Comparison of Rapid Antidepressant and Antisuicidal Effects of Intramuscular Ketamine, Oral Ketamine, and Electroconvulsive Therapy in Patients With Major Depressive Disorder

A Pilot Study

Dorna Kheirabadi, MD, Gholam Reza Kheirabadi, MD,† Zahra Mirlohi, MD,‡ Mohammad Javad Tarrahi, PhD,§ and Amir Norbaksh, MD||¶*

Abstract:

Purpose/Background: This study was devised to compare the antidepressant and antisuicidal effects of oral and intramuscular (IM) ketamine versus electroconvulsive therapy (ECT).

Methods/Procedures: In our pilot study, 45 patients with major depressive disorder (based on *Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition*, criteria) in the age range of 18 to 70 years who were determined suitable candidates for ECT got randomly divided into 3 equal groups. Each group received one of these treatment modalities: 0.5 mg/kg of IM ketamine; 1 mg/kg of oral ketamine; and ECT in 6 to 9 sessions during 3 weeks. Depression and suicidal ideation scores were recorded using the Hamilton Depression Rating Scale and the Beck Scale for Suicidal Ideation, respectively, at baseline, 24 hours, 1 week, 2 weeks, and 3 weeks within the intervention. The measurements were repeated 1 week and 1 month after the end of the intervention as well. Vital signs and adverse effects were noted. Finally, satisfaction levels of patients for each method were recorded and compared between groups.

Findings/Results: The Hamilton Depression Rating Scale and the Beck Scale for Suicidal Ideation scores significantly improved in all groups compared with baseline with no significant differences between the 3 groups. The adverse effects for ketamine-consuming groups such as dissociative symptoms were brief and transient, whereas memory loss for the ECT group remained up to 1 month in some patients. Ketamine-receiving groups preferred it more than ECT.

Implications/Conclusions: Oral and IM ketamine probably have equal antidepressant in addition to more antisuicidal effects compared with ECT but had less cognitive adverse effects and higher preference by patients. Thereby, ketamine can be an alternative method in the treatment of patients with severe and/or suicidal MDD.

Key Words: ketamine, electroconvulsive therapy, antidepressant effects, major depressive disorder, suicidal ideation

From the *Department of Anesthesiology, School of Medicine, Behavioral Sciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran; †Behavioral Sciences Research Center, Department of Psychiatry, School of Medicine; ‡Department of Psychiatry, School of Medicine; §Department of Epidemiology and Biostatistics, School of Health, IsfahanUniversity of Medical Sciences, Isfahan, Iran; ||South Coast Specialty Surgery Center; and ¶Opiate Detox Institute, Costa Mesa, CA.

Received June 29, 2020; accepted after revision August 21, 2020.

Reprints: Zahra Mirlohi, MD, Department of Psychiatry, Khorshid Hospital, Ostandari St, Isfahan, Iran (e-mail: z_mirlohi@yahoo.com).

The Isfahan University of Medical Sciences (IUMS) provided funding for this study as a residential thesis; the IUMS had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.psychopharmacology.com).

ISSN: 0271-0749

DOI: 10.1097/JCP.0000000000001289

(*J Clin Psychopharmacol* 2020;40: 588–593)

Major depressive disorder (MDD) is a common psychiatric disorder with 17% prevalence and a significant healthcare cost.[1] The common therapeutic strategies include pharmacotherapy (which acts through serotonin, dopamine, and norepinephrine systems) and electroconvulsive therapy (ECT).[2] One of the most significant disadvantages of antidepressants is their delayed response, which can last up to 2 to 4 weeks. This is especially concerning in patients with symptoms of agitation or suicidal ideation.[3]

Although ECT has the benefit of rapid antidepressant effects, it is considered an invasive treatment. Electroconvulsive therapy's main complications include cognitive impairment, delirium, musculoskeletal pain/injury, and anesthesia-related complications.[4] Hence, selecting an effective treatment for MDD patients with symptoms of suicidal ideation or refractory to treatment remains challenging.

