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CASE-BASED REVIEW ARTICLE

Augmentation of phenelzine with aripiprazole and quetiapine in a treatment-resistant patient with psychotic unipolar depression: case report and literature review

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Irreversible monoamine oxidase inhibitor (MAOI) antidepressants have significant efficacy in treatment-resistant unipolar depression, but in some instances patients may not achieve remission. Among the adjunctive and augmentation strategies, certain second-generation antipsychotics (SGAs) have approval for inadequate responders to antidepressant therapy, including aripiprazole, brexpiprazole, and quetiapine, with lurasidone and the olanzapine/fluoxetine combination indicated for bipolar depression. Clinicians may eschew SGA options in part due to the limited literature on SGA–MAOI combinations, with only one published case involving aripiprazole, and none for olanzapine, lurasidone, or brexpiprazole. In addition to the limited publication history on SGA–MAOI treatment, clinicians may also be deterred by uncertainty regarding SGA mechanisms and the risk of serotonin syndrome or other adverse outcomes. This paper describes the case of a 54-year-old male with a history of psychotic unipolar depression treated with a combination of phenelzine, aripiprazole, and quetiapine, and reviews the 12 published cases of SGA–MAOI combination therapy with a focus on the pharmacological basis for serotonin syndrome, and the SGA mechanisms that should not be associated with a risk for this syndrome.

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Key words: Monoamine oxidase inhibitor, aripiprazole, quetiapine, depression, antipsychotic.

Clinical Implications

- Irreversible monoamine oxidase inhibitor (MAOI) antidepressants have significant efficacy in treatment-resistant unipolar depression and may be combined with most SGAs due to their absence of potent serotonergic agonism.
- Ziprasidone has moderate affinity for the serotonin transporter, and one case report exists of serotonin syndrome (STS) when combined with tranylcypromine.

Introduction

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial demonstrated that under 50% of unipolar patients achieve remission in monotherapy trials of selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), mirtazapine, or bupropion, necessitating consideration of antidepressant combinations, augmentation options, and eventually irreversible nonselective monoamine oxidase inhibitors (MAOIs), such as phenelzine, isocarboxazid, or phenelzine.[1,2] While MAOIs are among the most effective agents for treatment-resistant major depressive disorders,[3] in some cases MAOI monotherapy may not result in remission, leading clinicians to consider adjunctive strategies for patients who have failed numerous antidepressant combinations and for whom switching is not a clinically prudent consideration. Although many commonly used adjunctive options lack level Ia or Ib evidence,[4,5] four second-generation antipsychotic (SGA) medications have received regulatory approval as adjunctive agents for unipolar depression: olanzapine, quetiapine, and the dopamine partial agonists aripiprazole and brexpiprazole.[6,7] Unfortunately, no controlled efficacy studies have examined augmentation of an MAOI with an SGA,

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TABLE 1. Case reports of combined treatment with an irreversible nonselective MAOI and a second-generation antipsychotic

