Safety of Ketamine Augmentation to Monoamine Oxidase Inhibitors in Treatment-Resistant Depression:

A Systematic Literature Review and Case Series

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ABSTRACT

Objective: Ketamine is increasingly prescribed for treatment-resistant depression (TRD), often as add-on to regular antidepressants. Augmentation of ketamine to monoamine oxidase inhibitors (MAOIs) is advised against, as this practice might increase blood pressure or cause serotonin syndrome. Despite the potential relevance for patients, little is known about actual side effects of combined use. We summarize literature on the safety and add results of our case series.

Evidence Review: PubMed and Embase were searched from inception to July 2021 for English-language articles describing concomitant use of ketamine and MAOIs. The search strategy included terms for "ketamine" AND "monoamine oxidase inhibitor" including generic and brand names. Additionally, we describe the safety of twice weekly oral esketamine administration over the course of 5 weeks to 9 months in 8 TRD patients using MAOIs.

***Findings*:** After deduplication, we screened 138 articles and assessed 43 full texts. Twelve studies were included with a total of 39 patients receiving ketamine and MAOIs. Blood pressure and heart rate increased in multiple cases, though this was deemed clinically insignificant in all but 1 patient. No signs of hypertensive crisis or serotonin syndrome were observed. In our case series, we observed minor elevations in blood pressure and heart rate and no serious adverse events.

***Conclusions and Relevance*:** The results suggest that combined use of MAOIs and esketamine is less prone to severe side effects than presumed. The investigated sample size was small, and prescribed doses of MAOIs were relatively low. Further research is required before definite conclusions about the safety of this combination can be drawn.

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Approximately 30% of patients with major depressive disorder (MDD) show inadequate response to 4 subsequent treatment steps.[1] Monoamine oxidase inhibitors (MAOIs) have proven efficacy in patients who are unresponsive to prior treatment with other antidepressant drugs.[2–4] For the past two decades, the *N*-methyl-D-aspartate receptor (NMDA-R) antagonist ketamine and its *S*-enantiomer have also shown antidepressant effects in patients with treatment-resistant depression (TRD).[5–7] The antidepressant effects of a single ketamine administration last approximately 1 week,[6] and knowledge about long-term maintenance treatment is limited. The American Psychiatric Association consensus statement[8] and European perspective article[9] provide suggestions for a framework for off-label treatment with ketamine for TRD. In 2019, the US Food and Drug Administration and European Medicines Agency approved intranasal esketamine in conjunction with an oral antidepressant for TRD. To reduce the risk of relapse, ketamine and esketamine are often used as add-on to treatment with regular antidepressant medication. However, most trials investigating esketamine have excluded patients using MAOIs. The combination of ketamine and MAOIs is believed to possibly trigger serotonin syndrome or severe hypertension.[10–12]

By inhibiting the enzyme monoamine oxidase (MAO), MAOIs block the breakdown of monoaminergic neurotransmitters (serotonin, norepinephrine, and dopamine) and increase their availability in the central nervous system. MAOIs also block tyramine metabolization, and because excessive tyramine concentrations can cause hypertensive crisis, a low tyramine diet must be followed.[13] Administration of ketamine can also produce an increase in blood pressure and heart rate.[14]

While the antidepressant effects of ketamine are thought to stem from NMDA-R antagonism, ketamine has also been shown to elevate brain monoamine levels by increasing the release or by inhibiting the reuptake in vitro and ex vivo.[15–17] Amargós-Bosch et al[15] demonstrated an increased serotonin and norepinephrine efflux in the prefrontal cortex after ketamine administration in rats. A rat study by Tso et al[16] indicates effects of ketamine not only on efflux but also on uptake of dopamine, norepinephrine, and serotonin in different areas of the brain. The investigation of Nishimura and Sato[17] showed that ketamine inhibits monoamine transporters expressed in human embryonic kidney cells in a dose-dependent manner.

However, the clinical relevance of ketamine's effect on brain monoamine levels is still unclear.[18] There are no reports of the occurrence of serotonin syndrome as a result of ketamine addition to other serotonergic antidepressants. Simultaneously

Clinical Points

- Combined treatment with monoamine oxidase inhibitors (MAOIs) and ketamine usually is advised against because little is known about the risk of hypertensive crisis or serotonin syndrome. However, assurance of safety would enable access to a new treatment option for patients with highly treatment-resistant depression.
- To date, no signs of hypertensive crisis or serotonin syndrome have been described during concurrent use of ketamine and MAOIs.
- Conclusions regarding the safety of concurrent use of MAOIs and ketamine are limited by the small number of patients and relatively low dosages of MAOIs that have been investigated to date.

administering high ketamine doses and tranylcypromine in mouse models showed no effect on the median lethal dose in comparison with administering only ketamine in mice.[19] Moreover, multiple studies show that ketamine for depression is well-tolerated in general, with asymptomatic and transient rises in blood pressure (BP) and heart rate (HR) and no serious cardiovascular or other acute safety issues.[20–22]

TRD patients using MAOIs are generally excluded from add-on ketamine studies and treatment programs,[23,24] which in light of the aforementioned study findings may be overly cautious. Tapering of MAOIs can be time consuming and may cause worsening of depressive symptoms. Theoretically, continued use of a MAOI could also help prevent relapse after ketamine treatment. If safety can be assured, TRD patients who did not fully respond to MAOIs could be offered ketamine augmentation as a new add-on treatment option.

In this study, we evaluated symptoms of serotonin syndrome and hypertension during combined use of ketamine and MAOIs through a systematic review of the literature and a case series in 8 TRD patients.