Ketamine is a *N*-methyl-D-aspartate receptor antagonist. In doses of 2 to 10 mg/kg (depending on administering route), it behaves as an anesthetic agent.[5]

In recent years, ketamine has been used both as an analgesic and antidepressant agent.[6–8] Research has shown that it has transient psychiatric and hemodynamic effects.[9,10]

Ketamine is a glutamate modulator used as a novel antidepressant. Glutamate is an excitatory neurotransmitter that attenuates symptoms such as depressed mood and suicidal ideation specifically by acting on prefrontal cortex.[11–13]

The first clinical trial performed in 2000 revealed significant rapid antidepressant effect with infusion of 0.5 mg/kg of ketamine for 40 minutes in 8 MDD patients.[14] Another trial of intravenous (IV) ketamine found that its antidepressant effects lasted for at least 2 weeks.[15,16] Thus, use of IV ketamine was introduced as a treatment for depression.[17]

Domany et al[18] discovered that infusion of 0.2 mg/kg of ketamine for 5 minutes alleviated suicidal ideation at 90, 120, and 180 minutes after infusion according to the Beck Scale for Suicidal Ideation (BSSI). However, no significant reduction in BSSI scores was found on days 1, 2, 3, 7, and 14 after ketamine administration. Further studies were deemed necessary to study the effects of recurrent ketamine doses.[18] A systematic review concluded that a single infusion of ketamine has a short-term (up to 72 hours) favorable outcome on suicidal thoughts. In addition, more studies were required to discover methods to prolong the favorable outcomes.[19]

Phillips et al[20] concluded that repeated ketamine infusions led to cumulative and sustained antidepressant effects. However, further studies should be done to determine the optimal route of administration.[20]

Other routes of ketamine administration, such as the intramuscular (IM), seem also to be effective as an antidepressant.

Harihar et al[21] used 0.5 mg/kg of IM ketamine for 2 severely depressed patients. They administered it 2 times with a 3-day interval. They claimed that IM ketamine could rapidly attenuate depression and suicidal ideation, and responses were comparable with IV ketamine.[21]

More studies are needed to investigate the effects of IM route administration.[22–24]

Furthermore, oral ketamine has shown antidepressant effects.[25] A single dose of oral ketamine resulted in safe and rapid relief of depression and anxiety symptoms in refractory cases of depression.[26]

In a larger trial, oral ketamine hydrochloride (0.5 mg/kg) was administered daily for 14 patients with symptoms of depression or depression mixed with anxiety. The trial was continued up to 28 days. It was found that oral ketamine had both antidepressant and anxiolytic effects with similar response to IV ketamine.[27]

Ketamine Hydrochloride vial can be consumed orally by adding flavors and sweeteners to eliminate its bitter taste.[28,29]

Bioavailability of oral ketamine is estimated to be approximately 20% to 25%, whereas its bioavailability is nearly 100% in IM injection. Thus, it is necessary to apply higher doses in oral form compared with IM. We decided to choose 0.5 mg/kg of IM ketamine versus 1 mg/kg of oral form for our study.

Although the adverse effects are few and limited to infusion time, therapists should be aware of ketamine's potential for addiction.[17,30]

A Cochrane review, published in 2015 regarding ketamine and other glutamate receptor modulators for depression in adults, found no evidence of sustained antidepressant effects of oral and IM ketamine after 1 week. However, ketamine was the only glutamate modulator, which effectively relieved depression symptoms compared with placebo. This study suggests the need for further probing to assess long-term effects of ketamine and compare different routes of ketamine administration.[31]

A systematic review on oral ketamine for depression published in 2019 claimed that oral ketamine had considerable antidepressant effects and was tolerated well with most patients. However, this method was not as rapid as IV ketamine. It suggests that additional randomized clinical trials are required to warrant its antisuicidal effects and efficacy in refractory depression.[32]

Ghasemi et al[33] designed a trial to compare antidepressant effects of ECT compared with repeated doses of 0.5 mg/kg of IV ketamine. Their study demonstrated that ketamine was as effective as ECT in MDD patients but had more rapid antidepressant effects as ECT.[33]

Most studies focused on IV and oral administration of ketamine. Data for effectiveness of other routes such as IM are limited especially regarding its antisuicidal effects. It is still unclear whether different administration routes of ketamine have different outcomes or how they are compared with ECT. This study was performed with the aim of comparing antidepressant and antisuicidal effects of oral ketamine, comparing IM ketamine with ECT and studying patients' satisfaction and adverse effects in each method.

MATERIALS AND METHODS

This study was approved by the ethics committee of the Isfahan University of Medical Sciences and then registered in the Iranian Registry of Clinical Trials (IRCT) as a primary registry in the WHO Registry Network (IRCT Code: IRCT20090801002266N8). All participants completed a written informed consent after a thorough description of the study and before any study-specific procedure.

