Correspondence

Concurrent Use of Buprenorphine, Methadone, or Naltrexone Does Not Inhibit Ketamine's Antidepressant Activity

To the Editor:

Two recent studies that investigated the necessity of mu opioid receptors (MORs) for ketamine's antidepressant activity yielded divergent results (1,2). One found that acute naltrexone administration blocked the antidepressant effects of ketamine, while another found that patients receiving chronic naltrexone had good antidepressant responses to ketamine. Thus, whether ketamine's antidepressant activity depends on MORs or *N*-methyl-D-aspartate receptors is controversial. High-affinity MOR agonists such as buprenorphine and methadone are used to treat opioid use disorder, as they bind to the MOR and reduce the effect of additional MOR agonist administration (3). Therefore, if ketamine's antidepressant mechanism requires acute MOR activation, then concomitant use of such high-affinity MOR agonists should reduce ketamine's antidepressant effects.

Methods

To explore this issue, we examined retrospective treatment outcome data of 40 consecutive veterans treated with intravenous ketamine for treatment-resistant depression at the San Francisco VA Medical Center. All patients received up to six infusions of ketamine (0.5 mg/kg over 40 minutes) twice weekly for 3 weeks. Beck Depression Inventory-II data were collected immediately before each infusion. Inclusion criteria included two or more failed antidepressant trials, moderate-to-severe depression severity, and ability to give informed consent; exclusion criteria included active psychosis or active substance use other than cannabis. We employed a linear mixed model with terms for group, ketamine dose number, and their interaction and an unstructured correlation matrix to compare changes in Beck Depression Inventory-II scores over the treatment course in the MOR versus non-MOR groups. We also examined the efficacy of ketamine in one patient being treated long-term with naltrexone.

Results

Groups were similar in age, gender, and prior antidepressant trials (Table 1). During ketamine treatment, 7 patients were on stable doses of MOR agonists for >12 months, 1 patient was receiving long-acting injectable naltrexone, and 27 patients were not on opioidergic drugs. Ketamine treatment was safe and well tolerated in all patients without any serious adverse events. Importantly, we observed no differences in vital sign changes between cohorts receiving ketamine.

The linear mixed model revealed significant reductions in Beck Depression Inventory-II scores over the six infusions ($p < .001$), with no difference between the MOR agonist and non–MOR agonist groups before ($p = .82$) or after ($p = .11$) completing treatment (Figure 1). To better characterize these similar treatment responses, we conducted a power analysis that demonstrated 80% power to detect a moderate effect size

Table 1. Demographic and Treatment Characteristics of the Three Patient Cohorts Who Received Ketamine Therapy for Depression

Cohort/Patient	Age, Years	Sex	Opioid Agent	Dose	Treatment Duration, Months	Indication	Failed AD Trials	Prior ECT
MOR Cohort (n = 7)								
Average	43 ± 6.6	1 F/6 M		BUP ~14.5 mg MTD ~111 mg	>12		8.7 ± 1.9	1
Data per patient								
	33	M	BUP	15 μg TD daily	>12	Pain	4	N
	70	M	BUP	24 mg daily	>12	OUD/pain	9	N
	24	M	BUP	16 mg daily	>12	OUD	18	N
	38	M	BUP	16 mg daily	>12	OUD	7	N
	41	F	BUP	2 mg daily	>12	Pain	5	N
	33	M	MTD	62 mg daily	>12	OUD	5	N
	66	M	MTD	160 mg daily	>12	OUD	13	Y
NTX Cohort (n = 1)	57	F	NTX	380 mg IM once every 4 weeks	4	AUD	13	Y
Non-MOR Cohort (n = 27), Average	54 ± 2.7	10 F/17 M					7.0 ± 0.75	18

The MOR cohort received BUP or MTD (n = 7), the NTX cohort received NTX (n = 1), and the non-MOR cohort received no opioid-interacting agents (n = 27).

