Evaluation of Combination Treatment with Monoamine Oxidase Inhibitors and Stimulants

Alexander Yang[1], Alesia Cloutier[2,3,4], Agustin Yip[3,5]

1. Harvard Medical School 2. Harvard South Shore Psychiatry Residency Training Program 3. Department of Psychiatry, Harvard Medical School 4. VA Boston Healthcare System 5. McLean Hospital

Treatment-resistant depression (TRD) is an all-too-common clinical occurrence for which monoamine oxidase inhibitors (MAO-I) have a place in stepwise pharmacotherapy, notwithstanding potentially life-threatening adverse effects from drug-drug and -food interactions. A complicating factor is that patients with TRD very often present with severe comorbidities necessitating the use of medications with which MAO-Is have a hypothetical interaction. For instance, the concurrent use of stimulants among TRD patients with co-morbid attention-deficit/hyperactivity disorder (ADHD) is fraught with concerns for such adverse events as hypertensive crisis, and serotonin syndrome, among others.

Systematic Review

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines were followed for the current systematic review. The protocol for this systematic review, however, was not registered prior to conducting the review.

Database

MEDLINE/PubMed

Terms

MAO-I, amphetamine, stimulant

Time

Jan 1960 - Aug 2020

***no restrictions on article type, study quality, randomization or use of control**

3638 total articles

63 after title screen

42 after duplicate removal

25 articles reviewed

Authors	Year	Study	Medication Combination	Outcome
Lloyd and Walker[1]	1965	Case report	Dexamphetamine Phenelzine	Death secondary to cerebral hemorrhage
Kriskó et al.[2]	1969	Case report	Tranylcypromine Dextroamphetamine	Nonfatal hyperpyrexia
Roecker and Lane[3]	1961	Case report	Dextroamphetaminemeamobarbital and MAOI (not specified)	Stupor and comatose
Bodner et al.[4]	1995	Case report	Isocarboxazid 30mg/day Trazodone 150mg/day Methylphenidate 10-20mg/day	Serotonin Syndrome Unclear if serotonin syndrome was secondary to combined MAOI and stimulant treatment or if it was secondary to antidepressant and MAOI combination.
Vytopil et al.[5]	2007	Case report	Modafinil 200mg/day Tranylcypromine 80mh/day	Acute Chorea and hyperthermia
Kinslow et al.[6]	2018	Case report	Tranylcypromine 40mg/day Armodafinil 250mg/day	Hypertensive emergency – BP 186/120 with associated severe headache, blurry vision, nausea and neck stiffness
O'dea and Rand[7]	1969	Randomized Control Trial	pretreatment of mice with MAOI (Tranylcypromine, isocarboxazid, phenelzine, mebanazine, pargyline, and nialamide) doses of 1/3rd and 2/3rd LD50 prior to treatment with tranylcypromine.	Results indicated a sharp increase in toxicity of amphetamine in mice pretreated with MAOI. The most effective at increasing toxicity of amphetamine was mebanazine, and phenelzine and pargyline were the least. Approximately 8-15% of the mice had terminal convulsant within the first two hours after pretreatment. Results indicated that the mechanism of interaction was secondary to increased catecholamines in peripheral and central stores.
Feighner et al[8]	1985	Case series (13 patients with Treatment resistant Depression [TRD])	Dextroamphetamine or methylphenidate combined with MAOI	No adverse events. Safe and effective
Sovner[9]	1990	Case report	Dextroamphetamine 10mg/day Tranylcypromine 40mg/day	No adverse events. Safe and effective
Fawcett et al[10]	1991	Prospective Clinical Trial of 32 patients in inpatient and outpatient setting with TRD	Pemoline 112.5mg/day or Dextroamphetamine 40mg/day Combined with tranylcypromine, phenelzine isocarboxazid, or pargyline	Twenty-five (78%) of these patients experienced at least 6 months of symptom remission with a stimulant + MAOI combination. Many patients required adjunctive antidepressant treatment, including tricyclics and lithium. Side effects were not excessive, though 6 patients (3 unipolar and 3 bipolar) cycled to mania (N = 1) or hypomania (N = 5). None developed hypertensive crises.
Myronuk et al.[11]	1996	Case report (ADHD and MDD)	Methylphenidate 40mg/day Moclobemide 600mg/day	No adverse events. Safe and effective
Clemons et al.[12]	2004	Case report (Narcolepsy)	Modafinil 200mg/day Tranylcypromine 25mg BID	No adverse events. Safe and effective
Shelton et al.[13]	2004	Case report (ADHD and TRD)	Phenelzine 45mg/day Methylphenidate 17.5mg/day	No adverse events. Safe and effective
Ashton et al.[14]	2004	Case report (Dysthymia)	Modafinil 100mg/day Phenelzine 30mg TID	No adverse events. Safe and effective
Feinberg et al.[15]	2004	Case report (TRD)	Tranylcypromine 50mg/day Methylphenidate 15mg TID	No adverse events. Safe and effective
Tobe et al.[16]	2015	Case series (MDD)	Either selegiline 24mg/day or Tranylcypromine 120mg/day AND Modafinil 400mg/day	No adverse events. Safe and effective
Thomas et al.[17]	2015	Literature Review and Retrospective case review of MAOI combined with psychotropic medications.	Patient 1: transdermal selegiline patch 12mg/day and amphetamine Patient 2: phenelzine 60mg/day, methylphenidate, desipramine 75mg/day and trazodone 300mg/day	Literature review concluded that positive outcomes were reported overall. Patient1: No adverse effects Patient 2: mild hypotension and tachycardia
Israel[18]	2015	Literature and Case report treated for ADHD and severe TRD.	Selegiline patch titrated to 12mg/day Lisdexamfetamine titrated to 50mg/day	Patient developed tachycardia that was chosen to be managed with Atenolol 25mg/day. He had marked improvement in mood with no severe adverse events.
Newton et al.[19]	2005	Randomized single-blind placebo controlled study (treated nine methamphetamine dependent patients with either selegiline or placebo).	Oral selegiline (10mg/day) or placebo AND IV methamphetamine (15-30mg)	The study found that IV administration of moderate doses of methamphetamine were safely tolerated. No adverse events.
Azzaro et al.[20]	2007	Prospective randomized trial (12 healthy patients)	Selegiline patch 6mg/day And Sympathomimetic agent (either pseudoephedrine 60 up to 3 times daily (every 8 hours) OR phenylpropanolamine 25 mg up to 6 times in 24 hours (every 4 hours	No adverse medical outcomes. Three of the 12 patients treated with selegiline patch and phenylpropanolamine experienced a mild increase in blood pressure with no adverse medical outcome.
Harris et al.[21]	2009	Phase 1 clinical trail (12 non-dependent cocaine experienced patients)	Selegiline patch 6mg/day AND Infused IV cocaine (0.5mg/kg over 10minutes, followed by 2mg/kg over 4 hours)	There were no pharmacological interactions that occurred in their 12 patients.
Schindler et al.[22]	2003	Controlled prospective trial in squirrel Monkeys	Monkeys were given 0.1 and 1.0mg/kg IV doses of d-methamphetamine following at least 7 days of treatment with 0.3mg/kg IM of selegiline	The results indicated that selegiline could be safely combined with methamphetamine. They even reported effects of methamphetamine on blood pressure and heart rate were significantly reduced with pretreatment with selegiline.