Forty-five patients in the 20- to 70-y age range participated in this study. Patients were diagnosed with MDD and also had one of the symptoms of suicidal ideation, treatment resistance, severe symptoms, and agitation. They were referred by their psychiatrist for ECT. All patients were reevaluated for accurate diagnosis using the *Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition*, criteria and were assigned to study if they had inclusion criteria. The patients were randomly allocated to 3 arms (15 patients in each arm) via block randomization method by a nurse who had no further role in the study.

Patients with a history of severe hepatic, cardiac, renal, or urologic diseases and those with a previous psychotic, manic, or hypomanic episode, substance abuse, and depression due to medical condition were excluded from this study.

The medications that patients were receiving before enrolment in the study were not changed except in cases where concurrent use of them with ketamine and ECT was prohibited.

Participants who were inserted in the ECT arm received 6 to 9 sessions of ECT during 3 weeks the same as their routine ECT treatment program in our hospital. Patients were fasting for at least 8 hours before procedure. Succinylcholine was administered under the supervision of an anesthesiologist and his expert team. The ECT electrical stimulus was firstly set at 20 J using DGX machine and then was titrated based on the duration of induced seizure. The ECT electrodes were placed bifrontotemporal. The duration of induced tonic-colonic seizure was considered to be at least 20 seconds to provide a suitable response. Constant hemodynamic monitoring was done throughout the procedure. Vital signs including pulse rate (PR), respiratory rate (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and peripheral capillary oxygen saturation (Sp_{O_2}) were recorded continuously and repeated 30 minutes after operation.

The participants in the IM ketamine arm took 0.5 mg/kg of IM racemic ketamine (*R*-ketamine) repeated for 6 to 9 injections in gluteus medius site (gluteal injection) during 3 weeks (with a 2- to 3-day interval) under supervision of a psychiatric resident in the psychiatric emergency department. We used vials of 500 mg in 10 mL of ketamine hydrochloride for IM injections. The PR, RR, SBP, DBP, and Sp_{O_2} were recorded for this group in the same manner.

The third group of participants received 1 mg/kg of oral *R*-ketamine (by adding flavors and sweeteners to eliminate its bitter taste) every 2 to 3 day up to 6 to 9 sessions during 3 weeks. They also received it under the supervision of a psychiatric resident and in the psychiatric emergency department. The PR, RR, SBP, DBP, and Sp_{O_2} were recorded in the same fashion. The complications and potential adverse effects of each patient were also documented during the study.

The Hamilton Depression Rating Scale 17 (HDRS-17) and the BSSI were used to determine depression and suicidal ideation scores, respectively,[34–36] before and 24 hours after the first intervention, then every week up to 3 weeks (intervention time), and eventually 1 and 4 weeks after the end of the intervention (follow-up time). After 4 weeks from the last therapeutic session, a Likert questionnaire was asked to determine the acceptance levels of treatment in each group, which consisted 4 items including the following:

1. Patient's agreement to engaging in the treatment (from 1 = completely disagree to 5 = fully agree)
2. Patient's preference over other medications used before (from 1 = no preference to 5 = prefer current intervention to other medications)
3. Patient's motivation to continue this treatment (from 1 = not at all motivated to 5 = fully motivated)
4. Patient's overall satisfaction of the current method (from 1 = unsatisfied to 5 = fully satisfied).

The collected data were analyzed using SPSS 20 and reported as n (%) or means ± SD using repeated measures of analysis of variance (ANOVA), the 1-way ANOVA for quantitative

TABLE 1. Comparison of the Demographic Characteristic, Comorbidities, and Current Medications of Participants

Variable	Groups	ECT n = 12	Oral Ketamine n = 12	IM Ketamine n = 15	*P*
Sex, male, n (%)		5 (33.3%)	6 (40%)	8 (53.3%)	0.529
Age, mean ± SD		41.6 ± 15.44	39.13 ± 9.84	41.6 ± 8.43	0.8
Current medications	SSRIs	9 (60%)	9 (64%)	9 (60%)	0.964
	SNRI	1 (6.7%)	2 (14.3%)	6 (40%)	0.061
	Antipsychotics	8 (53.3%)	7 (50%)	8 (53.3%)	0.979
Comorbidity	Personality disorders	3 (20%)	3 (23.1%)	2 (13.3%)	0.792
	OCD	1 (6.7%)	2 (15.4%)	1 (6.7%)	0.665
	Anxiety disorders	4 (26.7%)	5 (38.5%)	5 (33.3%)	0.799

OCD, obsessive compulsive disorder; SNRI, serotonin norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitor.

data, and the Tukey test for post hoc analysis (the Shapiro-Wilk test showed that the data have normal distribution). Kruskal-Wallis test was used to compare agreement, preference, motivation, and satisfaction scores because they did not follow the normal distribution.