SYSTEMATIC REVIEW

Methods

PubMed/MEDLINE and Embase were searched from inception to July 28, 2021, for English-language articles describing concomitant use of ketamine or esketamine and a MAOI. The search strategy included different terms for "ketamine" AND "monoamine oxidase inhibitor" including generic and brand names for the different MAOIs. The full search syntax can be found in the Supplementary Appendix 1. Two researchers (M.K. and J.K.E.V.) performed the search and selection process independently. Reference lists were hand searched for other relevant articles. Articles describing safety and efficacy of simultaneous administration of both ketamine and MAOIs in human subjects were included. Discrepancies were resolved by discussion. Relevant information regarding the patient population, ketamine or esketamine and MAOI treatment and clinical outcomes were extracted by two researchers (M.K. and J.K.E.V.). The Joanna Briggs Institute (JBI) critical appraisal tools for cohort studies, case series, and case reports were used for quality assessment of the included studies.[25] The systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-AnalysEs (PRISMA) statement.

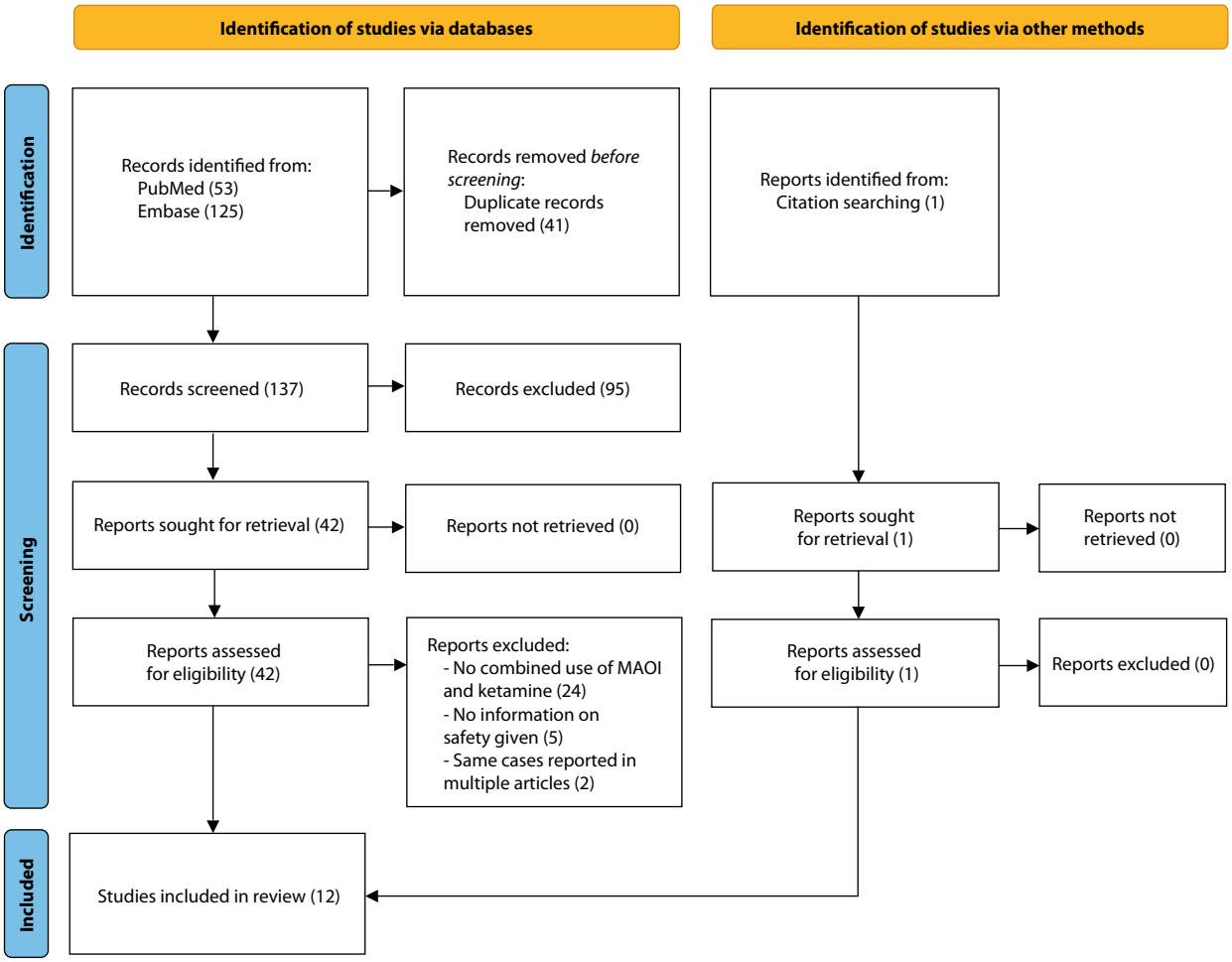
Results

The systematic search yielded 53 hits in PubMed/MEDLINE and 125 in Embase (Figure 1). After deduplication, a total of 137 references were screened for title/abstract. Forty-two references were screened for full text. Twenty-four articles described no combined use of MAOI and ketamine, and 5 articles[26–30] provided no specific information on safety; these were excluded. Two reports[31,32] described a case that was previously described. One article[29] was found via hand searching. Twelve articles reporting data on 39 patients were included in the review.[12,20,33–42] Extracted data from these articles are summarized in Table 1. Quality assessment of the included studies can be found in the Supplementary Table 1. All 4 case reports and the cohort study showed good reporting quality according to the JBI critical appraisal tools. Even though the quality of the case series was evaluated as poor, those data were included because they provide relevant evidence relating to the safety of combining MAOIs and ketamine.

