Tricyclic Antidepressants and Monoamine Oxidase Inhibitors: Are They Too Old for a New Look?

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Abstract

Through unintentional discovery, monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) were the first antidepressant classes to be used clinically and have been widely available for over half a century. From the 1950s to the 1980s, these two classes of antidepressants were the sole antidepressant tools available to psychiatrists. With the advent of the selective serotonin reuptake inhibitors (SSRIs) in the 1980s and 1990s, the prescribing of the MAOIs and TCAs has fallen significantly worldwide. In this chapter, we take a closer look at the arc of MAOI discovery and clinical use, and how these two classes of drugs compare to each other. This is important because relatively few studies compare these older classes of drugs to the newer classes of antidepressants. Finally, we

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argue that TCAs, and particularly MAOIs, should continue to play an important role in the modern treatment of depression, especially in the treatment-resistant patient.

Keywords
Antidepressant classes · Major depression · Monoamine oxidase inhibitors · Prescribing considerations · Psychopharmacology · Treatment-resistant depression · Tricyclic antidepressants

1 Historical Background

The "golden age" of psychopharmacology of the 1950s saw the serendipitous discovery of two distinct classes of psychotropic medications, monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). This was a critical period for psychiatry as the field was experiencing a paradigm shift with the emergence of the "medical model" of psychiatric illness (i.e., that psychiatric illnesses consisted of reliably identifiable symptoms that could respond to somatic treatments).

The systematic use of hydrazine compound derivatives as antidepressants may have occurred in the early 1950s, but the original concept of using such compounds dated back to the research laboratories of Emil Fischer as early as the 1870s. While Emil Fischer went on to synthesize phenyl hydrazine a few years later, the drug appeared largely dormant in terms of its research and clinical use over the next four decades. In the early 1950s, its use as a prominent therapeutic modality was better elucidated. The antituberculosis drug iproniazid, with known MAOI properties, is credited with the first documented case of serotonin syndrome in a patient treated for tuberculosis in the mid-1950s. The observed mood benefits, which were an accidental finding, planted the seed for the first antidepressant in the 1950s. As one observer noted:

> Patients were dancing in the halls tho there were holes in their lungs. – Observation of tuberculosis patients receiving iproniazid at the Sea View Hospital, NY, 1953 (Sandler 1990).

The effects of this random discovery were monumental with close to half a million early adopters within the first year. Though touted as a "psychic energizer," the fall of iproniazid was heavily influenced by liver toxicity and hypertensive crisis, which significantly dampened enthusiasm for the drug's clinical use. However, the overall development of MAOI antidepressants in this time period arguably became a cornerstone in psychopharmacology, inspiring numerous advancements that followed.

Unlike MAOIs, the TCAs were a novel class of drugs created by modifying the phenothiazine ring and substituting sulfur for an ethylene bridge. It was the search for better antipsychotic drugs, following the relative success of chlorpromazine, that led clinicians and researchers down the path to the development of imipramine, the prototypical TCA, which was subsequently FDA approved in 1959. At that time,

the mechanism of action of imipramine was unknown, and it was classified based on the drug's benzene ring, in contrast to current antidepressant nomenclature, which classifies medications based on their actions on specific neurotransmitter systems (Hillhouse and Porter 2015). Though imipramine failed as an antipsychotic, patients had significant mood benefits. In his famous 1958 essay, Kuhn described the differences noted in psychiatric patients receiving imipramine:

> The patients get up in the morning of their own accord, they speak louder and more rapidly, their facial expression becomes more vivacious. They commence some activity on their own, again seeking contact with other people, they begin to entertain themselves, take part in games, become more cheerful and are once again able to laugh. (Kuhn 1958).

In the 1960s, Sulser and Axelrod converged on the idea that both TCAs and MAOIs exerted their therapeutic effects by increasing synaptic serotonin and catecholamine concentrations. This in turn set the stage for an era of rational drug development with newer medication classes targeting specific neurotransmitter classes across a multitude of sites (Ramachandraih et al. 2011).

