Combination Therapy with Monoamine Oxidase Inhibitors and Other Antidepressants or Stimulants: Strategies for the Management of Treatment-Resistant Depression

Samantha J. Thomas,[1] Mirae Shin,[2] Melvin G. McInnis,[3] and Jolene R. Bostwick[2,4,*]

[1]Meijer Pharmacy, Dewitt, Michigan; [2]Pharmacy Services, University of Michigan Health System, Ann Arbor, Michigan; [3]Department of Psychiatry, University of Michigan Health System, Ann Arbor, Michigan; [4]College of Pharmacy, University of Michigan, Ann Arbor, Michigan

Treatment-resistant depression (TRD) is a major health concern. More than 40% of patients treated for major depressive disorder with an appropriate antidepressant dose for an adequate duration fail to respond. Further, approximately half of adults with major depressive disorder fail to achieve sustained remission despite various medication trials. The utilization of monoamine oxidase inhibitors (MAOIs) for the treatment of depression in clinical practice today is low due to their widely known adverse effects, some of which may be life threatening, and the risk for dietary and drug interactions. For these reasons, MAOIs are not recommended to be prescribed along with other antidepressants or certain prescription or nonprescription drugs. Pharmacologic options are limited for individuals with TRD, however, and there is a paucity of data on the efficacy of MAOIs in combination with other antidepressants for the management of TRD. We performed a search of the PubMed database (inception through January 25, 2015) to identify cases that illustrate the potential utility, as well as risks, of combination treatment with MAOIs and other antidepressants for the management of TRD; 18 articles met the criteria for our search. In addition, we performed a retrospective case series by reviewing the medical records of 29 adults treated for depression with an MAOI plus another psychotropic agent (an antidepressant or stimulant medication) between 2003 and 2012 at a large Midwestern teaching hospital. We compared the findings of the published experience with our local experience to allow for more informed decisions regarding pharmacotherapy in patients with TRD. We separated the local experience into two groups: 15 cases with the selective MAO type B inhibitor selegiline combined with medications presumed to increase the risk of serotonin syndrome and 14 cases with nonselective MAOIs (phenelzine and tranylcypromine) combined with other contraindicated medications. Although risks of combination treatment certainly exist with selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, or clomipramine, the current literature supports cautious use of combining MAOIs with other antidepressants in patients with TRD who have failed multiple treatment modalities. In addition, the data from the 29 patients receiving combination therapy with an MAOI and another antidepressant or stimulant medication revealed that 21% improved significantly, with no complications. This case series and literature review suggest that when used under close supervision and under the care of an experienced clinician in psychiatry, combination therapy may be a consideration for the management of TRD in patients not responding to monotherapy or other combinations of antidepressants.

KEY WORDS serotonin syndrome, monoamine oxidase inhibitor, MAOI, combination antidepressants.
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Treatment-resistant depression (TRD) is a major health concern. More than 40% of patients treated for major depressive disorder (MDD) with an appropriate antidepressant dose for an adequate duration fail to respond.[1] Further, approximately half of adults with MDD fail to achieve sustained remission despite various medication trials.[2] Despite TRD now being a major public health concern, there is a paucity of data for the management of TRD to guide informed decision-making about pharmacotherapy. The lack of consensus on the definition of treatment resistance contributes to the deficiency of data.[3] Definitions range from a poor response after proper dosing and duration of a single antidepressant to response failure after adequate dosing and duration of two or more antidepressants from different classes,[3–5] which has become the working definition of TRD.[2]

Monoamine oxidase inhibitors (MAOIs) were one of the first classes of medications used for the treatment of depression.[6] These agents inhibit the enzyme monoamine oxidase, which is present in the brain and other tissues such as the intestine and liver.[6] MAOIs currently available in the United States, including selegiline, tranylcypromine, phenelzine, and isocarboxazid, irreversibly bind and inactivate monoamine oxidase, thus preventing the degradation of neurotransmitters such as serotonin, epinephrine, norepinephrine, and dopamine, leading to their accumulation.[6] The use of MAOIs is limited due to their widely known adverse effects and risk for dietary and drug interactions. These include the risk of hypertensive crisis when tyramine-rich foods are consumed, as well as the risk of serotonin syndrome, which can occur when MAOIs are combined with other medications, which may be life threatening.[6, 7] For this reason, it has historically been recommended that MAOIs not be prescribed along with other antidepressants or certain prescription drugs (e.g., tramadol, meperidine, dextromethorphan, or methadone) and nonprescription drugs. Psychotropic agents that are contraindicated or recommended to be used with caution in combination with MAOIs are listed in Table 1.[6, 8, 9] In addition, a recent case study highlights the concern for severe hypertension due to the combination of high caffeine intake in combination with tranylcypromine.[10] Given the severity of the risks involved with using MAOIs, in addition to the lack of marketing, fear among prescribers, and lack of experience using MAOIs, the overall use of these agents in clinical practice today is low.[11]

Largely, given the severity of the adverse effects and reactions, as well as relatively low utilization, a paucity of data is available on the efficacy of MAOIs in combination with other antidepressants for the management of TRD. Considering the limited pharmacologic options in individuals with TRD, additional evidence is needed to support the clinical use of combination antidepressant therapy with MAOIs and other psychotropic agents, when appropriate. Thus, in this case series and literature review, we aimed to illustrate the potential utility, as well as risks, of combination treatment in patients for the management of TRD by comparing published experience with our local experience (case series) to allow for more-informed decisions regarding pharmacotherapy in patients with TRD.

