Safety and Tolerability of Concomitant Intranasal Esketamine Treatment With Irreversible, Nonselective MAOIs:
A Case Series

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Intranasal esketamine has been approved to treat adults with treatment-resistant depression (TRD) and depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior in conjunction with an oral antidepressant. However, per esketamine prescribing information, concomitant use with monoamine oxidase inhibitors (MAOIs) may increase blood pressure.[1] This case series reviews the safety of 3 female patients with TRD who received intranasal esketamine in conjunction with MAOI pharmacotherapy.

Case 1

The first patient, a 74-year-old woman, was initiated on phenelzine in November 2020. The patient did not achieve remission, and thus she started augmentation with esketamine in April 2021. During the first treatment with esketamine 56 mg, the patient's blood pressures at baseline, 40 minutes postdose, and 2 hours postdose were 116/79 mm Hg, 137/85 mm Hg, and 200/99 mm Hg, respectively. Although the patient was asymptomatic, she was given amlodipine 10 mg. A repeat blood pressure measurement approximately 3 hours postdose was 110/66 mm Hg. During the patient's next esketamine treatment 4 days later, her afternoon dose (15 mg) of phenelzine was held and she received 84 mg of intranasal esketamine. The patient's baseline, 40 minutes postdose, and 2 hours postdose blood pressures were 101/59 mm Hg, 128/80 mm Hg, and 142/78 mm Hg, respectively. The patient switched from phenelzine to tranylcypromine after a taper in February 2022 due to cognitive issues, such as confusion, and unsteadiness, as well as due to a lack of response to phenelzine therapy at a tolerable level. Throughout her remaining 37 treatments with esketamine and either phenelzine or tranylcypromine over approximately 11 months, she showed no significantly elevated blood pressure readings (Figure 1).

Case 2

The second patient, a 32-year-old woman, was initiated on esketamine in June 2019. After 73 esketamine treatments, the patient started augmentation with tranylcypromine for persistent suicidal ideation in November 2020. Throughout the patient's concomitant 49 treatments with esketamine and tranylcypromine over approximately 14 months, she had no significantly elevated blood pressure readings (Figure 1).

Case 3

The third patient, a 61-year-old woman, was initiated on esketamine in March 2017, as a participant in the SUSTAIN-3 study, an esketamine open-label long-term extension study (NCT02782104). After 152 treatments, the patient did not achieve remission and thus started augmentation with tranylcypromine in March 2020. Throughout the patient's subsequent 9 treatments with intranasal esketamine and MAOI therapies over approximately 2 months, she showed no significantly elevated blood pressure readings (Figure 1).

Discussion

Treatment of TRD with esketamine is approved to be initiated with an oral antidepressant. However, the clinical trials that led to the approval of esketamine for TRD excluded patients currently taking MAOIs, and there are limited data regarding esketamine and MAOI interactions.[2] It is not uncommon for individuals with TRD to be taking MAOIs after failure of many other therapies[3]; however, given the lack of safety data and risk of elevated blood pressures, prescribers are often hesitant to use MAOIs in combination with other antidepressant therapies.[4]

One previously published case report[5] showed no evidence of significantly elevated blood pressures with concomitant esketamine and tranylcypromine. Additionally, a recent retrospective cohort study[6] that investigated cardiovascular changes when administering subcutaneous or intravenous esketamine with tranylcypromine for TRD found no clinically significant changes in blood pressure or heart rate. To our knowledge, this is the first case series that reviews the safety and tolerability of concomitant intranasal esketamine therapy with various MAOI therapies, specifically phenelzine and tranylcypromine.