In the coming years, newer MAOIs (i.e., isocarboxazid, phenelzine, and tranylcypromine, referred to as the "classic MAOIs") emerged with higher potency and fewer side effects relative to iproniazid. The classic MAOIs, along with selegiline, are currently the four FDA-approved MAOIs in the USA. The use of selegiline for depression is relatively recent: it was initially restricted to Parkinson's disease, but over time lower dose selegiline transcutaneous patches (e.g., Emsam) have demonstrated therapeutic benefit for depressive symptoms, while bypassing dietary restrictions with fewer side effects.

Historically, MAOIs were classified either by chemical structure (e.g., hydrazine versus non-hydrazine [tranylcypromine]), or through receptor isoform selectivity (MAO-A, MAO-B, or both), as well as their reversibility (reversible or irreversible) (Thase et al. 1995). Two MAO receptor isoforms, MAO-A and MAO-B, were identified with the older drugs irreversibly inhibiting both isoforms. It was later shown that selective blockade of MAO-A alone also offered similar therapeutic benefits compared to inhibition of both MAO-A and MAO-B. Adrenaline, noradrenaline, and serotonin are deaminated through MAO-A receptors, whereas benzylamine and B-phenylethylamine are substrates for MAO-B receptors. Dopamine and tyramine use both isoforms. This encouraged the search for both reversible and selective MAO-A inhibitors for depression and MAO-B for Parkinson's disease.

2 Studies Comparing MAOI and TCA Antidepressants: Do Certain Subtypes of Depression Respond Selectively to One Class of Antidepressant?

Compared to placebo, MAOIs and TCAs have consistently demonstrated superior treatment of depressive symptoms both in terms of response and remission, respectively, defined as a Hamilton Depression Rating Scale (HDRS) improvement of 50%

in depressive symptoms and a score of less than or equal to 7. Initially, there were relatively few studies comparing the efficacy of MAOIs and TCAs; these early studies pointed to TCAs having an efficacy advantage over MAOIs. However, subsequent studies demonstrated superior efficacy of the MAOIs, especially in depression with atypical features (Lecrubier and Guelfi 1990).

More recent studies focused on individual drugs within these two classes. Rowan et al. (1982) looked at the efficacy of phenelzine and amitriptyline compared to placebo for neurotic depression and found similar effect sizes, both demonstrating a significant improvement over placebo. The same studies also inferred that both phenelzine and amitriptyline improved symptoms of depressed mood and content of thought; phenelzine fared better for anxiety symptoms, and amitriptyline was superior at improving anergia. The authors also concluded that MAOIs may be a preferred class of medications for comorbid anxiety and depression (Rowan et al. 1982).

Thase et al. (1995) conducted a systematic review, which compared the efficacy of the three classic MAOIs between 1959 and 1992. This review of 55 randomized controlled trials (RCTs) included 36 RCTs involving MAOIs versus placebo and 44 RCTs involving MAOIs compared to one another. The authors found an estimated response rate of phenelzine to be 54.3% (±9.6%) in placebo-controlled studies; further, phenelzine demonstrated a small advantage over TCAs among outpatient studies, a gap that closed significantly when the sample of atypical depression was removed from the analysis.

As a result, the scientific community arrived at a consensus that atypical depression was a separate, distinct clinical presentation of major depressive disorder (MDD), which was then reflected in the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association 1994). Overall, studies from this era consistently demonstrated MAOIs to have superior clinical efficacy in this atypical subtype of depression.

Though the MAOI's appeared to be superior for atypical depression, imipramine, the prototypical TCA, had greater antidepressant efficacy in hospitalized, depressed patients than phenelzine (Martin 1963). In contrast, other TCA versus MAOI (imipramine versus phenelzine) studies in psychiatric inpatients found comparable efficacy at higher doses of phenelzine (Davidson et al. 1981). These differences could largely be explained by dose discrepancies, study design as well as study duration. For example, the target phenelzine dose was 81 mg/day; subsequent studies have determined this to be a reasonably effective dose among outpatients as well.