Author, year	Case description	Outcome
Welner, 1996[12]	Male with treatment-resistant anxious unipolar depression on chlordiazepoxide 50 mg/d + phenelzine 60 mg/d responded in 2 days to the addition of risperidone 2 mg/d, with significant decrease in agitation. Phenelzine was next increased to 75 mg/d, and one week later, at the patient's request, the risperidone dose was increased to 3 mg/d with improved mood and concentration to the extent that the patient contemplated returning to work.	Significant response to the addition of risperidone within 2 weeks, but development of dystonia necessitated reduction in risperidone dose to 0.5 mg qhs. Ongoing orthostasis with falls resulted in need to taper off risperidone and decrease phenelzine to 60 mg/d. Improvement persisted after risperidone was tapered off and patient returned to work. Chlordiazepoxide was also successfully tapered.
Stoll & Haura, 2000[13]	Case series of three treatment-resistant unipolar patients (ages 45, 47, 57) and two bipolar patients (ages 57, 63) on tranylcypromine to which low-dose risperidone was added, initially at 0.5 mg qhs.	Significant response seen within 3–14 days at doses of 0.5 mg qhs ($n = 1$), 1 mg ($n = 1$), 1.5 mg ($n = 2$), and 2 mg ($n = 1$). Sustained response and remission in 4 of 5 cases over 8–14 months of combined treatment. One patient tapered off risperidone despite initial response due to complaints of sedation.
Sokolski & Brown, 2006[8]	42-year-old male with treatment-resistant unipolar depression. Low-dose quetiapine (50 mg/d) added for insomnia induced by phenelzine 75 mg/d.	Quetiapine 50 mg/d was well-tolerated with significant improvement in sleep duration.
Kohen *et al.*, 2007[9]	72-year-old female on phenelzine 30 mg/d for several years developed cogwheel rigidity, tremor and myoclonic jerks one week after quetiapine increased from 50 to 100 mg/d.	Quetiapine and phenelzine were discontinued with subsequent resolution of these symptoms within 24 hours.
Goforth & Carroll, 2007[15]	52-year-old female who experienced a partial response to tranylcypromine 60 mg/d for 4 weeks had adjunctive aripiprazole 10 mg/d added.	Aripiprazole 10 mg/d was well-tolerated with marked symptomatic improvement, but not to the point of remission.
Koerhuis *et al.*, 2008[10]	60-year-old female with treatment-resistant unipolar depression. She initially underwent a course of 26 ECT sessions, after which quetiapine 600 mg/d was added to the combination of tranylcypromine 60 mg/d + lithium 400 mg/d (serum level 0.50 mmol/L) when higher doses of the latter two medications were not tolerated.	Quetiapine 600 mg/d was well-tolerated, and the patient experienced symptomatic remission.
Rim & Gitlin, 2010[14]	60-year-old female with treatment-resistant unipolar depression elected to discontinue bupropion XL 450 mg and duloxetine 120 mg while remaining on ziprasidone 40 mg/d. After a 14-day washout, tranylcypromine was slowly added to ziprasidone. 24 hours after the MAOI dose was increased to 50 mg/d (day 23 of MAOI therapy), the patient reported acute onset of shivering, tremors, diaphoresis, fever, vomiting, diarrhea, confusion, with myoclonic jerks seen in the ER.	Ziprasidone and tranylcypromine were discontinued with subsequent resolution of these symptoms over 24 hours. One week later, restarted tranylcypromine, and this was titrated to 80 mg/d with orthostasis as the only adverse effect.
Frayne *et al.*, 2014[11]	31-year-old pregnant woman with history of treatment-resistant bipolar depression maintained throughout her pregnancy on the combination of lithium 900 mg/d (serum level 0.40–0.50 mmol/L), phenelzine 105 mg/d, and quetiapine 600 mg/d.	Patient remained euthymic on this combination, which was well-tolerated.

and as of 1 June 2016 there are only 12 case reports of psychiatric outcomes involving the combination of an SGA and an MAOI (Table 1), four of which involve quetiapine,[8–11] six with risperidone,[12,13] one with ziprasidone,[14] and one with aripiprazole.[15] Given the increasing utility of SGAs for more resistant forms of depression, there is a compelling need to add to the knowledge and literature regarding combined SGA and MAOI treatment.

Case Report

Mr. X was a 54-year-old white male admitted to a forensic psychiatric facility with a diagnosis of major depression, severe with psychotic features, in partial remission. The committing offense involved an attempted robbery perpetrated during a psychotic episode. There was strong suspicion that the psychotic symptoms may have been induced by substance use, and after admission to the forensic hospital, psychotic symptoms were generally not evident. However, the patient continued to experience significant persistent depressive symptoms despite trials of numerous antidepressant monotherapies and augmentation strategies that at one point included the combination of clomipramine 300 mg/d augmented with quetiapine up to 1200 mg/d (putatively for depression augmentation and depression-related sleep difficulties) + bupropion 450 mg/d + buspirone 60 mg/d + lithium 600 mg qhs. This individual failed to achieve significant symptomatic response and remained reclusive, with depressed mood, decreased energy, poor appetite, and poor self-care, although he was not psychotic. Based on the search for a novel antidepressant mechanism not found in the combination of the tricyclic antidepressant