These preliminary data suggest that when clinically indicated, concomitant use of intranasal esketamine with an irreversible, nonselective MAOI may be safe in some subjects acutely and long-term. However, careful blood pressure monitoring is necessary as evidenced by blood pressure elevation seen with phenelzine, but not tranylcypromine, in our first patient. It is important to consider that this

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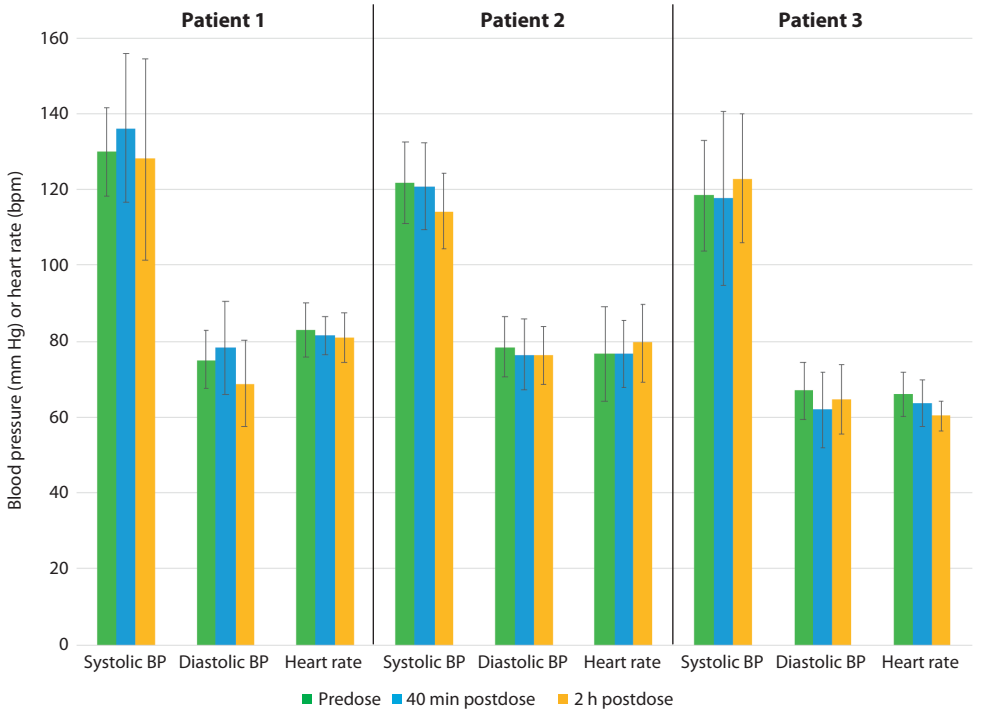
Figure 1. Mean Blood Pressure and Heart Rate at Predose, 40 minutes Postdose, and 2 Hours Postdose Timepoints[a]



[a]*P* values were calculated using an analysis of variance single factor test with an α level of 0.05. Standard deviation for each data set is displayed with error bars. Two-sample *t* test revealed a statistically significant decrease in diastolic blood pressure between the predose and 2 hours postdose ($P = .0052$) and between the 40 minutes postdose and 2 hours postdose ($P = .0008$) measurements. Otherwise, there was no statistically significant difference between systolic blood pressure ($P = .166$) and heart rate ($P = .475$) measurements (n = 38). Two-sample *t* test revealed a statistically significant decrease in systolic blood pressure between the predose and 2 hours postdose ($P = .0007$) and between the 40 minutes postdose and 2 hours postdose ($P = .0037$) measurements. Otherwise, there was no statistically significant difference between diastolic blood pressure (*P* value = .358) and heart rate ($P = .369$) measurements (n = 49). Two-sample *t* test revealed no statistically significant difference between predose, 40 minutes postdose, and 1 hour postdose measurements of systolic blood pressure ($P = .814$), diastolic blood pressure ($P = .518$), or heart rate ($P = .096$) (n = 9). For specific values, refer to Supplementary Table 1.

phenomenon of blood pressure elevation specifically seen during this patient's first esketamine administration could be due to intranasal esketamine alone.[7] Given that this case series includes only 3 patients, there is still a need for more data to show that esketamine and MAOIs can be safely used in combination. However, given the role of MAOIs and esketamine in TRD, clinicians may need to consider the risks and benefits of treatments including this combination. Further studies should be pursued to examine the safety of combining intranasal esketamine and MAOI pharmacotherapies in TRD.

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Supplementary material: Available at Psychiatrist.com.