Administered MAOIs consisted of nonselective irreversible MAOIs in most cases (n = 21 tranylcypromine, n = 8 phenelzine). The daily dose of tranylcypromine ranged from 10–60 mg/d and of phenelzine from 15–105 mg/d. In 8 patients, transdermal selegiline was administered with a dose (when specified) of 6 mg/d (n = 6) or 12 mg/d (n = 1). Three patients received moclobemide: 2 received 600 mg/d, and the other dose was unspecified. A majority of patients received intravenous (IV) racemic ketamine (n = 20) in dosages ranging from 0.5–1.5 mg/kg or esketamine (n = 17) in dosages up to 75 mg or ranging from 0.25 to 0.3 mg/kg. Two patients received intranasal (IN) administration: 1 ketamine (up to 60 mg/kg) and 1 esketamine (up to 56 mg). Fourteen patients received subcutaneous (SC) esketamine in dosages up to 0.5 mg/kg. The number of administrations, when specified, ranged from 1 to 60. One patient received ketamine as an IV anesthetic during hospitalization; all other patients received ketamine as treatment for depressive symptoms.

Multiple reports mentioned increases in BP and HR.[12,35,37,38,40] The patient described by Dunner et al[35] had a baseline BP ranging from 91 to 108 mm Hg systolic and from 56 to 70 mm Hg diastolic. The BP at 40 min after dosing ranged from 99 to 135 mm Hg systolic and 60 to 82 mm Hg diastolic. Lu et al[37] reported elevations in BP and HR, but these did not persist after 2 hours and did not require any intervention or termination of treatment. Bottemanne et al[33] found no significant hemodynamic changes in 3 patients within 2 hours of ketamine administration. Wang and Swainson[40] calculated the mean BP and HR in 3 patients for all treatments at baseline and during ketamine infusion (number of sessions = 45, 10, and 10, respectively). Their mean ± SD baseline systolic BP and mean highest systolic BP

Figure 1. PRISMA 2020 Flow Diagram



Abbreviation: MAOI = monoamine oxidase inhibitor.

during infusion was 125.4 ± 14.5 mm Hg and 128.5 ± 15.5 mm Hg, respectively. The mean diastolic BP was 78.9 ± 9.4 mm Hg (baseline) and 78.9 ± 9.8 mm Hg (highest during infusion). Mean ± SD HR was 81.5 ± 10.1 bpm (baseline) and 81.3 ± 9.4 bpm (highest during infusion). Ludwig et al[38] compared the mean and changes in BP and HR after esketamine infusion in patients with (n = 14) and without (n = 38) tranylcypromine use. Surprisingly, they noted a decrease in mean diastolic BP and HR after esketamine administration. The decrease in diastolic BP was smaller in the tranylcypromine group whereas the HR did not differ significantly. In patients taking tranylcypromine, the systolic BP increased by approximately 3 mm Hg, while the other group showed a decrease in systolic BP of almost 9 mm Hg. The mean absolute BP was within the normal physiologic range, and individual BP increases were asymptomatic. Nine patients received esketamine administration while on and off tranylcypromine. This did not seem to impact cardiovascular measures; no clinically relevant differences were found in mean changes or mean absolute cardiovascular parameters. Ludwig et al conducted a linear regression analysis in their cohort and observed a significant dose-response relationship between tranylcypromine and BP, especially relevant for the systolic BP with tranylcypromine doses higher than 40 mg.

Overall, no patients showed signs of hypertensive crisis or serotonin syndrome. Katz et al[12] reported clinically significant changes in vital signs in 1 patient. This patient had a significant comorbid cardiac history and experienced a non–ST-segment elevation myocardial infarction (NSTEMI) during the treatment course. This NSTEMI was not deemed to be related to the ketamine administration by the authors because it did not occur at the time of an infusion. The authors did not further elaborate on how any causal relationship could be discarded.

In the cases for which psychiatric outcomes were reported (n = 19), all patients showed improvement in depressive symptoms, suicidal intent, and/or anxiety with the combined use of ketamine and MAOI.

CASE SERIES

Methods

Patients with treatment-resistant depression received off-label "compassionate use" treatment in one academic

