Supplementary material

CNS Drugs

Cardiovascular effects of combining subcutaneous or intravenous esketamine and the MAO-Inhibitor tranylcypromine for the treatment of depression: A retrospective cohort study

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Table 1 Summary of the existing literature on the use of ketamine during MAOI therapy in humans

Ref. No.	Article	N	Sex	Age	Diagnoses	(Es)Ketamine dose	MAOI daily dose	Outcome
17	Doyle 1990	1	female	42	Emergency laparotomy, depression	ketamine 1,5 mg/kg IV	tranylcypromine 20 mg	No sympatomimetic crisis during anaesthetic induction with ketamine
18	Bartova et al., 2015	2	female	43, 74	TRD	esketamine 12,5–75 mg IV	tranylcypromine 10 – 80 mg	No relevant cardiovascular changes
20	Katz et al., 2018	2 3	male female	60, 71 26, 55, 62	Major depressive episode with and without psychotic features, bipolar depression	ketamine 0,5 mg/kg IV	tranylcypromine 10 – 60 mg, phenelzine 45 mg, selegeline 12 mg	All patients showed increases in average BP and HR after ketamine administration, however, these were not deemed clinically significant. One patient with a history of cardiovascular comorbidities experienced transient, asymptomatic BP increases up to 180/110.
21	Dunner et al., 2020	1	female	61	Chronic major depressive disorder	nasal esketamine (28–56 mg)	tranylcypromine 60 mg	BP increases, but not to the extent of hypertension
22	Wang & Swainson, 2020	2 1	female male	51, 70 57	TRD in major depressive disorder, bipolar disorder	ketamine 0,5 mg/kg IV	phenelzine 45 - 105 mg	Statistically significant systolic BP increases, which were transient and clinically insignificant
19	Bottemanne et al., 2020	3	not disclosed	56, 19, 40	TRD in major depressive disorder, bipolar disorder	ketamine 0,5 – 0,75 mg/kg IV	phenelzine 45 mg	No hemodynamic changes

Ref. No.= reference number, MAOI = monoamine oxidase inhibitors, IV= intravenous, TRD = Treatment resistant depression, BP = Blood pressure.

Table 2 Descriptive statistics of individual esketamine doses. Characteristics and potential confounders stratified by medication status of tranylcypromine at the time of esketamine administration

	TCP+	TCP-	p-value
N (%)			
Sex			.364[a]
Female	38 (46.3)	174 (40.9)	
Male	44 (53.7)	251 (59.1)	
Hypertension			<.001[a]
Yes	26 (31.7)	275 (64.7)	
No	56 (68.3)	150 (35.3)	
On antihypertensive Medication	26 (31.7)	284 (66.8)	<.001[a]
Mean (SD)			
Age	58.43 (14.52)	45.19 (16.0)	<.001[b]
BMI	27.41 (4.96)	25.18 (4.36)	<.001[b]
Serum creatinine	101.28 (20.07)	81.10 (17.90)	<.001[b]
Number of antihypertensive drugs[c]	2.09 (0.86)	1.49 (0.68)	<.001[b]

TCP+ = Taking tranylcypromine, TCP- = Not taking tranylcypromine.BMI = Body mass index [a] p-values were calculated using chi-squared tests. [b] p-values were calculated using independent sample t-tests. [c] for those receiving antihypertensive medication.

Table 3 Results of the sensitivity analysis on substituted baseline measures

Parameter	F-value	p-value
ΔBPsys	F(1,481)=66.44	<.001
ΔBPdia	F(1,481)=42.02	<.001
ΔHR	F(1,430)=1.19	.277
Mean BP systolic	F(1,481)=31.08	<.001
Mean BP diastolic	F(1,481)=8.35	.004
Mean HR	F(1,430)=1.70	.193

Sensitivity analysis comparing cardiovascular parameters (mean change in systolic blood pressure (ΔBPsys), diastolic blood pressure (ΔBPdia) and heart rate (ΔHR) and mean absolute BP and HR) during esketamine administration between patients receiving (TCP+) or not receiving (TCP-) tranylcypromine in cases without substituted baseline values. P-values were calculated using ANCOVAs controlling for creatinine and age.

Table 4 Results of the sensitivity analysis of the subgroup of patients with cases for TCP+ and TCP-

Parameter	F-value	p-value
ΔBPsys	F(1,371)=101.02	<.001
ΔBPdia	F(1,371)=54.11	<.001
ΔHR	F(1,335)=0.04	.844
Mean BP systolic	F(1,371)=54.91	<.001
Mean BP diastolic	F(1,371)=7.50	.006

Mean HR	F(1,335)=0.30	.587

Sensitivity analysis comparing cardiovascular parameters (mean change in systolic blood pressure (ΔBPsys), diastolic blood pressure (ΔBPdia) and heart rate (ΔHR) and mean absolute BP and HR) during esketamine administration between patients receiving (TCP+) or not receiving (TCP-) tranylcypromine in cases without changes in TCP medication status. P-values were calculated using ANCOVAs controlling for creatinine and age.