It should be highlighted that the cases we included in the case series are separated into two groups: cases including the selective MAO type B inhibitor selegiline and cases including nonselective MAOIs (phenelzine and tranylcypromine). Selegiline confers more selective MAO-B inhibition at low doses, which improves tolerability and minimizes risk for dietary interactions with tyramine.[12] However, as the dose increases, selegiline becomes less selective for MAO-B.[13] A wider safety margin exists with the transdermal formulation of selegiline compared with nonselective MAOIs and oral selegiline, even in dosages up to 12 mg/day.[14] Enhanced safety with the transdermal formulation is due to avoidance of first-pass metabolism and the ability to minimize the inhibition of MAO-A in the gastrointestinal tract.[12, 14] Although selegiline, in any form, still confers risk in combination with other antidepressants, its selectivity should be distinguished from that of other nonselective MAOIs.

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*Address for correspondence: Jolene R. Bostwick, Clinical Associate Professor of Pharmacy, Department of Clinical, Social, and Administrative Sciences, College of Pharmacy, University of Michigan, and Clinical Pharmacist, Adult Psychiatry, University of Michigan Health System, 1500 E. Medical Center Drive, 9D9814 University Hospital, Ann Arbor, MI 48109-0018; e-mail: jkingsbu@med.umich.edu.

Table 1. Psychotropic Agents Contraindicated or Recommended to Be Used with Caution in Combination with Monoamine Oxidase Inhibitors[6, 8, 9]

Psychotropic Class	Medications	Potential Reaction
Selective serotonin reuptake inhibitors	Fluoxetine, paroxetine, sertraline, citalopram, escitalopram, fluvoxamine, vilazodone	Serotonin syndrome
Tricyclic antidepressants	Amitriptyline, imipramine, clomipramine, nortriptyline, amoxapine, desipramine, doxepin, trimipramine, protriptyline	Serotonin syndrome, hypertensive crisis
Serotonin and norepinephrine reuptake inhibitors	Venlafaxine, duloxetine, desvenlafaxine, milnacipran	Serotonin syndrome
Sympathomimetic amines	Amphetamines, methylphenidate, pseudoephedrine, phenylephrine, modafinil, phenylpropanolamine, ephedrine, phentermine	Hypertensive crisis
Other antidepressants	Bupropion, mirtazapine, St. John's wort, maprotiline, quetiapine, lithium	Increased risk of serious adverse effects
Other monoamine oxidase inhibitors	Isocarboxazid, phenelzine, tranylcypromine, selegiline, linezolid	Hypertensive crisis, serotonin syndrome

Methods

Literature Review

A literature search of the PubMed database was performed. Any relevant article available in English from inception through January 25, 2015, was included. Key search terms included *monoamine oxidase inhibitor, MAOI, selective serotonin reuptake inhibitor, TCA, stimulants, trazodone, antidepressants, treatment-resistant depression, depression, major depressive disorder, combination, selegiline, phenelzine,* and *tranylcypromine.* Controlled and noncontrolled studies, open-label studies, case reports, and case series were included.

Case Series

In addition, a retrospective case series was performed by reviewing the medical records of 29 adult patients treated for depression at a large Midwestern teaching hospital; this case series was approved by the University of Michigan institutional review board. More specifically, 14 cases of a nonselective (nonselegiline) MAOI combined with other contraindicated medications and 15 cases of selegiline combined with medications presumed to increase the risk of serotonin syndrome are described. Inclusion criteria consisted of any adult patient (≥ 18 yrs of age) with a diagnosis of depression who was treated with an MAOI (tranylcypromine, phenelzine, selegiline, or isocarboxazid) plus another psychotropic agent, including an antidepressant or stimulant medication, between 2003 and 2012 was included. Of the 29 patients, six cases were further reviewed and are described in Data S1. These six cases were representative of the three most common combinations encountered: trazodone and an MAOI, tranylcypromine and other antidepressants, and selegiline and other antidepressants. A positive and negative clinical outcome was chosen to exemplify each combination. Information was gathered to determine safety of treatment and efficacy of combination therapy.

Medical records were reviewed and data were collected on medications used, along with dosages and durations of therapy. Duration of therapy was critical to fully determine the tolerability of therapy, given the half-lives of certain antidepressants. Any symptoms and/or adverse effects that were experienced were documented to determine tolerability to combination therapy. Patient demographics, medical and family history, summary of illness, indication for combination treatment, any necessary laboratory

values, diet, past medication trials, social history, and allergies were also collected. Diet was evaluated based on information provided in the medical record, given that foods rich in tyramine may be the cause of any symptoms or adverse effects. Finally, use of other serotonergic agents was noted, when applicable.