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clomipramine augmented with quetiapine (the metabolite norquetiapine possesses norepinephrine reuptake and 5-HT_{2C} antagonism), aripiprazole was chosen due to its known efficacy as an adjunctive agent and the general low risk of extrapyramidal symptoms when started at doses <5 mg/day, begun on 23 January 2015, after the other adjunctive medications–lithium, buspirone–and bupropion were tapered off due to lack of efficacy. At that time, the patient did not wish to taper off quetiapine due to concerns about sleep quality. Adjunctive aripiprazole up to 15 mg/d achieved only modest benefit, so the treating clinician requested a formal psychopharmacology consultation to explore remaining therapeutic options. The patient indicated to the consultant that he did not wish to consider electroconvulsive therapy (ECT), but he would agree to an MAOI trial provided that he could remain on both aripiprazole and quetiapine. Phenelzine was started on 10 April 2015 at 15 mg qam while still on aripiprazole 15 mg and quetiapine 1000 mg/d. Over the next two months, quetiapine was decreased slowly to 300 mg qhs to minimize the risk of orthostasis as the MAOI dose was titrated upward, and both phenelzine and aripiprazole were steadily increased. By mid-June of 2015, the patient was on a combination of aripiprazole 20 mg/d, phenelzine 30 mg tid, and quetiapine 300 mg qhs, with a significant objective antidepressant response. The patient stated at one point that his mood was the best it had been "for years" on this combination, but he did complain of orthostasis, resulting in a temporary withdrawal of phenelzine on 9 September 2015 due to falls. After a 14-day washout of phenelzine, levomilnacipran was added to aripiprazole and quetiapine. When adjunctive levomilnacipran up to 80 mg/d failed to achieve any response, the patient insisted he would rather return to phenelzine despite the prior orthostasis problem.

Discussion

There is a significant response rate to irreversible nonselective MAOIs among depressed patients who fail other pharmacotherapeutic options.[16] Despite the abundant literature on MAOIs in treatment-resistant depression, these agents remain underutilized due to two safety concerns: (1) hypertensive crises from exposure to the pressor effects of tyramine-rich foods or sympathomimetic medications, and (2) STS due to concomitant use with agents that potently promote serotonergic neurotransmission: SSRI and SNRI antidepressants,[17–19] higher doses of tricyclic antidepressants (TCAs),[20] and an array of other compounds such as meperidine, tramadol, dextromethorphan, and chlorpheniramine that possess significant serotonin reuptake activity from the parent compound or its principal metabolite.[21]

The dietary requirements for MAOI treatment have been greatly simplified over the past two decades, as modern quantification methods delineate the exact tyramine content per 100-gram (or for sauces, 100 mL) servings of numerous foods.[21] Contrary to popular misconceptions, the number of such high-tyramine-content foods and sauces is relatively small, and the risk is manageable through patient education. (See Gillman [2011][21] for a list of such foods and sauces.)

The more vexing problem relates to clinician uncertainty regarding the pathophysiology of STS and the risk related to combination therapy with MAOIs. STS is the product of excessive central serotonergic tone, with compelling evidence that agonism at the $5HT_{2A}$ receptor primarily mediates the effects.[22,23] Thus, the 2007 FDA decision to place warnings about STS risk on antimigraine agents that act as 5-HT_{1B} and 5-HT_{1D} agonists (i.e., triptans) when combined with potent serotonin reuptake inhibitors was roundly criticized, especially after careful analysis of the suspected cases involving this interaction found that most did not meet the criteria for STS.[24,25]

For an agent to induce STS when combined with an MAOI it must provide a significant level of serotonergic signaling, a fact that engenders some confusion given the discrepant literature on TCAs. Prior to the advent of clomipramine, earlier TCAs were significantly less potent serotonin reuptake inhibitors. While there are case reports of significant reactions between TCAs (clomipramine aside) and MAOIs,[20] there are also extensive case series and reviews that document the safety of combining MAOIs with TCAs other than clomipramine.[26–32] Trazodone also exhibits no STS risk when coadministered with MAOIs, likely related to two important aspects of its pharmacology: (1) weak affinity for the serotonin transporter (Ki > 200 nM for trazodone and its primary metabolite meta-chlorophenylpiperazine), and (2) significant antagonism at the 5-HT_{2A} receptor, a feature that is protective for STS.[33–35]

Evidence for the safety of combining MAOIs with psychotropics that lack potent serotonin reuptake inhibition is also seen in the absence of case reports of STS for bupropion, mirtazapine, and psychostimulants.[36] Importantly, the MAOI must possess significant MAO-A inhibition, as serotonin is a substrate of MAO-A. Selective MAO-B inhibitors for Parkinson's disease (PD) are commonly coadministered with SSRIs due to the high prevalence of depression in the PD population. Rasagiline is indicated for PD and has 14-fold selectivity for MAO-B over MAO-A. Due to theoretical concerns related to its small but measurable MAO-A effects, rasagiline was studied in a large prospective trial of STS risk ($N = 1504$).[37] No STS cases were identified among those randomized to rasagiline + antidepressants ($n = 471$), 74.5% of whom were on SSRIs,[37] although it should be noted that there are two case reports in the