Table 1. Cases of Concomitant Ketamine and MAOI Use Reported in the Literature

Study	Age (y), Sex	(Psychiatric) Diagnosis	MAOI	Ketamine Treatment	Clinical Results (Efficacy)	Safety
Doyle 1990[34]	42, F	Depression. Emergency laparotomy for ruptured ectopic pregnancy in hemodynamically unstable condition	Tranylcypromine 20 mg/d	IV ketamine 1.5 mg/kg, single dose	Not applicable	Patient's hemodynamic course remained unchanged with induction and intubation
Szymkowicz et al 2013[39]	Age/sex unspecified	TRD with suicidal ideation	Phenelzine 45 mg/d	IV ketamine, 0.5 mg/kg, 6 infusions every other day	Response was produced	No significant physiologic or psychological side effects
Zigman and Blier 2013[42]	37, F	MDD with suicidal ideation, history of remote pituitary adenoma resection, treated for vitamin B_{12} deficiency and hypothyroidism	Moclobemide 600 mg/d	IV ketamine, 0.5 mg/kg, single infusion	Immediately after the 40-min infusion, dysphoria decreased from 10/10 to 3/10, anxiety from 8/10 to 0/10, and suicidal ideation from 9/10 to 0/10. Benefits lasted approx. 8 d	Vital signs were stable throughout, and there were no medical adverse events
Wink et al 2014[41]	29, F	ASD, MDD, anorexia nervosa, OCD	Transdermal selegiline (dose unspecified)	IN ketamine, 20 mg increased up to 60 mg, 12 treatments over 42 days	Acute state (within 24 h): improvement in mood, dramatically improved BDI and MADRS scores	Ketamine was well-tolerated. Adverse events: transient sedation, dizziness, numbness of limbs and face, blurred vision lasting approximately 90 min post dose, headache lasting 6–10 h post dose. No notable change in BP, HR, or body temperature.
Bartova et al 2015[18]	P1: 43, F P2: 74, F	P1: TRD P2: TRD, Graves' disease	P1: tranylcypromine 10 mg/d P2: tranylcypromine 20 mg/d	P1: IV esketamine, initial dose 12.5 mg increased to 75 mg, frequency and no. of infusions unspecified P2: IV esketamine, initial dose 25 mg increased to 50 mg twice weekly, no. of infusions unspecified	P1: Good antisuicidal effects P2: Good antisuicidal effects lasting approximately 24 h	P1: No relevant changes in vital signs P2: No relevant cardiovascular/vital signs changes
Kallmunzer et al 2016[36]	63, M	Unipolar depression (severe suicidal ideation), alcohol abuse (recovered)	Moclobemide (dose unspecified)	IV esketamine, 0.3 mg/kg, 7 infusions over 10 wk	MMSE baseline score: 27 MMSE discharge score: 26	Stable response, no evidence of serious cardiovascular side effects Recurrent headaches between wk 2 and 5
Katz et al 2018[12]	P1: 62, F P2: 55, F P3: 26, F P4: 71, M P5: 60, M	P1: bipolar depression, remote coronary artery dissection, remote STEMI, HTN, HLD P2: MDD with psychotic features, obesity, urinary incontinence P3: MDD P4: MDD with psychotic features, COPD P5: MDD with psychotic features, DM2, HTN, hypothyroidism	P1: tranylcypromine 40 mg/d P2: tranylcypromine dose ranging from 10 to 60 mg/d P3: phenelzine 45 mg/d P4: tranylcypromine 40 mg/d P5: selegiline 12 mg/d	IV ketamine P1: 0.5 mg/kg, 60 infusions P2: 0.5 mg/kg, 53 infusions P3: 0.5 mg/kg, 40 infusions P4: 30 mg, 4 infusions P5: 0.5 mg/kg, 2 infusions	No information given	All but 1 patient were treated without significant changes in blood pressure or cardiovascular adverse events. One patient (with comorbid cardiac history) experienced transient and asymptomatic increases in blood pressure to the 180s/110s during rare infusions that required temporary pauses in the infusion. An NSTEMI was experienced by this patient during study, not thought to be related to the ketamine infusions
Bottemanne et al 2020[33]	P1: 56 P2: 19 P3: 40 Sex unspecified	P1: TRD P2: bipolar TRD with suicidality P3: TRD	P1: phenelzine 45 mg/d, increased to 75 mg/d P2: phenelzine 45 mg/d, increased to 60 mg/d P3: switch from moclobemide 450–600 mg/d to phenelzine 45 mg/d during ketamine treatment	IV ketamine P1: 0.5 mg/kg, spaced 72 h apart, 6 infusions P2: 0.5 mg/kg, spaced 72 h apart, 9 infusions P3: 0.5 mg/kg, 3 infusions in 1 week, then 3 infusions of 0.75 mg/kg spaced 72 h apart, then 4 weekly infusions of 0.75 mg/kg	P1: MADRS decreased from 45/60 to 18/60 P2: MADRS score decreased from 49/60 to 34/60 and there was a significant reduction in suicidal ideation P3: MADRS score reduction from 41/60 to 18/60	No significant hemodynamic changes. During infusion, mean ± SD systolic blood pressure was 123 ± 9.8 mm Hg, mean diastolic blood pressure was 80 ± 12.2 mm Hg, mean heart rate was 91 ± 10.9 bpm. Ketamine infusion was not associated with a significant increase in blood pressure within 2 hours of administration

continued

Table 1 (continued). Cases of Concomitant Ketamine and MAOI Use Reported in the Literature