Results

Eighteen articles were identified and reviewed, and are described in Table 2.[15–32] Additionally, the medical records of 29 patients that mentioned the use of MAOIs in combination with other antidepressants were reviewed. These data are presented in two separate tables: Table 3 summarizes 15 cases in which the selective MAOI selegiline was used, whereas Table 4 summarizes 14 nonselegiline cases. Indications for combination therapy included depression (eight cases), TRD (six cases), recurrent MDD (nine cases), bipolar disorder (five cases), and borderline personality disorder (one case). Combinations encountered include an MAOI in combination with either trazodone (16 cases), a tricyclic antidepressant (TCA) (four cases), bupropion (two cases), an SSRI (one case), or mirtazapine (one case). Additionally, MAOIs were combined with two or more antidepressants in five cases. Of note, these patients represented a heterogeneous group, with various indications and treatment regimens.

Among the 29 patients reviewed at our institution, six patients (21%) who received combination therapy experienced improvement in mood, with no or minimal tolerable adverse effects. Only one of these patients was receiving transdermal selegiline (Table 3, case 4), whereas four were treated with tranylcypromine (Table 4, cases 5, 8, 11, and 13) and one with phenelzine (Table 4, case 12). Similarly, seven patients (24%) demonstrated no or minimal improvements in mood. Documented adverse effects requiring discontinuation of one or more of the medications occurred in 13 patients (45%), including three suspected cases of serotonin syndrome, which were neither confirmed nor required acute intervention. Two patients using the selegiline patch discontinued treatment due to rash and other reasons. There were no reports of major serious consequences due to combination therapy with MAOIs. The most common adverse effects included hypotension, constipation, fatigue, dry mouth, and dizziness. The most frequent combinations included either trazodone or a TCA combined with an MAOI, sometimes with an additional psychotropic agent. The average duration of therapy for combination MAOI with trazodone was 21 months. At the time of this writing, the majority of patients receiving combination treatment with an MAOI, a TCA, and possibly another antidepressant were still taking the combination, with the exception of two cases.

Discussion

The following highlights the findings from both the literature review and our case series. There were six combinations encountered, consisting of MAOIs in combination with other antidepressants and/or stimulants.

MAOI plus SSRI/SNRI

There is a paucity of controlled, prospective data on combination therapy with an MAOI and a selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) due to the general recommendations to avoid combination use. Combination therapy of MAOIs and SSRIs or SNRIs is dangerous due to the increased risk for serotonin syndrome.[6, 33, 34] Further, deaths associated with combination use involving SSRIs have been reported in patients receiving therapeutic and overdose amounts.[35, 36] To avoid this, it is recommended that SSRIs or SNRIs be discontinued for at least 2 weeks before beginning MAOI therapy, with the exception of fluoxetine, which requires a 5-week washout period.[37] Our single case of fluoxetine combined with an MAOI was uninformative (see details in Table 3, case 1), as the MAOI was discontinued at an outside hospital for unknown reasons. Further, in case 1 in Table 4 and case 2 in Table 3, when the SNRIs venlafaxine and duloxetine were used in combination with an MAOI and trazodone, no positive outcomes were noted. Data support avoiding combinations of SSRIs or SNRIs with MAOIs (regardless of MAO selectivity), as the risk most often exceeds any potential benefit, particularly with concomitant use of trazodone.[6, 15, 16, 33]

MAOI plus Trazodone

Trazodone is effective for sleep, and an open-label study and case series have shown that low-dose trazodone may be a safe and effective treatment option for insomnia associated with

Table 2. Summary of Published Literature Describing Patients Who Received MAOIs in Combination with Other Antidepressants or Stimulant Medications[15–32]

Combination Assessed	Study Details	Treatment	Summary
MAOI plus SSRI	Case series of 8 select reviews of adverse event reports to the manufacturer[15]	Fluoxetine plus MAOI	Seven cases were fatal when the MAOI (6 cases used tranylcypromine) was added to or started after the initiation of fluoxetine.
	Case series of 12 patients taking fluoxetine plus MAOI and 6 patients who started an MAOI at least 10 days after stopping fluoxetine[16]	Fluoxetine plus MAOI	Therefore, use of fluoxetine plus an MAOI or in "close proximity" to an MAOI is contraindicated.[15] In general, the authors recommended against combining serotonergic antidepressants, such as SSRIs, with MAOIs until more controlled data become available; however, the authors also highlighted that combination therapy may be used in treatment-resistant patients along with close monitoring and cautious dosing strategies.[16]
MAOI plus Trazodone	Case series of 13 patients with MAOI-induced insomnia[17]	Trazodone 25–200 mg/day plus phenelzine, tranylcypromine, or isocarboxazid	Overall, response to trazodone was favorable. Problematic adverse effects included orthostatic hypotension, lightheadedness, daytime sedation, nocturnal myoclonus, nausea, memory recall, and a manic episode in a patient who also had bipolar disorder. One patient experienced a fall during the course of treatment.[19] Additional well-controlled, longer term studies are warranted; however, low-dose trazodone may be a safe and effective treatment option for MAOI-induced insomnia.
	Open trial of 21 patients with major depression and MAOI-induced insomnia[18]	Trazodone 50–75 mg at bedtime plus phenelzine, tranylcypromine, or isocarboxazid	
	Case report of combination therapy for TRD[19]	Trazodone 300–600 mg/day plus phenelzine 90–120 mg/day plus lithium	

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Table 2. (continued)