Results

Of the 3638 articles screened, 25 research studies were found to be of relevance. The majority of cases reported support that the use of MAO-Is in combination with a stimulant is safe. This is not true for all cases, however.

Case

The patient is a 31 yo man with TRD and attention deficit-hyperactivity disorder (ADHD) who had failed numerous trials comprising multiple antidepressant classes (including ketamine) and somatic therapies (electroconvulsive therapy [ECT] and transcranial magnetic stimulation [TMS]).

He presented with unremitting active suicidal ideation, having recently made a serious suicide attempt while admitted to an inpatient psychiatric unit. The patient had been maintained on mixed amphetamine salts for some time prior to presentation.

The patient was treated with a combination of transdermal selegiline patch (12mg/day) and mixed amphetamine salts, which was well tolerated with no adverse effects. He had marked improvement in mood and resolution of suicidal ideation. He was discharged home with outpatient follow up.

Discussion

Currently, the combination of MAOI and stimulants are contraindicated. We report a patient whose severe TRD was successfully treated with combined MAOI (selegiline patch) and stimulant (amphetamine) treatment. Similarly, the literature review indicates a large majority of recent reports demonstrating successful treatment with combined MAOI and stimulants. There are, however, other reports of serious adverse effects. This combination may be cautiously considered with close monitoring for side effects. Ultimately, however, further studies are needed to elucidate the drug-drug interaction within the appropriate clinical setting and prescribing practices.

References

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