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Concurrent use of ketamine and monoamine oxidase inhibitors in the treatment of depression: A letter to the editor

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Subanesthetic doses of ketamine can induce rapid antidepressant effects [1]. Research suggest that this effect is mediated in part by a glutamate surge leading to a cascade of events that result in synaptogenesis and reversal of the negative effects of chronic stress and depression [6]. Paired with the tremendous unmet need for novel therapeutic approaches, ketamine's use as a treatment for psychiatric disorders has rapidly increased, outpacing research on its safety [2].

Most published studies to date of ketamine for depression have been conducted with patients who are medication-free or whose medications are tightly controlled. Hence, there is very little data describing how ketamine may potentially interact with standard oral antidepressants or other psychotropic medications. Of specific concern, patients referred to our program are commonly treated with a monoamine oxidase inhibitor (MAOI), or may transition to one. Ketamine's ability to potentiate monoaminergic effects on cardiovascular function raises special concern for these patients.

Ketamine causes dose-dependent stimulation of the CNS that leads to increased sympathetic nervous system outflow, producing an increased heart rate and blood pressure [7]. A recent observational study by Riva-Posse and colleagues of 66 patients receiving 684 infusions with a 0.5 mg/kg dose intravenously over 40 min suggested that blood pressure changes with ketamine infusions for depression are mild, well tolerated and clinically insignificant [8].

Conflict of interest

Dr. Sanacora has received consulting fees from Allergan, Alkermes, AstraZeneca, Avanier Pharmaceuticals, Axsome Therapeutics BioHaven Pharmaceuticals, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb, Hoffman La-Roche, Intra-Cellular Therapies, Janssen, Merck, Naurex, Navitor Pharmaceuticals, Novartis, Noven Pharmaceuticals, Otsuka, Praxis Therapeutics, Sage Pharmaceuticals, Servier Pharmaceuticals, Taisho Pharmaceuticals, Teva, Valeant, and Vistagen therapeutics over the last 36 months. He has also received additional research contracts from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Hoffman La-Roche, Merck, Naurex, and Servier over the last 36 months. Free medication was provided to GS for an NIH-sponsored study by Sanofi-Aventis. In addition, he holds shares in BioHaven Pharmaceuticals Holding Company and is a co-inventor on a patent 'Glutamate agents in the treatment of mental disorders' (Patent number: 8778979).

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The rest of the authors have no conflicts of interest.

MAOI's exert their effects by preventing the deamination of monoamine oxidase in the brain and body. MAO-A deaminates primarily serotonin, epinephrine and norepinephrine, and is predominant in sympathetic nerve terminals in the Central Nervous System (CNS). MAO-B primarily deaminates dopamine and tyramine, and is present in the CNS and other organ systems. MAO's typically limit the amount of catecholamines stored in "stable" and "mobile" collections in pre-synaptic vesicles via noradrenaline (NA) turnover. With MAO-A inhibition there is a greater concentration of available catecholamines stored in brain and sympathetic terminals [9], with theoretically greater NA release with "indirect" stimulation (rather than "direct" stimulation at the post-synaptic site of NA activity) of sympathetic nerves by indirect sympathomimetic agents (including tyramine and ephedrine) potentially leading to sympathetic or hypertensive crisis [10]. For this reason, preference exists for direct sympathetic agents such as phenylephrine which work directly at the post-synaptic adrenergic receptors, however only case studies exist describing the concurrent use of indirect sympathomimetics and MAOI's and severe hypertension [10].

While its primary anti-depressant activity is thought to be due to its effects at the NMDA receptor and related downstream effects, ketamine's sympathomimetic activity is thought to be related to the blockade of extraneuronal catecholamine uptake in the nervous system [9,11]. This mechanism is somewhat novel, not considered either a direct nor indirect sympathometic, despite possibly potentiating sympathetic activity or sympathomimetics [9,12]. Notably, there are no absolute contraindications and this combination has likely been used many times in clinical practice for anesthetic purposes. A retrospective observational cohort study of 280,000 surgical procedures, including 51 patients concurrently treated with MAOIs, found no differences in hemodynamic outcomes compared to untreated surgical patients, although it was not clear how often ketamine was used [10]. In mouse models, those treated with high doses of ketamine while receiving tranylcypromine had no significant difference in LD_{50} (lethal dose 50%) than untreated mice receiving ketamine [12], in fact there was an increase in LD_{50} confirming a negative relationship.