Combination Assessed	Study Details	Treatment	Summary
MAOI plus TCA	6-wk randomized study of 135 patients with mild or moderate depression[20]	Treatment groups consisted of phenelzine alone, isocarboxazid alone, trimipramine alone, phenelzine plus trimipramine, or isocarboxazid plus trimipramine. Dosage ranges were as follows: phenelzine 15–60 mg/day, isocarboxazid 10–30 mg/day, and trimipramine 50–150 mg/day	The majority of studies emphasized the importance of drug and dietary restrictions, and no serious adverse effects were reported. However, these studies do report dizziness and orthostatic hypotension, prolonged P-R interval, weight gain, and manic switch from combination treatment. One study reported greater efficacy in trimipramine only users.[20] This study also found that MAOIs and TCAs are more likely to be effective in individuals with high depression scores, TRD, or atypical depression.[20] Further, this combination should only be used in patients with TRD at low risk for suicide, given the risk of toxicity in overdose.[21] Overall, these studies do not support greater efficacy of combined treatment compared to monotherapy. There is a need for additional data regarding this combination, and alternative options for TRD, such as lithium or thyroid augmentation, should be considered first.[24]
	Chart review of 150 inpatients and 51 outpatients[21]	MAOI plus TCA (primarily amitriptyline and imipramine)	
	Double-blind study of 80 patients with major depressive disorder[22]	Amitriptyline monotherapy, tranylcypromine monotherapy, or combination treatment with amitriptyline plus tranylcypromine	
	Case report of a 30-yr-old man with refractory depression[23]	Trimipramine 100 mg/day added to phenelzine 60 mg/day	
	Case report of a 65-yr-old man with a history of major depression[24]	Tranylcypromine plus trimipramine (dosing details not provided)	
	Open-label study of 25 patients with TRD; responders (n=12) were followed for 3 yrs[25]	Isocarboxazid at dosages up to 50 mg/day plus amitriptyline at dosages up to 200 mg/day	

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Table 2. (continued)

Combination Assessed	Study Details	Treatment	Summary
MAOI plus bupropion	Case report of a 27-yr-old woman with chronic major depression[26]	Tranylcypromine plus bupropion at dosages up to 60 and 300 mg/day, respectively	After numerous medication trials, and even use of ECT in two patients,[27] this combination resulted in sustained remission of depression. No serious adverse effects were noted. The authors highlighted the lack of controlled studies and recommended combination therapy be better studied. They highlighted the risk of hypertensive crisis and other complications, including tachycardia and cardiac rhythm disorders, with combination therapy and note that careful use of this combination may be warranted in treatment-refractory cases.
	Case reports of a 63-yr-old man and a 54-yr-old man, both with TRD[27]	Tranylcypromine plus bupropion at dosages up to 20 and 300 mg/day, respectively, in the first patient, and up to 50 and 450 mg/day, respectively, in the second patient	
MAOI plus Stimulants	Review and case report of a 38-yr-old man with major depression and undiagnosed attention deficit hyperactivity disorder[28]	Tranylcypromine 50 mg plus methylphenidate at dosages up to 45 mg/day	Positive outcomes were reported overall. The authors supported the prudent addition of a low-dose stimulant to MAOI therapy in patients with refractory depression to prevent MAOI-related adverse events, including orthostatic hypotension and sedation.[28] No major adverse effects were observed; however there was one case of hypertension due to nonadherence of dietary restrictions, but no cases of hypertensive crisis were recorded. Cases of manic switches were reported in one study.[30] A subset of patients in this study was also treated with other antidepressants, including trazodone and tricyclic antidepressants.[30] Additional controlled research to further evaluate the safety and efficacy of stimulant and MAOI combination treatment is needed.[30] Given the potential risks of combination therapy with stimulants, such combinations should be used following a trial of more well-established combination regimens and careful evaluation of patient-specific factors.
	Case report of a 31-yr-old woman with TRD[29]	Phenelzine 15 mg 3 times/day plus methylphenidate 10 mg every morning and 7.5 mg at noon	
	Report of 32 patients with severe TRD[30]	Low-dose pemoline or dextroamphetamine added to tranylcypromine, isocarboxazid, or pargyline, titrated based on tolerability and partial response	

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Table 2. (continued)

Combination Assessed	Study Details	Treatment	Summary
MAOI plus Antidepressants plus Stimulants	Authors reviewed the medical records of 16 patients with TRD and provided additional case details for two cases[31] Case study of a 70-yr-old man without adequate response to his regimen[32]	Combination of an MAOI plus TCA, MAOI plus direct stimulant, or MAOI, TCA, plus stimulant Trazodone plus fluoxetine plus methylphenidate plus alprazolam plus neuroleptic (unspecified) plus ECT plus isocarboxazid 5 mg/day (other dosages not specified)	Most patients exhibited fair to good improvement. There were no instances of hypertensive crises in these studies. Orthostatic hypotension was the most frequent adverse effect and other less common complaints include anxiety, restlessness, agitation, irritability, nausea, dizziness, impairment of short-term memory, insomnia, and hypomania.[31] The authors concluded that this combination is safe and effective and may especially be beneficial in patients who experience postural hypotension with the use of MAOIs, as the stimulant can help to normalize blood pressure. It is recommended that patients receiving combination therapy with all three agents first begin the TCA at bedtime, followed by a daytime MAOI after 4–5 days. After another 4–5 days, the stimulant should be added at low doses and titrated until blood pressure is stable and clinical improvement is noted.[31] The author of the second study highlights the importance of caution when coprescribing MAOIs in combination with other medications, emphasizing informed consent, strong collaboration between the prescriber and patient, using low doses of MAOIs, as well as ensuring that the prescriber is well versed in psychopharmacology.[32]

ECT = electroconvulsive therapy; TRD = treatment-resistant depression.