In 1992, Thase et al. (1992) published an open-label study with 60 patients who had failed a trial of imipramine (mean maximum dose of 260 mg), who were then treated with either phenelzine (60 mg/day) or tranylcypromine (38.5 mg/day). This study found that 58% of those failing to respond to imipramine responded to the MAOIs, with significant reversal of neurovegetative symptoms. In particular, the majority of the patients who received tranylcypromine experienced reversal of anergia. While the amphetamine-like properties of tranylcypromine are known to be more activating than phenelzine, it is unclear if this propensity had a significant

bearing on drug selection at the time of the study. Finally, another trial (Thase et al. 1995) further compared the four FDA-approved MAOIs from five previously published RCTs but could not conclude relative efficacy of one over another. However, the relative superiority of certain target symptoms, such as melancholia and anergia, favored tranylcypromine, whereas patients with anxious depression responded better to phenelzine (Thase et al. 1995). This symptomatic distinction is likely critical in identifying which depressed patients are most appropriate for a specific MAOI. Failure to do so may contribute to worsening of certain target symptoms, leading to potential MAOI discontinuation, biasing the perception of the relative ineffectiveness of this drug class.

A review of MAOIs by Quitkin et al. (1979) detailed the use of phenelzine in "non-endogenous depression." This depressive presentation terminology is not typically used in modern psychiatry: the authors defined endogenous depression as, "disabling depressive symptomatology," "anxious depressives," and a "concoction of anxiety with mild neurotic symptoms similar to the anxious hysteria" (Quitkin et al. 1979). In this trial, patients with non-endogenous depression who had previously failed TCAs or benzodiazepines were randomized to phenelzine at doses ranging between 45 and 75 mg/day or placebo. The phenelzine group had significant improvement in mood symptoms, anxiety, hypochondriasis-agitation as well as change in psychomotor status. A subsequent study by Robinson et al. (1978) reaffirmed these findings and inferred that response to phenelzine occurred most in patients with non-endogenous depressive symptoms at daily doses greater than 30 mg. The literature consensus of this era supported a significant benefit of both MAOIs and TCAs over placebo (Davidson et al. 1981; Himmelhoch et al. 1982; Rowan et al. 1982; Liebowitz et al. 1984; Paykel 1995; Birkenhager et al. 2004).

In summary, studies that compared TCAs to MAOIs did not offer a clear therapeutic distinction favoring either class; however, both classes of medications demonstrated convincing antidepressant efficacy in comparison to placebo. Studies did highlight possible niche uses of the two classes, with atypical depression and depression comorbid with personality disorder, or perhaps severe anxiety, being slightly more responsive to MAOIs, and TCAs offering an edge over MAOIs in hospitalized depressed patients. However, in general, these distinctions are no longer considered when discerning the class or type of medication initiated to treat depression.

3 More Recent Studies of Tricyclic Antidepressants and Monoamine Oxidase Inhibitors

Since the 1980s, there has been a paucity of literature comparing MAOIs to TCAs. One study by Liebowitz et al. (1984) compared phenelzine to imipramine in atypical depression in a double-blind, randomized placebo-controlled trial ($N = 60$) and demonstrated significantly higher response rates with phenelzine (67%) compared to imipramine (43%) or placebo (29%). Atypical depression included histrionic or labile symptoms and, along with borderline personality, was measured using the

Schedule for Affective Disorder and Schizophrenia rating scale (SAD-C) as well as the 90-item Hopkins Symptoms Checklist (SCL-90). Outcome measures were determined using the Clinical Global Impression-Improvement Scale (CGI-I), SAD-C, SCL-90, and Hysteria-Dysphoria Symptoms ratings (HDS; extracted from the SAD-C). Notably, imipramine did not perform better than phenelzine on any of the primary or secondary outcome measures (Liebowitz et al. 1984). While the preliminary report was published in 1984, the final report in 1988 outlined four broad atypical features including hyperphagia, hypersomnolence, leaden feeling, and rejection sensitivity.

Birkenhager et al. (2004) conducted a 5-week, inpatient, randomized trial comparing phenelzine to tranylcypromine in 77 patients who met DSM-IV criteria for MDD and had failed either a TCA (imipramine or clomipramine at therapeutic serum levels) or fluvoxamine. Response was defined as a 50% reduction in depressive symptoms as determined by the HDRS, and depression severity was measured using the HDRS and the CGI. Thirty-nine patients received tranylcypromine (mean dose 60.5 mg day $\pm$2.9) and thirty-eight patients received phenelzine (mean dose 79 mg day $\pm$2.7). Forty to fifty percent of subjects showed response with no clear difference between the two medications. This study further supported the contention that MAOIs may be of significant benefit in severely treatment-refractory depression (Birkenhager et al. 2004).