We reviewed the literature describing concurrent use of ketamine and MAO-Is and found three cases, and we add five compiled in Table 1. In these cases[1], ketamine infusions were administered using standard antidepressant dosing parameters (0.5 mg/kg IV over 40 min).[1] While there is a theoretical concern for sympathetic potentiation, all but one of the patients were treated without significant changes in blood pressure or cardiovascular adverse events. One patient[2] experienced transient and asymptomatic increases in blood pressure to the 180's/110's during rare infusions that required temporary pauses in the infusion. This same patient, who had a significant comorbid cardiac history, experienced an NSTEMI at one point during her treatment course, which did not occur during an infusion, and was not thought to be related to the ketamine infusions.

As ketamine is an oft used anesthetic agent, the combination of ketamine and an MAOI has likely been used far more often than published. However while these eight cases are encouraging, we cannot state this combination is safe; it is essential to note that this

[1]Patient has been previously discussed in reference 5.
[2]New reported cases from our clinical service have been previously discussed in reference 6.

represents an extremely small number of cases which may not detect even relatively common occurrences of serious adverse events. The concurrent use of ketamine and MAO-Is should be pursued only with caution. Further research is needed to confirm safety of ketamine alone, and in combination with other pharmacologic agents. The type and quality of information required to provide this type of safety data can only be achieved through more formal surveillance through an organized registry.

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Table 1

Patient cases.

Age, sex	Psychiatric diagnosis	Medical comorbidities	Number of ketamine infusions	Dose of ketamine	MOA-I and dosage	Other medications	Average Baseline Blood Pressure and Heart Rate	Average of Max Blood Pressures and Heart Rate during infusions	Reference[b]
43, Female	MDD	Unknown	unknown	25–75 mg	tranylcypromine 10–80 mg	lithium (unknown dose)	Data unavailable	Data Unavailable	Bartova et al [3], 2015
74, Female	MDD	Unknown	unknown	25–50 mg	tranylcypromine 20 mg	Data Unavailable	Data unavailable	Data Unavailable	Bartova et al [3], 2015
42, Female	Anesthesia for procedure correcting a ruptured ectopic pregnancy	unknown	1	1.5 mg/kg	tranylcypromine 10 mg	succinylcholine 1.5 mg/kg, fentanyl, nitrous oxide, isoflurane, vecuronium (doses unknown)	Data unavailable	Data Unavailable	Doyle [4], 1990
62, Female[c]	Bipolar Depression	remote coronary artery dissection, remote STEMI, HTN, HLD	60	0.5 mg/kg	tranylcypromine 40 mg	aspirin 81 mg, atorvastatin 80 mg, enoxaparin 40 mg, lurasidone 40mg, lamotrigine 100mg,metoprolol 50 mg, trazadone 150 mg	127/74 HR:60	148/84 HR:65 (*max 180's/ 110's*)	This paper
55, Female	MDD with psychotic features	Obesity, urinary incontinence	53	0.5 mg/kg	tranylcypromine 10 mg–60 mg	atenolol 50 mg, gabapentin 600mg, Lithium 600mg, lorazepam 1 mg, mirabegron 50 mg, oxybutinin 10 mg, perphanazine 8 mg qd	122/81 HR:71	132/90 HR:73	This paper
26, Female	MDD	none	40	0.5 mg/kg	phenelzine 45mg	alprazolam 2mg qd,norethindrone-e.estradiol-iron 1mg–10 mcg–10 mcg	109/71 HR:75	118/80 HR:79	This paper
71, Male	MDD with psychotic features	COPD	4	30 mg	tranylcypromine 40mg	memantine 10 mg, olanzapine 10 mg, tiotropium 18mcg	157/75 HR:69	170/84 HR 73	This paper
60, Male	MDD with psychotic features	DM2, HTN, hypothyroidism	2	0.5 mg/kg	selegeline 12 mg	buspirone 10mg, methylphenidate 5 mg, risperidone 2 mg, Lamictal 200 mg Metformin 500 mg, lisinopril 2.5 mg, levothyroxine 150 mcg,	122/80 HR: 81	148/90 HR 86	This paper