Table 3. Summary of the 15 Case Series Patients Who Received Combination Therapy with Selegiline and Other Antidepressant or Stimulant Medications

Case	Age, Race	Diagnosis	Relevant Medical History	Combination Therapy (Maximum Total Daily Doses)	Concomitant Medications	Duration of Combination Therapy	Outcomes
1	53-yr-old Caucasian woman	Bipolar depression	Coronary artery disease, hyperlipidemia	Selegiline 6-mg patch and fluoxetine 40 mg	Lithium, aripiprazole, rosuvastatin, ezetimibe	8 mo	Improved mood and energy, followed by admission to outside hospital for severe depression where selegiline was discontinued for unknown reason
2	57-yr-old Caucasian man	Recurrent MDD	Atrial fibrillation, hyperlipidemia, alcohol abuse	Selegiline 12-mg patch, duloxetine 90 mg, and trazodone 100 mg	Aspirin, intranasal budesonide, clonazepam, flecainide, simvastatin	3 mo (duloxetine for 1 mo)	Denied benefit from selegiline; experienced dry mouth, blurred vision, weight gain, sleeplessness, poor concentration, memory loss, vertigo, and constipation
3	67-yr-old Caucasian man	Recurrent severe MDD	Anxiety, Parkinson's disease, essential tremor, degenerative joint disease	Selegiline 60 mg and trazodone 300 mg	Diazepam, lamotrigine, ziprasidone, propranolol, primidone, gabapentin	4 mo	Discontinued combination therapy due to unspecified "intolerability" and a lack of improvement in mood
4	36-yr-old Caucasian woman	Severe depression	Anxiety, osteopenia, sexual dysfunction, hypothyroidism, ADD	Selegiline 12-mg patch and trazodone 50 mg	Amphetamine, alendronate, perphenazine, doxycycline, levothyroxine, lamotrigine	10 mo (and ongoing)	Improved mood and sleep
5	62-yr-old Caucasian man	Recurrent MDD	Type 2 diabetes mellitus, hypertension, traumatic brain injury, alcohol and opioid dependence	Selegiline 9-mg patch and trazodone 200 mg	Irbesartan, metformin, atorvastatin	4 mo	Improved energy, motivation, and optimism, but discontinued combination treatment due to morning fatigue and decreased cognitive efficiency

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Table 3. (continued)

Case	Age, Race	Diagnosis	Relevant Medical History	Combination Therapy (Maximum Total Daily Doses)	Concomitant Medications	Duration of Combination Therapy	Outcomes
6	24-yr-old Caucasian woman	MDD	None	Selegiline 6-mg patch and trazodone 50 mg	Quetiapine, lithium, clonazepam, lorazepam, ethinyl estradiol/ norgestimate	9 mo	Considerable improvements in depressive symptoms, but patient switched from trazodone to a benzodiazepine for sleep
7	40-yr-old Caucasian woman	Bipolar depression	None	Selegiline 9-mg patch and trazodone 50 mg	Lithium, aripiprazole	2 mo	Patient discontinued trazodone after feeling better and insomnia resolved
8	42-yr-old Caucasian man	Depression	HIV, diabetes, obesity, anxiety, hyperlipidemia	Selegiline 6-mg patch and trazodone 150 mg	Sildenafil, topiramate, insulin glargine, insulin aspart, levothyroxine, lisinopril, aspirin, testosterone, pirbuterol, fluticasone, emtricitabine/ tenofovir/efavirenz	Unknown	Patient lost to follow-up; seen by outside psychiatrist
9	71-yr-old Caucasian woman	Bipolar depression	Hypertension, GERD, osteoarthritis	Selegiline 12-mg patch and trazodone 50 mg	Losartan, amlodipine, triamterene, fexofenadine, aspirin, albuterol, olanzapine, eszopiclone	Nearly 2 yrs	Patient tolerated combination well, but trazodone was discontinued in case selegiline was switched to tranylcypromine due to concerns for an interaction
10	26-yr-old Caucasian woman	Borderline personality disorder with MDD	IBS, alcoholism, cannabis abuse	Selegiline 12-mg patch, bupropion 300 mg, and trazodone 150 mg	Aripiprazole, clonazepam, lamotrigine, ferrous sulfate	1 yr, 8 mo; bupropion for 6 mo	Patient discontinued selegiline due to ineffectiveness; remained depressed, fatigued, anxious
11	30-yr-old Caucasian man	TRD	IBS, rheumatoid arthritis, GERD, borderline hypertension	Selegiline 6-mg patch and bupropion XL 450 mg	None	1 mo	Discontinued bupropion in preparation for ECT after patient felt it would provide better symptomatic relief