RESULTS

Considering the aim of this study, 45 MDD patients including 22 male and 23 female patients diagnosed with MDD were divided into 3 groups. The patients' age range was between 20 and 70 years. The method of case selection, allocation, and follow-up is depicted in a Consolidated Standard Of Reporting Trial flow diagram (Supplemental Figure 1, http://links.lww.com/JCP/A691).

There were no significant differences between the 3 groups regarding age and sex.

Table 1 shows demographic features, comorbidities, and recent medications in groups.

Depression scores were significantly decreased for all 3 intervention groups ($P < 0.001$ for the HDRS). Although the intervention *P* value between groups (which was shown by ANOVA) was not significant, interaction *P* value was significant (Table 2 and Supplemental Figure 1, http://links.lww.com/JCP/A691).

Suicide scores were significantly reduced for all 3 intervention groups ($P < 0.001$ for the BSSI). Although both the intervention and interaction *P* values were not significant, the differences between groups at second day (24 hours after the first intervention) and second week during intervention were significant (Table 2 and Supplemental Figure 2, http://links.lww.com/JCP/A692). Post hoc tests demonstrated that these differences were related to differences between the ECT group versus both oral and IM ketamine groups.

Using of spearman correlation test showed that the scores of depression and suicide were correlated ($r = 0.348$, $P = 0.03$).

Supplemental Table 1, http://links.lww.com/JCP/A694 shows the agreement, motivation, preference, and overall satisfaction scores between the 3 groups that were assessed 1 month after the final intervention. Although all the scores were lower in ECT groups, the differences were not significant.

There were no significant changes in hemodynamic parameters including PR, SBP, DBP, RR, and SpO_2 compared with baseline in all groups (not shown).

TABLE 2. The BSSI Scores and the HDRS at the Baseline, Intervention, and Follow-up Times

Scores	Time		ECT Group, Mean ± SD n = 12	Oral Ketamine, Mean ± SD n = 12	IM Ketamine, Mean ± SD n = 15	*P* (Between Groups)
BSSI score	Baseline		10.75 ± 5.61	8 ± 4.19	8.1 ± 5.61	0.380
	Intervention time	First day	5.66 ± 3.98	2.7 ± 1.35	3 ± 3.25	0.045
		First week	4.33 ± 3.65	2.16 ± 1.33	2 ± 2.6	0.065
		2nd week	3.91 ± 3.47	1.66 ± 1.37	1.53 ± 2.09	0.033
		Third week	3.75 ± 4.6	1.25 ± 1.13	1.33 ± 2.16	0.069
	Follow up time	1 wk	1.75 ± 2.63	1.83 ± 1.7	1.86 ± 2.64	0.992
		1 mo	4.25 ± 4.45	3.75 ± 2.9	3.13 ± 2.55	0.688
	P (with in groups)		<0.001	<0.001	<0.001	
HDRS score	Baseline		21.83 ± 4.63	21 ± 2.73	21 ± 2.9	0.789
	Intervention time	First day	16 ± 3.71	13.7 ± 2	14 ± 2.4	0.106
		First week	14.6 ± 3.3	14.1 ± 2.36	13.26 ± 2.9	0.449
		Second week	14 ± 3.07	13.25 ± 2.26	11.66 ± 4.35	0.208
		Third week	13.25 ± 3.8	12.16 ± 2.72	10 ± 4.85	0.109
	Follow-up time	1 wk	9.5 ± 5.35	12.83 ± 3.18	10.86 ± 5.11	0.230
		1 mo	13.83 ± 3.58	15.75 ± 3.19	16.2 ± 3.12	0.170
	P (with in groups)		<0.001	<0.001	<0.001	

Electroconvulsive therapy and ketamine both were tolerated well. Adverse effects such as dissociative symptoms and nystagmus occurred for most patients in both ketamine groups and lasted between 0.5 and 4 hours.

The main complications associated with ECT were cognitive and memory impairments, which could last up to 1 month (58.3% of patients). Other adverse effects included headache, nausea, and musculoskeletal pain in the same order. Supplemental Table 2, http://links.lww.com/JCP/A695 shows the prevalence of each side reported in groups.

