs, this has created a frozen and distorted evidence base, whereby absence of contemporary standard RCT-validated proof is misinterpreted as proof of inefficacy. We note, however, that MAOIs coexist with many agents discovered decades ago that have entered practice without an evidence base comparable to modern standards. Nevertheless, there is an overt need for contemporary MAOI studies to address this gap.

More broadly, the primacy of RCTs in evidence hierarchies has been the subject of criticism, including by Louis Lasagna, a leading clinical pharmacologist who played a pivotal role in advocating for RCT-based drug approval standards at the US Food and Drug Administration, but later cautioned against overreliance on them. Reflecting on his earlier work, he remarked, “In contrast to my role in the 1950s, which was trying to convince people to do controlled trials, now I find myself telling people that it’s not the only way to truth.”¹¹

He echoed the concerns of Bradford Hill, who in his 1965 Heberden Lecture observed: “If one came to the conclusion that the only way to find out the truth about a medication was to use a controlled clinical trial, it would mean, not that the pendulum had swung too far, but that it had come completely off its hook.”¹²

Such perspectives reinforce the logic and need for a more inclusive and broad-based evidentiary framework, especially when assessing older treatments with extensive long-term real-world data underscoring their effectiveness. Ideally, a worldwide evidence database for MAOI efficacy in clinical practice should be established (including practice-based registries and observational effectiveness studies).

There are pitfalls in attempting to reconcile research findings from recent and preceding decades. Head-to-head comparisons and network meta-analyses¹³ tend to suffer from inconsistent diagnostic criteria among included cohorts and from lumping classic MAOIs with the less effective selective MAO-A inhibitors.¹⁴ A reappraisal of decades-long clinical experience from tertiary care settings and independent experts is essential to recognizing that newer pharmacotherapies have not made MAOIs obsolete. Moreover, recent retrospective studies have shown encouraging results mostly in refractory patients,¹⁵ which reinforces the lessons gleaned from extensive practical experience.

We suggest that rational treatment algorithms should therefore consider

MAOI treatment as a viable option after failure of 2 antidepressants from differing classes, rather than relegating it to last-line status after invasive or experimental interventions. They should also be considered for treatment-resistant depressive conditions prior to introducing ECT, given their comparative side effect profiles.¹⁶ Moreover, MAOIs can be safely coadministered with ECT¹⁷ and may offer adjunctive clinical benefits.

We thus emphasize the need for renewed attention to the classic MAOIs in clinical practice and research.¹⁸ This brings us back to the opening quote by Oscar Wilde: “The one great duty we owe to history is to rewrite it.”

With prescription rates dwindling and consumer costs soaring, the coming years will prove pivotal in determining whether MAOIs will fade away entirely, forgotten by most or ill-remembered—it is unclear which is worse. The last generation of psychiatrists with extensive experience using these drugs has entered the twilight phase of their careers. Our International Expert Group receives increasingly frequent reports of patients who cannot find a doctor willing to prescribe an MAOI, even after many years of unresolved depressive symptoms and a multitude of failed treatment regimens. Other prospective patients have no access to an MAOI on their national drug market, and others still cannot (or can no longer) sustain the ever-mounting cost of treatment.

There is no great singular answer we can offer here to reverse the anti-MAOI trend, which will and has cost lives. Reclaiming the legacy of MAOIs demands that clinicians and policymakers reassess historical biases, so that clinical knowledge prevails over bias and inertia—notwithstanding that a new generation of MAOI trials conducted to contemporary standards would be a major contribution. These could involve standard RCT procedures assessing efficacy but should certainly involve real-world effectiveness

studies, which have a greater capacity to identify both their effectiveness and clinical niches.

A future-oriented psychiatry must ensure that yesterday's misconceptions do not dictate tomorrow's prescriptions.

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