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See supplementary material for this case report at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Safety and Tolerability of Concomitant Intranasal Esketamine Treatment With Irreversible, Non-Selective MAOIs: A Case Series

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List of Supplementary Material for the article

1. Table 1 — Mean Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate Predose, 40 Minutes Postdose, and 2 Hours Postdose

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1

Column1	Mean Systolic Blood Pressure Pre-Dose	Mean Systolic Blood Pressure 40-minutes Post-Dose	Mean Systolic Blood Pressure 2-hours Post-Dose	Minimum Systolic Blood Pressure Pre-Dose	Minimum Systolic Blood Pressure 40-minutes Post-Dose	Minimum Systolic Blood Pressure 2-hours Post-Dose	Maximum Systolic Blood Pressure Pre-Dose	Maximum Systolic Blood Pressure 40-minutes Post-Dose	Maximum Systolic Blood Pressure 2-hours Post-Dose
Patient #1	130.1 mmHg	136.2 mmHg	128.2 mmHg	98 mmHg	93 mmHg	89 mmHg	148 mmHg	167 mmHg	200 mmHg
Patient #2	121.8 mmHg	120.9 mmHg	114.4 mmHg	96 mmHg	97 mmHg	92 mmHg	179 mmHg	144 mmHg	142 mmHg
Patient #3	118.4 mmHg	117.9 mmHg	123.0 mmHg	96 mmHg	92 mmHg	104 mmHg	138 mmHg	169 mmHg	154 mmHg
	Mean Diastolic Blood Pressure Pre-Dose	**Mean Diastolic Blood Pressure 40-minutes Post-Dose**	**Mean Diastolic Blood Pressure 2-hours Post-Dose**	**Minimum Diastolic Blood Pressure Pre-Dose**	**Minimum Diastolic Blood Pressure 40-minutes Post-Dose**	**Minimum Diastolic Blood Pressure 2-hours Post-Dose**	**Maximum Diastolic Blood Pressure Pre-Dose**	**Maximum Diastolic Blood Pressure 40-minutes Post-Dose**	**Maximum Diastolic Blood Pressure 2-hours Post-Dose**
Patient #1	75.2 mmHg	78.3 mmHg	68.8 mmHg	53 mmHg	49 mmHg	48 mmHg	91 mmHg	99 mmHg	99 mmHg
Patient #2	78.5 mmHg	76.5 mmHg	76.3 mmHg	60 mmHg	53 mmHg	59 mmHg	93 mmHg	97 mmHg	92 mmHg
Patient #3	67.0 mmHg	62.1 mmHg	64.8 mmHg	57 mmHg	55 mmHg	53 mmHg	81 mmHg	84 mmHg	83 mmHg
	Mean Heart Rate Pre-Dose	**Mean Heart Rate 40-minutes Post-Dose**	**Mean Heart Rate 2-hours Post-Dose**	**Minimum Heart Rate Pre-Dose**	**Minimum Heart Rate 40-minutes Post-Dose**	**Minimum Heart Rate 2-hours Post-Dose**	**Maximum Heart Rate Pre-Dose**	**Maximum Heart Rate 40-minutes Post-Dose**	**Maximum Heart Rate 2-hours Post-Dose**
Patient #1	83.1 BPM	81.6 BPM	81.1 BPM	70 BPM	72 BPM	67 BPM	96 BPM	90 BPM	95 BPM
Patient #2	76.8 BPM	76.7 BPM	79.6 BPM	48 BPM	57 BPM	60 BPM	99 BPM	100 BPM	105 BPM
Patient #3	66.1 BPM	63.8 BPM	60.3 BPM	60 BPM	57 BPM	56 BPM	78 BPM	75 BPM	66 BPM

Mean systolic blood pressure, diastolic blood pressure, and heart rate pre-dose, 40-minutes post dose, and 2-hours post dose are shown for each patient, respectively. Additionally the maximum and minimum systolic blood pressure, diastolic blood pressure, and heart rate pre-dose, 40-minutes post dose, and 2-hours post dose are shown for each patient, respectively. These values correlate with the data displayed in Figure 1.