DISCUSSION

The results show that antidepressant effect of repeated doses of 0.5 mg/kg of IM ketamine and 1 mg/kg of oral ketamine were equivalent to ECT during intervention, but this effect did not sustain on follow-ups and duration of antidepressant effect were more favorable for ECT group (Supplemental Figure 1, http://links.lww.com/JCP/A691).

The antisuicidal effects of repeated doses of 0.5 mg/kg of IM ketamine and 1 mg/kg of oral ketamine were the same as ECT, and their effects continued equally even up to 1 month after the last intervention.

The most reduction in the HDRS and BSSI scores occurred at 24 hours after the first intervention in all 3 groups and did not return to baseline after 1 month (Supplemental Figure 1, http://links.lww.com/JCP/A691 and Supplemental Figure 2, http://links.lww.com/JCP/A692 These data suggest that despite the short half-life of ketamine, repeated administration of this drug can lead to sustained antidepressant and antisuicidal effects comparable with ECT.

Significant lower suicide scores in both oral and IM ketamine groups compared with the ECT group at 2 time points during the intervention may indicate that the antisuicidal effects of ketamine may be superior to ECT.

Ketamine, which is an *N*-methyl-D-aspartate receptor antagonist, proved its antidepressant qualities in subanesthetic doses since 1990.[37]

The effects of ketamine seem to be mediated by the glutamate pathway, which results in synaptogenesis and the reversal of the negative effects of chronic stress and depression, especially in the prefrontal cortex.[13]

In several studies, intravenous ketamine (0.5 mg/kg) was used and significant antidepressant and antisuicidal ideation effects were reported.[14–16] These rapid antidepressant and antisuicidal effects of ketamine are in contrast to the monoamine-based antidepressant that takes at least 2 to 3 weeks to manifest their full antidepressant effect.[3]

Other studies suggest that repeated doses of ketamine could be a strategy for MDD patients and could lead to prolonged therapeutic outcomes. In 1 study, 8 infusions of 0.5 mg/kg of ketamine resulted in an 85% reduction in depressive symptoms and a mean relapse time of 19 days after the final ketamine infusion.[9] Other investigations showed more than 3 months of relapse time in some patients after 6 sessions of 0.5 mg/kg of ketamine administrations.[38]

A study on patients with treatment-resistant depression and chronic suicidal ideation illustrated that there were no significant differences between patients who received 6 ketamine infusions (0.5 mg/kg for 45 minutes) and saline placebo for 3 weeks. For a 3-month follow up, no reduction in depression severity or suicidal ideation was observed. Small sample size, uncontrolled outpatient medication regimens, and restriction to outpatients, which may cause lower levels of suicidal ideation than would be found in emergency or inpatients settings, are considered as limitations of this study. They suggest that this dose is not sufficient in severely and chronically ill patients.[39]

Another placebo-controlled trial revealed that 1 mg/kg of oral ketamine thrice weekly for 21 days could result in rapid and persistent resolve of depressive symptoms in outpatients with treatment resistant depression along with trivial adverse effects.[40]

A pilot study claimed that IV, IM, and subcutaneous administration of ketamine had comparable antidepressant effects at a range doses of less than 0.5 or equal to 0.5 mg/kg.[23]

A trial on a treatment-resistant patient with MDD and end-stage ovarian cancer showed an IM injection of 6 doses of 1 mg/kg of ketamine, resulting in a significant rapid antidepressant effect, which persisted 6 to 7 days after injection.[22] In addition, 0.5 mg/kg of oral ketamine was administered daily for 14 patients with MDD for 28 days and the antidepressant effect was obvious.[27] Although other studies have been performed, data on oral and IM routes are still limited.[31]

Our study showed that 1 mg/kg of oral and 0.5 mg/kg of IM ketamine may create rapid and sustained antidepressant effects (at least for 1 month) and reduce suicidal ideation equal ECT when administered in repeated doses (6–9 sessions during 3 weeks).

Comparison of the adverse effects between ketamine groups and the ECT group was noticeable.

The ECT is an invasive therapeutic method that requires anesthesia induction and requires constant supervision of an anesthesiologist and an intensive care team. The most observed adverse effects in patients receiving ECT were headache, nausea, musculoskeletal pain, and lastly memory deficiency, which could remain up to 1 month after operation in 58.3% of ECT patients. In another hand, the most significant complications in patients receiving IM or oral ketamine included dissociative symptoms and nystagmus. None of these signs and symptoms lasted more than 4 hours after each intervention, and they were easy to observe or manage by a psychiatric resident and a nurse.