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Table 3. (continued)

Case	Age, Race	Diagnosis	Relevant Medical History	Combination Therapy (Maximum Total Daily Doses)	Concomitant Medications	Duration of Combination Therapy	Outcomes
12	45-yr-old Caucasian man	TRD	Chronic back pain, ED, palpitations, lumbar degenerative disc disease	Selegiline 6-mg patch and bupropion SR 450 mg	Sildenafil	1 mo	Patient discontinued selegiline for unknown reasons; felt symptoms may have worsened
13	39-yr-old Caucasian woman	TRD	Migraines, IBS, history of alcohol abuse	Selegiline 9-mg patch and nortriptyline 100 mg followed by tranylcypromine 20 mg and nortriptyline 50 mg	Disulfiram, liothyronine, lorazepam, aripiprazole	8 mo for selegiline; 1 mo for tranylcypromine	Switched from selegiline to tranylcypromine after slight increase in blood pressure; tranylcypromine titration halted and nortriptyline discontinued due to suspicion of serotonin effects
14	32-yr-old Asian woman	TRD	None	Selegiline 12-mg patch and nortriptyline 100 mg	Quetiapine, clonazepam	1 wk	Experienced significant pruritis associated with selegiline patch
15	19-yr-old Caucasian man	Recurrent MDD	None	Selegiline 12-mg patch and nortriptyline 150 mg followed by tranylcypromine 80 mg and nortriptyline 150 mg	Ziprasidone, lithium	1 yr for selegiline; 2 yrs, 8 mo for tranylcypromine	Selegiline discontinued per discussions with ECT team; improvements seen with tranylcypromine, but nortriptyline discontinued due to fatigue

ECT = electroconvulsive therapy; ED = erectile dysfunction; IBS = irritable bowel syndrome; MDD = major depressive disorder; TRD = treatment-resistant depression.

Table 4. Summary of the 14 Case Series Patients Who Received Combination Therapy with Nonselegiline MAOIs and Other Antidepressant or Stimulant Medications

Case	Age, Race	Diagnosis	Relevant Medical History	Combination Therapy (Maximum Total Daily Doses)	Concomitant Medications	Duration of Combination Therapy	Outcomes
1	56-yr-old Asian man	Depression	Hyperlipidemia, GERD, hyperparathyroidism, impotence, insomnia, vitamin D deficiency	Phenelzine 45 mg, venlafaxine 300 mg, and trazodone 25 mg	Aripiprazole, atorvastatin, levothyroxine, tadalafil, pantoprazole	1 mo	Patient fell and hit head; began ECT thereafter
2	67-yr-old Caucasian woman	Depression	Anxiety, ADD, hypothyroidism, migraines, hypertension, atypical chest pain, remote history of alcohol abuse	Phenelzine 75 mg and trazodone 200 mg	Omeprazole, levothyroxine, clonazepam, potassium chloride, orlistat, probiotic, intranasal fluticasone	Nearly 1 yr	Discontinued both phenelzine and trazodone due to possible serotonin syndrome
3	52-yr-old Caucasian woman	TRD	Long history of alcohol and opioid abuse (in remission), Crohn's disease, osteopenia, atypical chest pain, hypertension	Tranylcypromine 50 mg and trazodone 75 mg	Liothyronine	3.5 yrs	Discontinued trazodone due to difficulties with sweating, palpitations, flushing, and dizziness; experienced modest improvements in mood during this time
4	45-yr-old woman, race not reported	Recurrent MDD	Hypothyroidism	Tranylcypromine 80 mg and trazodone 100 mg	Levothyroxine, iron supplement, omeprazole, metronidazole gel	Nearly 8 mo	Exhibited moderate improvement, but trazodone discontinued due to cognitive clouding
5	63-yr-old Caucasian man	Recurrent MDD	Osteoarthritis	Tranylcypromine 70 mg and trazodone 100 mg	Divalproex, clonazepam, simvastatin	4 mo	Demonstrated improvements in mood, but discontinued trazodone due to lack of efficacy
6	58-yr-old Caucasian man	Depression	Migraines, osteopenia, primary hyperparathyroidism, GERD	Phenelzine 75 mg and trazodone 50 mg	Lorazepam, diltiazem, pantoprazole	10 mo	Dramatic improvements with increased phenelzine dose, but patient discontinued trazodone due to daytime sedation

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Table 4. (continued)