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literature of STS and one of acute confusional state with features of STS related to use of escitalopram or sertraline.[38–40]

Within the class of atypical antipsychotics, most possess significant antagonism of 5-HT_{2A} receptors and moderate partial agonism of 5-HT_{1A} receptors, while the dopamine partial agonists aripiprazole, brexpiprazole, and cariprazine also have partial agonism at dopamine D_2 and D_3 receptors.[41,42] Quetiapine's active metabolite norquetiapine is a moderate NRI,[43] but this mechanism should not be associated with serotonin syndrome; the sole case of STS with the NRI desipramine occurred in the context of an overdose on 300 mg of tranylcypromine.[44] There are also no case reports for the newer NRIs reboxetine and atomoxetine; moreover, the data indicate that NRIs with high affinity for the norepinephrine transporter significantly block the pressor response from tyramine exposure.[45]

Given the pharmacological mechanism underlying STS, the use of atypical antipsychotics with an MAOI would not be expected to provoke STS, and this syndrome was not described in the six risperidone cases,[12,13] one case of aripiprazole combined with tranylcypromine,[15] and in three of four quetiapine cases.[8–11] There is one case of a 72-year-old female on phenelzine 30 mg/d for several years who developed cogwheel rigidity, tremor, and myoclonic jerks one week after quetiapine was increased from 50 to 100 mg/d.[9] While the temporal association is compelling, the lack of a plausible pharmacological mechanism to induce STS by 100 mg/d of quetiapine suggests that there may be other possible explanations, especially given two case reports in which a quetiapine dose of 600 mg/d was tolerated.[10,11] Alternative scenarios include unintentional overdose of the MAOI, as occurred with the desipramine case described previously, or that what appeared as STS was instead severe extrapyramidal effects due to the modest kinetic interaction between phenelzine, a cytochrome P450 3A4 inhibitor, and quetiapine.[46] The sole source of concern for STS when an atypical antipsychotic is used together with an MAOI is ziprasidone, which has moderate SNRI effects (Ki = 53 nM at the serotonin transporter; 48 nM at the norepinephrine transporter).[47] Importantly, the combination of ziprasidone and tranylcypromine has been reported to induce STS 24 hours after tranylcypromine, started 23 days previously, was increased to 50 mg.[14] No psychiatric outcomes with olanzapine, iloperidone, asenapine, or lurasidone have been reported when combined with an MAOI. There is one pharmacokinetic study involving transdermal selegiline combined with olanzapine or risperidone that documented no safety concerns in healthy volunteers,[48] but orthostasis was a significant issue in the case described here and in one risperidone-treated patient on tranylcypromine.[12]

Conclusions

Monoamine oxidase inhibitors represent an effective but underutilized treatment modality often due to lack of understanding regarding mechanisms underlying hypertensive crises or serotonin syndrome. Newer antipsychotics possess multiple receptor affinities, and, with the exception of ziprasidone, none are potent serotonin agonists and should not induce STS in the presence of an MAOI. Importantly, many atypical antipsychotics have proven valuable for the treatment of depressive disorders and are ideal candidates for augmenting MAOIs in patients with inadequate response. Four of these agents have FDA-approved adjunctive indications in unipolar depression: olanzapine, quetiapine, aripiprazole, and brexpiprazole.[6,7] Lurasidone has an FDA indication for bipolar depression as monotherapy and as an adjunct to lithium or valproate, and double-blind monotherapy data in mixed unipolar depressive episodes,[49–51] and cariprazine has recent positive data in a double-blind unipolar adjunctive trial.[52] While the combination of an atypical antipsychotic and an MAOI may carry a risk of orthostasis in middle-aged and older patients, concerns about STS should not be the factor preventing its use. The case described herein is only the second to report an outcome where aripiprazole was combined with an MAOI, and hopefully will inspire clinicians to consider certain atypical antipsychotics, and the dopamine partial agonists in particular, as viable options for MAOI-treated patients.

Disclosures

Dr. Meyer reports receiving personal fees for speaking from Otsuka America Inc. and from Sunovion Pharmaceuticals, outside the submitted work. Drs. Cummings and Proctor hereby declare that they have nothing to disclose.

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