Study	Age (y), Sex	(Psychiatric) Diagnosis	MAOI	Ketamine Treatment	Clinical Results (Efficacy)	Safety
Dunner et al 2020[35]	61, F	Persistent depressive disorder (recurrent chronic major depressive disorder) with moderately severe anxious distress and with melancholic features	Tranylcypromine 60 mg/d	IN esketamine spray, doses ranging from 28 to 56 mg, twice weekly for 4 wk	Baseline depression and anxiety scores (including HARS, QIDS, HDRS, and MADRS) were in moderate range of anxiety and depression. At the end of treatment all mood and anxiety ratings were in normal range	No evidence of hypertension or serotonin syndrome
Lu et al 2020[37]	P1: F P2: M P3: F P4: M P5: F P6: F Age 36–84	Moderate or severe depression, suicidality P1: paranoia P2: pressure-inducing brain tumor P6: PTSD and ECT-related memory loss	Transdermal selegiline 6 mg/d	IV ketamine, 0.5 mg/kg, up to 3 infusions in 2 weeks, until significant improvement or 3 treatments were reached	All patients' MADRS scores decreased with an average of 15 (± 7)	Some patients had mild dissociative symptoms or elevated BP/HR, but none of these persisted after 2 h and did not result in additional intervention or treatment termination
Wang and Swainson 2020[40]	P1: 51, F P2: 57, M P3: 70, F	P1: TRD, hypothyroidism, migraine, gastroesophageal reflux disease, tobacco use disorder, obesity, HTN, dyslipidemia P2: TRD, DM2, alcohol use disorder, gestroesophageal reflux disease, previous ventricular septal defect repair P3: TRD, bipolar II disorder	P1: phenelzine titrated from 15 mg twice daily to 45 mg twice daily, initiated from the 29th ketamine infusion P2: phenelzine 60 mg and 45 mg daily P3: phenelzine titrated from 15 mg daily to 30 mg twice daily, initiated from the 8th ketamine infusion	IV ketamine 0.5 mg/kg P1: 73 infusions, weekly to twice weekly P2: 10 infusions P3: 8 infusions twice weekly, 10 infusions weekly	P1: IV ketamine was beneficial during duloxetine washout before initiation of phenelzine P2: good response P3: good effect	P1 and P3: treatment well-tolerated without precipitating an episode of hypertensive crisis P2: minor and transient BP and HR elevations that were well tolerated without precipitating an episode of hypertensive crisis. Over the total of 66 infusions in all patients, the mean ± SD baseline and highest systolic BP were, respectively, 125.4 ± 14.5 mm Hg and 128.5 ± 15.5 mm Hg (P = .011). The mean ± SD baseline and highest diastolic BP were, respectively, 78.9 ± 9.4 mm Hg and 78.9 ± 9.8 mm Hg (P = .98). The mean baseline and highest HR were, respectively 81.5 ± 10.1 bpm and 81.3 ± 9.4 bpm (P = .73).
Ludwig et al 2021[38]	Cohort study N = 43	Unipolar depression: n = 35 Bipolar depression: n = 14 Schizoaffective disorder: n = 3 Diagnosed HTN: n = 30	Tranylcypromine: n = 14 No tranylcypromine: n = 38 (9 both on and off tranylcypromine) Daily dose of tranylcypromine ranging from 10 to 60 mg	Esketamine 0.25–0.5 mg/kg First dose IV, subsequent doses SC In total, 507 doses Mean ± SD: TCP+: 6.29 ± 6.3 TCP–: 11.79 ± 9.56	No information given	A significant difference in mean BP and changes in BP between TCP+ and TCP– patients. Mean HR decreased in both groups and did not differ significantly. Mean ± SD systolic and diastolic BP: TCP+: 128.93 ± 18.54 mm Hg, 77.63 ± 11.46 mm Hg TCP–: 119.69 ± 12.49 mm Hg, 75.33 ± 9.68 mm Hg Mean Δ systolic and Δ diastolic BP: TCP+: 2.96 ± 18.11 mm Hg, −2.81 ± 11.20 mm Hg TCP–: −8.84 ± 11.31 mm Hg, −10.77 ± 9.14 mm Hg The mean absolute BP for both groups was within the normal physiological range. All BP increases were asymptomatic, no hypertensive crises. No patients discontinued treatment because of hemodynamic events. The data suggest a significant dose-response relationship between TCP dose and systolic BP

Abbeviations: ASD = autism spectrum disorder, BDI = Beck Depression Inventory, BP = blood pressure, bpm = beats per minute, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, ECT = electroconvulsive therapy, F = female, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, HLD = hyperlipidemia, HR = heart rate, HTN = hypertension, IN = intranasal, IV = intravenous, M = male, MADRS = Montgomery-Asberg Depression Rating Scale, MAOI = monoamine oxidase inhibitor, MDD = major depressive disorder, MMSE = Mini-Mental State Examination, NSTEMI = non–ST-segment elevation myocardial infarction, OCD = obsessive-compulsive disorder, P = patient, PTSD = posttraumatic stress disorder, QIDS = Quick Inventory of Depressive Symptomatology, SC = subcutaneous, STEMI = ST-segment elevation myocardial infarction, TCP = tranylcypromine, TRD = treatment-resistant depression.

Table 2. Case Series

Age (y), sex	Psychiatric Diagnosis	Medical Comorbidities	Oral Esketamine Treatment	MAOI	Other Medication	Mean BP (mm Hg): Baseline 30 min 120 min	Mean HR (bpm): Baseline 30 min 120 min
60, M	TRD, bipolar II disorder	None	Twice-weekly treatment for 6 wk. Start dose 1 mg/kg, increased to 3 mg/kg	Tranylcypromine 40 mg/d	Quetiapine 200 mg, lorazepam 1 mg	144/88 153/96 146/92	68 79 73
55, M	TRD, personality disorder	Hypothyroidism	Twice-weekly ongoing treatment. Start dose 1.0 mg/kg, increased to 2.0 mg/kg. Treatment for 9 mo at the time of evaluation	Tranylcypromine 40 mg/d	Lorazepam 4 dd 1 mg, olanzapine 1 dd 25 mg, pantoprazole 1 dd 40 mg, zopiclone 1 dd 7.5 mg, levothyroxine 1 dd 50 µg	129/87 132/94 126/94	111 114 97
32, F	TRD	None	Twice-weekly treatment, in total 42 treatment sessions over the course of 5 mo. Start dose 0.5 mg/kg, increased to 2.0 mg/kg	Selegiline 50 mg/d (oral)	Trazodone 1 dd 200 mg, aripiprazole 1 dd 10 mg, lorazepam 2 dd 2.5 mg	114/76 116/79 113/77	75 72 77
57, M	TRD, ASD	Paroxysmal atrial fibrillation	Seven treatments in 5 wk. Dose increased to 2.0 mg/kg	Tranylcypromine 60 mg/d	Quetiapine 1 dd 75 mg	132/88 145/96 138/90	72 75 72
52, F	TRD, ASD	CVA, atrial septal defect, subclinical hypothyroidism	Twice-weekly ongoing treatment. Start dose 1 mg/kg, increased to 2 mg/kg. Treatment for 13 wk at the time of evaluation	Tranylcypromine 40 mg/d	Lithium 1 dd 400 mg, quetiapine 1 dd 275 mg, flupentixol 1 dd 5 mg, biperiden 2 dd 2 mg, levothyroxine 1 dd 25 µg, simvastatin 1 dd 40 mg, clopidogrel 1 dd 75 mg, metformin 2 dd 500 mg, pantoprazole 1 dd 40 mg	119/82 120/74 125/84	83 74 78
68, F	TRD, bipolar disorder	DM2, hypertension, decreased kidney function (GFR = 32 mL/min), hypothyroidism, appendectomy	Twice-weekly treatment for 6 wk. Dose increased to 3.0 mg/kg	Tranylcypromine 80 mg/d	Lithium 1 dd 500 mg, levothyroxine 1 dd 75 µg, atorvastatin 1 dd 20 mg, colecalciferol 5,600 IU weekly, furosemide 1 dd 40 mg, insulatard flexpen 1 dd 58 IU, metformin 2 dd 500 mg, tolbutamide 2 dd 1,000 mg, oxazepam 2 dd 5 mg	136/73 124/73 127/69	89 80 81
78, M	TRD, ASD	Arrhythmias (unspecified), TURP	Twice-weekly treatment for 6 wk. Dose increased to 3.0 mg/kg	Tranylcypromine 60 mg/d	Atenolol 1 dd 25 mg, oxazepam 3 dd 10 mg, vitamin D 1 dd 20 µg 800 IU	124/64 127/62 122/61	64 62 50
49, F	TRD	Asthmatic bronchitis, cholecystectomy, gastric ulcer	Twice-weekly treatment for 6 wk. Dose increased to 2.75 mg/kg	Phenelzine 60 mg/d	Biperiden 2 dd 1 mg, bisoprolol 1 dd 1.25 mg, budenoside 2 dd 200 µg, ipratropium 4 dd 20 µg, lorazepam 3 dd 1 mg, olanzapine 1 dd 15 mg, omeprazole 2 dd 20 mg, salbutamol 4 dd 100 µg	124/67 130/66 123/67	79 76 71