Case	Age, Race	Diagnosis	Relevant Medical History	Combination Therapy (Maximum Total Daily Doses)	Concomitant Medications	Duration of Combination Therapy	Outcomes
7	30-yr-old Caucasian man	Depression	Chronic low back pain, migraines, idiopathic thrombocytopenic purpura, alcohol dependence	Tranylcypromine 60 mg and trazodone 100 mg	Albuterol, sumatriptan, lamotrigine, lithium, propranolol, quetiapine, ziprasidone, carbamazepine, zolpidem, lithium	1 yr, 2 mo	Lack of improvement; switched from trazodone to temazepam for sleep as it was helpful in the past
8	62-yr-old Caucasian man	Recurrent MDD	Prostate cancer, ED, cardiac defibrillation, sarcoidosis, alcohol abuse	Tranylcypromine 70 mg and trazodone150 mg	Metoprolol, lisinopril, celecoxib, aspirin, clonazepam	≥ 4 yrs (and ongoing)	Mood improvements followed by a relapse when patient had to discontinue tranylcypromine due to financial problems; improved/good mood on reinitiation
9	53-yr-old Caucasian man	Depression	Renal failure, hypotension secondary to volume depletion, hypovolemic hyponatremia	Tranylcypromine 120 mg and trazodone 300 mg	Lamotrigine, lorazepam, lithium, liothyronine, quetiapine, amlodipine/ benazepril, pindolol	1.5 yrs	Patient discontinued trazodone as it was agitating and caused more sleep disturbances; lack of improvement in mood symptoms
10	41-yr-old Caucasian woman	TRD	Chronic pain, fatigue, fibromyalgia, back pain, headaches	Phenelzine 60 mg, desipramine 75 mg, and trazodone 300 mg	Topiramate, methylphenidate, lorazepam, pregabalin	2 yrs, 7 mo	Patient discontinued desipramine due to symptomatic hypotension and tachycardia; remained on tranylcypromine and trazodone for unknown duration; experienced mild improvements in mood

(continued)

Table 4. (continued)

Case	Age, Race	Diagnosis	Relevant Medical History	Combination Therapy (Maximum Total Daily Doses)	Concomitant Medications	Duration of Combination Therapy	Outcomes
11	56-yr-old Caucasian man	Recurrent MDD	Atrial fibrillation/flutter malnutrition, diabetes mellitus, hypertension, coronary artery disease, congestive heart failure	Tranylcypromine 70 mg, nortriptyline 100 mg, and trazodone 50 mg	Carvedilol, digoxin, gabapentin, fluvastatin, spironolactone, warfarin	5 yrs (and ongoing)	Phenelzine and nortriptyline ongoing with improvements in mood and stability of depression; trazodone stopped and restarted with no follow-up on most recent use
12	57-yr-old Caucasian woman	Recurrent MDD	Hyperlipidemia, hypothyroidism, fibromyalgia, hypertension	Phenelzine 60 mg, nortriptyline 150 mg, and trazodone 400 mg	Lithium, quetiapine, tizanadine, clonazepam, ipratropium solution, simvastatin, lisinopril, levothyroxine, medroxyprogesterone acetate	2 yrs, after which patient was lost to follow-up	Successfully remained on combination therapy with no relapse or significant adverse effects
13	73-yr-old Caucasian woman	Bipolar II disorder with depression	Hypertension, hypothyroidism, nonischemic dilated cardiomyopathy, remote history of acute renal failure	Tranylcypromine 40 mg and nortriptyline 125 mg	Hydrochlorothiazide, lisinopril, levothyroxine, iron supplement	Nearly 4 yrs (and ongoing)	Patient remained stable on this combination
14	67-yr-old Caucasian man	Bipolar depression	History of sciatica, history of alcohol dependence	Phenelzine 90 mg and mirtazapine 15 mg	Quetiapine, aripiprazole, propranolol	Nearly 3 mo	Discontinued phenelzine following hospital admission for symptoms of delirium and serotonin syndrome, potentially due to supratherapeutic doses both agents

MAOIs = monoamine oxidase inhibitors; ADD = attention-deficit disorder; ECT = electroconvulsive therapy; ED = erectile dysfunction; MDD = major depressive disorder; TRD = treatment-resistant depression.

MAOI use.[17–19] There are limited data on the use of higher doses of trazodone in combination with MAOIs for TRD.[18, 19] Overall, our cases also support safe and effective use of low-dose trazodone and MAOIs. It should be noted that the trazodone doses used are largely targeting insomnia and are not effective antidepressant doses. The addition of low-dose trazodone to MAOI therapy appeared to improve tolerability of the MAOI and overall clinical improvement of patients. Reasons for discontinuation of trazodone and MAOI combination therapy in our review included ineffectiveness, feeling overly tired, experiencing more sleep disturbance, or cognitive clouding. One patient we described in our case series stopped trazodone and MAOI combination treatment due to symptoms consistent with serotonin syndrome, although this was not definitively diagnosed (Table 4, case 2). Overall, however, patients receiving this combination averaged approximately 21 months of utilization. Further studies are needed, and the risks of combination treatment should remain a concern, including the risk of orthostatic hypotension, which should be monitored closely. It should be noted that higher doses of trazodone are likely associated with greater risk of serotonin syndrome, and the risk would likely outweigh potential benefit in most cases.