AD, antidepressant; AUD, alcohol use disorder; BUP, buprenorphine; ECT, electroconvulsive therapy; F, female; IM, intramuscular; M, male; MOR, mu opioid receptor; MTD, methadone; N, no; NTX, naltrexone; OUD, opiate use disorder; TD, transdermal; Y, yes.

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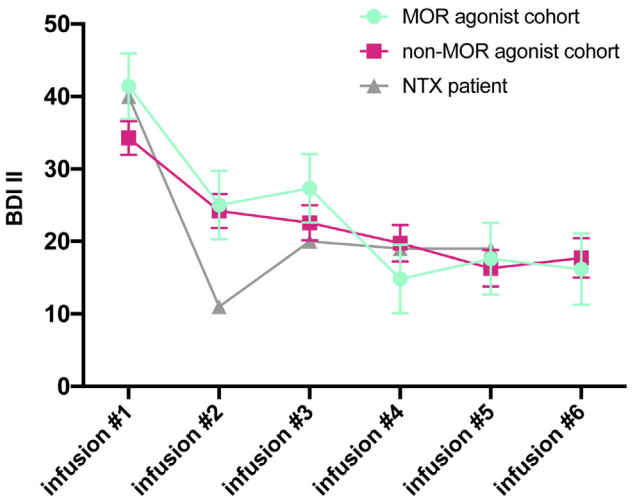

Figure 1. Antidepressant responses to six ketamine infusions comparing the mu opioid receptor (MOR) agonist cohort, non–MOR agonist cohort, and the naltrexone (NTX) patient. Values reflect marginal predicted mean Beck Depression Inventory-II (BDI II) scores from linear mixed models: MOR-pre: 41, MOR-final: 16 (n = 7); non-MOR-pre: 34, non-MOR-final: 16 (n = 27); group p = .82, time $p < .001$; group × time interaction p = .11. Responses are average BDI II scores administered just before each ketamine infusion, with errors expressed as standard error estimates from the linear mixed model. BDI II scores are also shown for the one patient on naltrexone (NTX-pre: 40, NTX-final: 19). Ketamine infusions were administered twice weekly for 3 weeks at 0.5 mg/kg over 40 minutes. The NTX patient received five infusions.

(Cohen's d = 0.49), which is smaller than the large effect of naltrexone on ketamine's antidepressant effect (Cohen's d = 2.5) reported in Williams *et al.* (1). Finally, the one patient on naltrexone had an antidepressant response to ketamine similar to the larger patient cohorts.

Discussion

Ketamine was safe and had similar antidepressant efficacy in patients concurrently on high-affinity MOR agonists and in 1 patient on naltrexone, compared with ketamine-treated patients not on opioidergic medications. This suggests that chronic use of opioidergic-interacting medications is not a contraindication for ketamine treatment of depression.

Consistent with our results, but contrary to the outcomes reported in Williams *et al.* (1), Yoon *et al.* (2) described 5 patients with alcohol use disorder pretreated with injectable naltrexone who demonstrated robust antidepressant responses to ketamine. These divergent results may be explained by differences in ketamine's activity in the setting of long-term versus immediate opioid administration. For example, long-term administration of MOR agonists can lead to changes in MOR expression (leading to tolerance) (4). Ketamine may drive MOR resensitization (5), which could provide a potential opioidergic mechanism for ketamine's antidepressant efficacy independent of *N*-methyl-D-aspartate receptor antagonism. The lack of observed opioid toxicity in the MOR agonist cohort, which could be expected if MORs were acutely resensitized by ketamine, makes this hypothesis less likely. Alternatively, the interaction between opioid manipulations and ketamine's efficacy may differ in patients with and without comorbid substance use disorders (2,6). The observed safety and efficacy of ketamine treatment in our treatment-resistant depression patients on long-term MOR agonist therapy establishes the potential for ketamine treatment in this dual-diagnosis population, in addition to informing the ongoing debate concerning ketamine's antidepressant mechanism.

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Article Information

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