Abbreviations: ASD = autism spectrum disorder, BP = blood pressure, bpm = beats per minute, CVA = cerebrovascular accident, dd = daily dose, DM = diabetes mellitus, GFR = glomerular filtration rate, HR = heart rate, IN = intranasal, IV = intravenous, MAOI = monoamine oxidase inhibitor, PRN = pro re nata, TRD = treatment-resistant depression, TURP = transurethral resection of the prostate.

and two specialized mood disorder treatment centers in the Netherlands, using generic oral esketamine in twice-weekly dosing. Esketamine treatment started at a dose of 0.5 or 1 mg/kg and was titrated over the course of 6 weeks based on antidepressant effects and tolerability to a maximum dose of 3 mg/kg. Key inclusion criteria were a diagnosis of MDD (Mini-International Neuropsychiatric Interview[43]) and treatment resistance defined as having had insufficient response to adequate treatment with at least 3 different classes of antidepressants. Esketamine treatment was provided as add-on to other antidepressants. Vital signs (BP and HR) were monitored in the first 6 weeks of treatment

Table 3. SAFTEE Scores for Symptoms Assessed in Case Series[a]

Symptom	P1	P2	P3	P4	P5	P6	P7	P8
Feeling nervous or hyper	2	−2	−3	0	−2	1	−1	0
Weakness or fatigue	0	0	0	−1	−1	2	0	2
Feeling strange or unreal	3	3	2	0	2	2	0	3
Hearing or seeing things	0	2	0	0	3	0	0	−1
Abnormal sensations	0	0	2	0	3	1	0	1
Headache	0	1	0	0	0	0	0	0
Muscle cramps/stiffness	1	0	−1	0	−1	−1	0	0
Muscle twitching or movements	1	0	−1	0	−1	−1	0	−2
Trouble sitting still	0	−1	−1	0	−1	0	1	−2
Tremor or shakiness	0	0	0	0	−1	−1	0	−2
Heartbeat rapid or pounding	0	0	0	0	−1	0	0	0
Trouble catching breath or hyperventilation	0	0	0	0	−1	0	0	−1
Chest pain	0	0	0	0	0	0	0	−1
Nausea or vomiting	0	0	3	0	0	0	0	0
Stomach or abdominal discomfort	0	0	1	0	0	0	0	−1
Sweating excessively	0	0	0	0	−1	0	0	0

[a]Scores shown as SAFTEE score at 30 min after esketamine administration in week 5 or 6 – baseline SAFTEE score.
Abbreviations: P = patient, SAFTEE = Systematic Assessment For Treatment Emergent Effects.

before esketamine administration and after 30 and 120 minutes. Side effects were assessed using the Systematic Assessment For Treatment Emergent Effects (SAFTEE) questionnaire,[44] which, among other things, covers items that could indicate the occurrence of hypertensive crisis or serotonin syndrome. These include feeling nervous or hyper, weakness or fatigue, feeling strange or unreal, hallucinations, abnormal sensations, headache, muscle cramps/stiffness, muscle twitching or movements, trouble sitting still, tremor or shakiness, heartbeat rapid or pounding, trouble catching breath or hyperventilation, chest pain, nausea or vomiting, stomach or abdominal discomfort, and sweating excessively. These SAFTEE items were assessed before and after esketamine administration on a scale of none (0), mild (1), moderate (2), and severe (3). Reported side effects 30 minutes after esketamine administration in week 5 or 6 (with the maximum esketamine dose) were compared to baseline.