A review of the MAOI and TCA antidepressant classes would be remiss without reviewing the findings of the largest prospective, open-label study of more than 2,700 enrolled MDD patients: the STAR*D (Sequential Treatment Alternatives to Relieve Depression) trial (Rush et al. 2006). This National Institute of Mental Health-sponsored study was conducted at more than 40 sites over a 6-year period at a cost of ~$35 million dollars. From the perspective of MAOIs, the findings were disappointing for tranylcypromine (response rate of 7%), while phenelzine was not included as an antidepressant in this trial. Further, in order to receive tranylcypromine or nortriptyline, patients had to qualify for Level 4 of the trial, which means that they had failed the three previous levels of the study. Psychiatric epidemiologists concur that the rates of remission dramatically fall with each failed trial of medications (Little 2009); therefore, by Stage 4 of the study the overall potential for success was low. Hence, the STAR*D trial's use of both TCAs and MAOIs was relegated to those highly predisposed to nonresponse, i.e., only those patients who had already failed at least three antidepressant/augmentation trials. Due to the overall response rate in the trial, this design aided in supporting the belief that older classes of medication were perhaps superior for treatment-resistant depression. It may have served the STAR*D trial better had Stage 4 been symptom driven, e.g., a depressed patient with anxiety would preferentially be given phenelzine, whereas an anergic depressed patient given tranylcypromine. Further, one could argue that the dose of tranylcypromine was suboptimal (mean dose of 36.9 mg) and few participants completed an adequate trial of the drug. Finally, limited evidence exists to support the idea that MAOIs are superior in treating depressed patients with comorbid personality disorders (Hori 1998); although this points to a limitation of STAR*D: the trial made no effort to *apriori* identify personality disorders.

A relatively recent meta-analysis compared the newer class of selective serotonin reuptake inhibitors (SSRIs) to TCAs and placebo for treatment of depression in the primary care setting (Arroll et al. 2005). This work is particularly important as the majority of MDD is treated in the ambulatory primary care setting, while most TCA trials have been conducted in inpatient psychiatric settings. This meta-analysis gathered data from established medical and psychiatric databases up until February 2003, including MEDLINE and Cochrane Databases. The findings reinforced the notion that both TCAs and SSRIs significantly improved both discrete and continuous outcomes of depression in primary care. With 890 patients on SSRIs (sertraline, citalopram, or escitalopram), 596 subjects on TCAs (doxepin or imipramine), and 1,267 patients on placebo, the meta-analysis determined a relative response rate (relative risk) of 1.26 and 1.37 for the TCA and SSRI arms, respectively, both statistically superior to placebo. The number needed to treat (NNT) was 4 for TCAs and 6 for SSRIs, while the number needed for adverse effects was slightly higher for TCAs, consistent with the concept that fewer side effects are observed with SSRIs than TCAs. Perhaps surprisingly, the authors further observed that tolerance and discontinuation rates between the two classes were largely negligent; hence, the authors concluded that TCAs at lower doses may have comparable efficacy, safety, and tolerance compared to the SSRIs in the primary care setting (Arroll et al. 2005).

In summary, despite evidence showing comparable to superior efficacy with these medication classes, the emergence of SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs), antidepressants with relatively fewer dangerous side effects and limited risks in overdose, significantly contributed to the decreased use of the TCAs and MAOIs. Further, the use of the MAOIs and TCAs in the landmark STAR*D trial was intentionally at a stage of greater treatment resistance, which did not allow these medications fair opportunity to demonstrate their potential efficacious advantages.