MAOI plus TCA

The literature on TCA-and-MAOI combination therapy is mixed. Small studies and case reports have demonstrated its safety, but the combination has generally been found to be less well tolerated than either agent alone.[20–22] In addition, there are studies that suggest that the combination is no more efficacious than either agent alone and should be reserved for individuals with high depression scores, TRD, or atypical depression.[20–22] Our patients who received TCA and MAOI combination therapy show sustained tolerability and efficacy (Table 3, cases 13–15; Table 4, cases 10–13). Three of the seven patients remained on this regimen for at least 2 years, two of whom also received trazodone in combination with the TCA and MAOI. The combination was discontinued in four patients due to one case of hypotension (patient was also receiving trazodone), one case with suspicion of serotonin syndrome, one patient who experienced fatigue with the combination, and one patient who could not tolerate pruritis associated with the selegiline patch. These results support existing data that this combination is relatively safe, with variable efficacies. If this combination is used, the TCA should be initiated first or at the same time as the MAOI.[9] It should be noted here that clomipramine, a TCA, exhibits potent inhibition of serotonin should not be used in combination with an MAOI.[38]

MAOI plus Bupropion

There are three existing cases published reporting on the use of bupropion and tranylcypromine in combination.[26, 27] Each of these cases resulted in improvement in depressive symptoms without reports of hypertension or other problematic adverse effects. Among the cases in our study, one patient continued combination treatment with bupropion and selegiline beyond 1 month, but efficacy was not well documented (Table 3, case 10). Of note, this patient was receiving transdermal selegiline, which poses a lower risk for hypertensive crisis due to its increased selectivity for MAO-B at this low dose, as previously highlighted. As such, it is not as sensitive to dietary tyramine intake as higher doses of transdermal or oral selegiline or other nonselective MAOIs. Two additional patients receiving bupropion in our case series did not demonstrate benefit with combination treatment (Table 3, cases 11–12). Given the limited published evidence, bupropion in combination with an MAOI may be considered; however, the risk for hypertension or other adverse effects should be monitored closely, and additional studies of this combination are needed.

MAOI plus Stimulants

Stimulants have been used safely in combination with MAOIs. Although stimulants are not indicated for the treatment of depression, these agents are used in clinical practice as an augmentation strategy for TRD.[39] The literature, of which the majority consists of case reports and case series, supports the use of stimulants in combination with an MAOI.[28–30] Stimulants may help to normalize blood pressure in those experiencing hypotension as a result of MAOI therapy. It should be noted that our case series did not highlight this combination. As with the other MAOI combinations, this should be reserved for treatment-resistant patients under the supervision of a qualified and experienced clinician, carefully assessing risk versus benefit.

MAOI plus Antidepressants plus Stimulants

The use of direct stimulants in combination with an MAOI plus another antidepressant has demonstrated safety and efficacy in case reports.[31, 32] Our patients showed mixed results. One patient taking amphetamine in addition to an MAOI and another antidepressant remained stable on this combination for longer than 10 months (Table 3, case 4). Another patient taking methylphenidate in addition to an MAOI and two antidepressants discontinued one of the antidepressants due to symptomatic hypotension and tachycardia, but the rest of her regimen remained the same (Table 4, case 10). The addition of stimulants to MAOI therapy has generally been avoided by physicians given the risk of hypertensive and hyperthermic crises. Blood pressure should be monitored closely as well as signs of other adverse effects. Similar to other combinations, this approach should be used with caution and under the supervision of a qualified and experienced clinician, particularly as a last resort option, including failure of electroconvulsive therapy.

Limitations

The limitations of a retrospective case series highlight recall bias and the nature of recorded clinical information. In the information we reviewed, patients may not have recollected their full diet or use of over-the-counter medications that may have contributed to adverse events. This potentially results in inaccurate records and thus adverse effects associated with diet, and medications prescribed by providers outside of our system may have been missed. As a retrospective case series, our data are strictly limited to medical records. Loss of patient follow-up could be mistaken as discontinuation of therapy, and the retrospective nature also relies on clear documentation in the medical record. Other limitations include variability among patients. Each patient presented with various depression severities, medications, formulations (patch vs oral, and selective vs nonselective MAO inhibition), and dosing regimens. These variances prevent the ability to make strong general conclusions on specific combination treatments.

Conclusion

Our case series and review of the literature suggest that when used under close supervision and under the care of an experienced clinician in psychiatry, combination therapy with MAOIs and other antidepressants (with the exception of SSRIs, SNRIs, or clomipramine) or stimulants may be a consideration for the challenging management of TRD in patients not responding to monotherapy or other combinations of antidepressants or augmentation strategies.

Two recent studies evaluated the use of the MAO type B inhibitor rasagiline in patients with Parkinson's disease in combination with various antidepressants and found no reports of serotonin toxicity.[40, 41] Coverage of this topic is important; however, recent literature to provide guidance on how to safely ude MAOIs for TRD in combination with other antidepressants or stimulant medications is sparse. The emerging use of electronic patient records offers the opportunity to gather therapeutic and outcomes data on larger numbers of patients. It is unlikely that clinical trials with a translational focus will be sponsored to study MAOIs and other currently used antidepressants in TRD. This is unfortunate, as longitudinal studies of individuals with TRD are needed and ideally will include embedded randomized controlled trials with combination treatment that includes MAOIs and other pharmacologic strategies. Focused environmental and pharmacologic inquiry aimed at determining why treatment resistance occurs and is sustained is needed. Our study with one health system shows that the data are accessible and that with existing data mining methods, we were able to show that one in five patients with TRD responded to a combination of an MAOI and other antidepressant. This is of major importance given that depression is so common and the finding that depression is the largest cause of disability and disability-adjusted life-years worldwide;[42, 43] disability due to depression is most likely TRD.

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Supporting Information

The following supporting information is available in the online version of this paper:

Data S1. Additional details for select patient cases organized by combination.