Results

Six patients used tranylcypromine in doses of 40 mg/d (n = 3), 60 mg/d (n = 2), and 80 mg/d (n = 1); 1 patient received oral selegiline (50 mg/d); and 1 patient received phenelzine (60 mg/d). Esketamine doses ranged from 0.5 mg/kg to 3.0 mg/kg per administration. The duration of esketamine treatment ranged from 5 weeks to 9 months. Data for these patients are summarized in Table 2, including mean BP and HR from the first 6 weeks of treatment. Overall, the combination of MAOI and esketamine in these patients did not evoke serious adverse events. BP and HR showed minor and transient elevations, mostly after 30 minutes: on average, systolic BP increased by 3 mm Hg (range, −12 to +13 mm Hg). Diastolic BP showed a 1 mm Hg increase on average compared to the baseline measurements (range, −8 to +8 mm Hg). HR decreased by 1 bpm on average (range, −9 to +11 bpm). Measurements after 120 minutes, compared to the baseline measurements, showed no mean difference (0 mm Hg) in systolic BP (range, −9 to +6 mm Hg), no mean difference (0 mm Hg) in diastolic BP (range, −4 to +7 mm Hg), and a decrease in HR by 5 bpm (range, −14 to +5 bpm). Six patients reported feeling strange or unreal, and 4 patients reported abnormal sensations. Weakness or fatigue and hearing or seeing things were reported by 2 patients. Headache, muscle cramps/stiffness, muscle twitching or movements, trouble sitting still, nausea or vomiting, and stomach or abdominal discomfort were all reported once. SAFTEE scores can be found in Table 3. No side effects requiring medical intervention occurred.

DISCUSSION

Our review of the literature shows that single and repeated administration of ketamine or esketamine in 39 patients using MAOIs was generally safe and well tolerated with regard to cardiovascular effects and symptoms of serotonin syndrome. Increases in BP and HR occurred frequently but were mild and transient and did not exceed the levels reported in other patients receiving ketamine or esketamine.[15–17,25] Moreover, the significant differences in BP between patients on and off tranylcypromine in the cohort study by Ludwig et al[28] were a result of a surprising drop in BP after esketamine administration in patients not using tranylcypromine. No signs of hypertensive emergency or serotonin syndrome were observed. A single case of NSTEMI was described in a patient with a cardiac history during the course of treatment. Although it did not occur during an infusion, it is difficult to rule out any causal relationship.

The results of our own case series are in line with the results of the literature review. No patients showed serious side effects indicative of serotonin syndrome or hypertensive crisis related to the combined use of esketamine and MAOIs.

Important limitations of currently available reports are the poor quality of the case series, the small number of investigated patients, and the fact that MAOI dosages were relatively low. In MDD treatment, 40–60 mg/d of tranylcypromine or 60–90 mg/d of phenelzine are common,[4] but higher dosages are also used in clinical practice (eg, up to 120 mg/d tranylcypromine if side effects are tolerated). Yet, in most reports, patients received low doses[13,14,24,29,30] and only few patients[14,25,28] received 60 mg/d tranylcypromine. In our case series, 1 patient received a daily dose of 80 mg tranylcypromine, 2 received 60 mg, and the other 3 patients used 40 mg. The results of the review therefore suggest good safety and tolerability, but these conclusions cannot automatically be drawn for higher MAOI dosages. The cohort study of Ludwig et al[28] suggests a significant correlation between tranylcypromine dose and systolic blood pressure after esketamine administration.

In evaluating the risk of hypertensive emergency, there are other factors to take into account such as ketamine dosage, dosing routes and formulations, and predictors for increased cardiovascular response to ketamine administration. Blood pressure increases more when using higher ketamine dosages, solution formulations, and routes

of administrations with earlier time to peak concentration (T_{max}) values.[45] IV, SC, and intramuscular (IM) ketamine administration were compared in a double-blind, placebo-controlled pilot study,[46] with SC administration having the least cardiovascular side effects. Elderly patients receiving ketamine for depression showed greater change in BP,[21,22,47] which is likely related to increased arterial stiffness.[48] Patients with a history of hypertension or a higher baseline BP also experience more BP elevations after subanesthetic ketamine than those without.[8,47,49] Furthermore, female sex and the norepinephrine transporter (NET) rs28386840 genotype (associated with lower transporter expression[50]) predict increased cardiovascular sequelae of ketamine administration.[48] It has not been investigated whether certain psychiatric disorders increase the risk for cardiovascular effects of ketamine treatment. However, this can be hypothesized in the case of posttraumatic stress disorder (PTSD), because these patients may have additional risk factors for hypertension.[51]

The influence of ketamine on the serotonergic system in humans has not been fully elucidated. Positron emission tomography (PET) studies in vitro[52] and in vivo in monkeys have showed binding affinity of ketamine for the serotonin reuptake transporter (SERT) at IV doses of 1.5 mg/kg[53] and 7.5 mg/kg.[54] Through SERT-binding, ketamine inhibits 5-hydroxytryptamine (5-HT) reuptake, as shown in other in vitro and animal studies.[54–57] However, a PET study[58] investigating ketamine's binding on the SERT in humans demonstrated no measurable occupancy after administration of an antidepressant ketamine dose (0.5 mg/kg IV) because the occupancy values were within the test-retest variability. The study did find a positive correlation between plasma ketamine levels and SERT occupancy. This finding suggests that SERT binding and subsequent 5-HT reuptake inhibition might occur at higher ketamine dosages, which is in line with the results of the animal studies. The risk of serotonin syndrome with regularly used antidepressant dosages of ketamine (eg, equivalents of 0.5 mg/kg IV) therefore appears limited, whereas this risk might increase with higher dosages, for instance when ketamine is used for anesthesia or in dose escalation for depression.[27]