4 The Under-Prescribing of Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: A Justifiable Phenomenon?

The meteoric rise of the MAOIs and TCAs profoundly influenced biological psychiatry and inspired the search for newer psychotropic medications. It led researchers and clinicians across the globe to search for neuroreceptor- and neurotransmitter-based treatment modalities to treat psychiatric illness. One outcome of this was the emergence of the SSRIs in the 1980s and newer antidepressants in the 1990s. These newer class antidepressant medications had safer side effect profiles, and greater safety (especially in regard to overdose), radically shifted psychiatrist and primary care physician prescribing practices away from the MAOIs and TCAs. Concurrently, patient and practitioner perception of these older classes were oftentimes detrimentally shaped by an exaggerated fear of their associated risks. While definitive risks exist, several perceived risks might have been mitigated by careful prescription practices. Instead, intelligent marketing by the pharmaceutical industry, fear of litigation, and promoting drugs that were relatively easy for primary care providers

to use led to the systematic exodus of MAOIs and TCAs from the psychotropic armamentarium starting in the early 2000s (Balon et al. 1999; Krishnan 2007). Two decades later, MAOIs and TCAs seemingly have become a historical footnote, with the current generation of early career psychiatrists rarely, if ever, using these vital classes of medications. A significant growing concern regarding the failure to employ these medications, particularly the MAOIs, exists in treatment-refractory depressed patients.

As previously mentioned, underutilization of MAOIs and their systematic withdrawal from clinical use started with the infusion of newer and safer medications. However, closer investigation of this under-usage suggests unwarranted fear and hesitancy on the part of treating clinicians. The perceived serious side effects of MAOIs, most notably serotonin syndrome and hypertensive crisis, have been demonstrated to be relatively rare, while the less serious and more common side effects (e.g., orthostatic hypotension, insomnia, weight gain, and sexual dysfunction) are not unique to the MAOIs. A 10-year population-based cohort study that looked at MAOI prescription practices in Canada between 1997 and 2007 found a drop in new prescriptions from 3.1/100,000 to 1.4/100,000. More alarming was the drop in overall prevalence of MAOI prescriptions from 400/100,000 to 216/100,000. During this period, only 1 in 500 prescriptions for MDD was an MAOI. Interestingly, the authors also tracked hospital visits during this same period in patients taking psychotropic medications. Out of 221 patients who presented to the hospital during the 10-year period, no reported cases of hypertensive urgency or serotonin syndrome were reported. While overdoses were observed, the perceived danger that contributed to lower prescription rates was not observed in the severity and frequency of observed side effects, further reiterating limited experiential bias over scientific rigor in selecting MAOI's for treating depression (Shulman et al. 2009).

A high profile editorial in the 1963 Lancet (Hypertensive crisis and monoamine oxidase inhibitors 1963) may have captured the tone for the hesitancy to use the MAOIs. This piece described reports of hypertensive crises induced by patients taking MAOIs who had cheese as a mainstay of their diets. While in some cases there was no cheese exposure, the authors' described accounts of "devastating headache," "intracranial bleeding," and urged the medical community to "reexamine use of MAOIs." Additionally, a few years later, a British pharmacist noticed severe headaches every time his wife consumed cheese while on an MAOI medication. It was later determined that consumption of aged cheeses mimics a clinical condition similar to pheochromocytoma (symptoms of sympathetic overdrive, i.e., palpitations, tachycardia, elevated blood pressure, increased respiratory rate, and headache) resulting from elevated levels of epinephrine and norepinephrine. This "cheese reaction" results from inhibition of tyramine breakdown that ordinarily occurs via the MAO enzymes in the lining of the gut (Sathyanarayana Rao and Yeragani 2009). A "high tyramine diet" (approximately 40 mg of tyramine/day) will have little effect on an unmedicated individual. However, in patients on an MAOI, even a small dose (i.e., 8 mg of tyramine) was shown to potentially induce a hypertensive urgency (Stahl and Felker 2008).

As critical as it is to effectively warn patients receiving an MAOI about dietary restrictions, it should be noted that commonly consumed foods in the modern era (e.g., pepperoni or cheese pizza), that were previously presumed to be dangerous if consumed while taking an MAOI, were found to be safe with no appreciable tyramine levels (Shulman and Walker 1999). A summary of sympathetic symptoms associated with tyramine doses as well as these revised dietary restrictions can be found in Tables 1 and 2, respectively. However, even the revised (reduced) tyramine dietary restrictions did not influence both patient and provider perceptions around MAOIs, as the rate of prescription of these medications continued to drop.