Given the rather positive effects on symptoms of depression, suicidality, and anxiety reported in the cases described in this review, we believe the combination of MAOI and ketamine definitely merits further, but careful investigation. The recent esketamine market authorization will likely lead to a further increase in prescription and use. Current phase III clinical trials with intranasal esketamine explicitly exclude patients from taking MAOIs,[59–62] but the prescribing information of the US Food and Drug Administration–approved nasal spray only advises close monitoring of blood pressure with concomitant use of MAOIs.[63] Our findings would encourage further investigation of ketamine and esketamine in patients using MAOIs, which is a necessary step before combined use could be advocated on a larger scale. The occurrence of serious adverse events can be detected only in larger study populations and through careful monitoring. Our findings thus add to the broader call for systematic monitoring of treatment outcomes and possible adverse effects of different forms of esketamine treatment, ideally using national or international registries.[64–67]

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Supplementary Material

Article Title: Safety of Ketamine Augmentation to Monoamine Oxidase Inhibitors in Treatment-Resistant Depression: A Systematic Literature Review and Case Series

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List of Supplementary Material for the article

1. Appendix 1 Search Syntax
2. Table 1 Quality Assessment According to the JBI Critical Appraisal Tools

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Appendix 1: search syntax

Pubmed: 28-7-2021: 53 hits

("esketamine"[Supplementary Concept] OR esketamine[tiab] OR ketamine[tiab] OR "ketamine"[MeSH Terms] OR ketamin*[tiab])

AND

("mao-i"[Tiab] OR "monoamine oxidase inhibitors"[Pharmacological Action] OR "monoamine oxidase inhibitors"[MeSH Terms] OR "monoamine oxidase inhibitor*"[Tiab] OR "hydrazine"[Supplementary Concept] OR "hydrazin*"[Tiab] OR "hydrazines"[MeSH Terms] OR "isocarboxazid"[MeSH Terms] OR "isocarboxazid*"[Tiab] OR "marplan"[Tiab] OR "nialamide"[MeSH Terms] OR "Niamid*"[Tiab] OR Nialamide[tiab] OR "phenelzine"[MeSH Terms] OR "phenelzine"[Tiab] OR "nardil"[Tiab] OR "nardelzine"[Tiab] OR "Hydracarbazine"[Tiab] OR "tranylcypromine"[MeSH Terms] OR "tranylcypromine"[Tiab] OR "parnate"[Tiab] OR "tranylcypromine"[MeSH Terms] OR "tranylcypromine"[Tiab] OR "jatrosom"[Tiab] OR "moclobemide"[MeSH Terms] OR "moclobemid*"[Tiab] OR "aurorix"[Tiab] OR "manerix"[Tiab] OR "rasagiline"[Supplementary Concept] OR "rasagiline"[Tiab] OR "azilect"[Tiab] OR "selegiline"[MeSH Terms] OR "selegiline*"[Tiab] OR deprenyl*[Tiab] OR "eldepryl"[Tiab] OR "emsam"[Tiab] OR "zelapar"[Tiab] OR "safinamide"[Supplementary Concept] OR "safinamide"[Tiab] OR "xadago"[Tiab])

Embase: 28-7-2021: 125 hits

('esketamine'/exp OR 'ketamin'/exp OR (esketamine OR ketamin*):ab,ti)

AND ('mao i' OR 'monoamine oxidase inhibitor*' OR 'hydrazin*' OR 'isocarboxazid' OR 'marplan' OR 'nialamide' OR 'phenelzine' OR 'nardil' OR nardelzine OR hydracarbazine OR tranylcypromine OR parnate OR jatrosom OR moclobemide OR aurorix OR manerix OR rasagiline OR azilect OR selegiline OR deprenyl OR eldepryl OR emsam OR zelapar OR safinamide OR xadago)

Supplementary Table 1: Quality assessment according to the JBI critical appraisal tools

Legend

Yes: ✔

No: X

Not applicable: –

Checklist for case reports	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or assessment methods and the results clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	Overall appraisal
Doyle et al. 1990[34]	✔	✔	✔	✔	✔	✔	✔	✔	✔
Zigman et al. 2013[42]	✔	✔	✔	✔	✔	✔	✔	✔	✔
Wink et al. 2014[41]	✔	✔	✔	✔	✔	✔	✔	✔	✔
Dunner et al. 2020[35]	✔	✔	✔	✔	✔	✔	✔	✔	✔

Checklist for case series	Were there clear criteria for inclusion?	Was the condition measured in a standard, reliable way for all participants included?	Were valid methods used for identification of the condition for all participants included?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there a clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow-up results of cases clearly reported?	Was there clear reporting of the presenting site(s)/ clinic(s) demographic information?	Was statistical analysis appropriate?	Overall appraisal
Szymkowicz et al. 2013[39]	✔	✔	✔	X	X	X	✔	✔	✔	–	X
Bartova et al. 2015[20]	✔	X	X	X	X	✔	✔	✔	X	–	X

Kallmunzer et al. 2016[36]	✔	✔	✔	X	X	✔	✔	✔	✔	–	X
Katz et al. 2018[12]	X	X	X	X	X	X	✔	✔	X	–	X
Bottemanne et al. 2020[33]	✔	✔	✔	X	X	X	✔	✔	X	–	X
Lu et al. 2020[37]	✔	✔	✔	X	X	✔	✔	✔	✔	–	X
Wang et al. 2020[40]	✔	✔	X	X	X	✔	✔	✔	✔	–	X

Checklist for cohort studies	Were the two groups similar and recruited from the same population?	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Was the exposure measured in a valid and reliable way?	Were con-founding factors identified?	Were strategies to deal with confoundin g factors stated?	Were the groups/ participants free of the outcome at the start of the study (or at the moment of exposure)?	Were the outcomes measured in a valid and reliable way?	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Were strategies to address incomplete follow up utilized?	Was appropriate statistical analysis used?	Overall appraisal
Ludwig et al. 2021[38]	✔	✔	✔	✔	✔	✔	✔	✔	✔	–	✔	✔