Not surprisingly and in light of perceived concerns, a 1990 survey of the prescription practices of 485 psychiatrists from Pennsylvania and Delaware showed that only 25% of psychiatrists prescribed MAOIs regularly (Clary et al. 1990). Similarly, a 1999 study of the prescribing practices of the psychiatrists by the Michigan Psychiatric Association ($N = 573$) found that only 25% of psychiatrists

Table 1 Sympathetic symptoms associated with range of dietary tyramine consumed

Amount of tyramine in milligrams	Adverse effects
6–8	Hypertension, tachycardia, GI symptoms
10–25	Headache, increased risk of bleeding/stroke
>25	Hypertensive crisis

Table 2 Updated dietary restrictions for use of MAOI class antidepressants

	Food/drink	Weight	Estimated tyramine milligram equivalent
Cheese	New York cheddar	1 oz	42 mg
	Swiss	1 oz	28 mg
	All aged cheese	1 cup	Considered high
	All cheddar (especially with storage)	1 oz	Considered high
	Other types of cheese (American cheese, pasteurized American cheese, Parmesan cheese, and Farmer's cheese)	1 oz	Acceptable
	Romano, cottage, ricotta, and cream cheese	Up to 2 oz	
Alcohol	Tap beer	12 oz	38 mg
	Red wine	4 oz	0–0.6 mg
	Canned beer	1 can	1.5 mg
Meat	Dry sausage	1 oz	3–43 mg
	Salami	1 oz	1.2–5.4 mg
	Smoked fish	1 oz	Considered high
	Aged chicken liver	1 oz	60 mg
	Pepperoni	1 oz	1.75 mg
	All canned meat consumed immediately upon opening	2–4 oz	Insignificant
	All fresh meat, poultry, fish or chicken liver consumed on day of purchase	2–4 oz	Insignificant

regularly prescribed MAOIs. The reasons listed for not prescribing MAOIs included preference for newer antidepressants medications, avoidance of dietary modifications, and side effect profile. Interestingly, despite their failure to prescribe these medications, close to 94% of psychiatrists believed MAOIs to be superior for use in atypical depression, and more than half described MAOIs as advantageous for melancholic depression and panic disorder (Clary et al. 1990). Similarly, Conway et al. (2015) described a group of 79 severely treatment-resistant depressed patients seen in a treatment-refractory depression referral clinic in the Midwestern United States that despite having on average eight previous adequate dose/duration trials of antidepressants, 37% had never been exposed to an MAOI. This reflects the current hesitancy of clinicians to employ MAOIs and may contribute to chronic suffering in refractory MDD.

Finally, the "wash-out" period is critical to understanding the pharmacokinetics of MAO receptors. In the case of irreversible blockade of medications such as phenelzine and tranylcypromine, it is important to allow a 2-week wash out period, as that is the time required to generate new MAO receptors. This is an important consideration, as many patients with some degree of treatment resistance, or ongoing psychiatric decompensation, requiring a medication change may find it impractical to wait 2 weeks. Consideration of potential short-term use of inpatient psychiatric hospitalization for the purpose of initiating an MAOI might be reasonable. Further complicating prescription practices, deinstitutionalization (the move from inpatient care of psychiatric patients in the pre-1960s) likely played a role in the decreased use of MAOIs, as most clinicians felt uncomfortable switching from a "standard" antidepressant to an MAOI in the outpatient setting. Though, as we argue in this chapter, the fears are often unfounded; rapid initiation of an MAOI in patients recently on a "standard antidepressant" may represent a beneficial use of inpatient psychiatric hospitalization going forward.

In conclusion, the evolution of psychopharmacology, since the earliest serendipitous discovery of antidepressants, rests on the historic standing of these two classes of medications. An understanding of these antidepressants not only furthered our knowledge of the discipline, but it also paved the way for newer, and arguably safer, methods of treating and alleviating mental illness. While several of the risks posed by these medications are real and dangerous, many can be mitigated through careful patient selection and psychoeducation. As the symptomology of the unfortunate relatively common occurrence of treatment-refractory depressive illness is elucidated, the need for providers to use *every* resource available, including the TCAs and MAOIs, becomes vital.

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