Considering comparable clinical effects of IM and oral ketamine versus ECT, and ketamine relative ease of administration compared with ECT, 1 mg/kg of oral and 0.5 mg/kg of IM ketamine may be a valuable antidepressants and antisuicidal treatment with lower risk and better tolerable adverse effects.

Finally, the consent to involve in the study, the motivation to maintain the therapeutic sessions, and the overall satisfaction of each 3 methods were similar with no significant difference, but the preference of ECT was lower among our 3 studied groups (Supplemental Figure 3, http://links.lww.com/JCP/A693).

Despite the benefits of ketamine use for rapid alleviation of depression symptoms and suicidal ideation, there are some limitations with this medication: Ketamine may not be unfavorable for bipolar, substance dependence, psychotic, or physically ill patients, whereas ECT would be safe for them; ketamine use would be limited to pure MDD patients without psychotic features or patients with a history of addiction or chronic systemic issues until further evidence is obtained. The potential risk of ketamine abuse remains as a problem for the current form of this drug, it is known as a "street drug" with potency of abuse, and it is a concern of psychiatrists prescribing ketamine.

Of course, the more trials with different dosage and number of participants or more follow-up sessions may be beneficial to establish the antidepressant and antisuicidal effects of ketamine in relation to ECT.

LIMITATIONS

Low sample size and sampling from a referral center may restrict the generalizability of the findings. It would be more

accurate if patients were selected based on having chronic or acute suicidal ideation.

In this study, we applied 1 mg/kg of oral ketamine with 20% to 25% systemic availability versus 0.5 mg/kg of IM ketamine with nearly complete systemic circulation, while we did not measure systemic ketamine concentration, so we cannot claim that exactly equivalent doses of ketamine in oral and IM route of administration had been compared in this study.

Because of ethical limitation for administration of placebo to severely depressed or suicidal patients, we did not choose a placebo group to compare treatment methods with, and this is a major limitation of our study.

Another limitation of this study was the impossibility of blinding to the type of intervention.

CONCLUSIONS

Oral and IM ketamine both probably have equal antidepressant and antisuicidal effects compared with ECT, while it has less cognitive adverse effects and higher preference by patients. Thereby, ketamine can be an acceptable alternative method in the treatment of patients with severe and suicidal MDD.

ACKNOWLEDGMENT

The authors thank all the participants in this study for their genuine cooperation for data collection.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

REFERENCES

1. Malhi GS, Mann JJ. Depression. *Lancet*. 2018;392:2299–2312.
2. Hashimoto K. Emerging role of glutamate in the pathophysiology of major depressive disorder. *Brain Res Rev*. 2009;61:105–123.
3. Gaynes BN, Warden D, Trivedi MH, et al. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. *Psychiatr Serv*. 2009;60:1439–1445.
4. Andrade C, Arumugham SS, Thirthalli J. Adverse effects of electroconvulsive therapy. *Psychiatr Clin North Am*. 2016;39:513–530.
5. White PF, Way WL, Trevor AJ. Ketamine—its pharmacology and therapeutic uses. *Anesthesiology*. 1982;56:119–136.
6. Vadivelu N, Schermer E, Kodumudi V, et al. Role of ketamine for analgesia in adults and children. *J Anaesthesiol Clin Pharmacol*. 2016;32:298–306.
7. Heidari SM, Mirlohi SZ, Hashemi SJ. Comparison of the preventive analgesic effect of rectal ketamine and rectal acetaminophen after pediatric tonsillectomy. *Int J Prev Med*. 2012;3:S150–S155.
8. Fond G, Loundou A, Rabu C, et al. Ketamine administration in depressive disorders: a systematic review and meta-analysis. *Psychopharmacology (Berl)*. 2014;231:3663–3676.
9. Aan het Rot M, Collins KA, Murrough JW, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry*. 2010;67:139–145.
10. Schoevers RA, Chaves TV, Balukova SM, et al. Oral ketamine for the treatment of pain and treatment resistant depression. *Br J Psychiatry*. 2016; 208:108–113.
11. Abdallah CG, Jiang L, De Feyter HM, et al. Glutamate metabolism in major depressive disorder. *Am J Psychiatry*. 2014;171:1320–1327.
12. Jaso BA, Niciu MI, Iadarola ND, et al. Therapeutic modulation of glutamate receptors in major depressive disorder. *Curr Neuropharmacol*. 2017;15:57–70.
13. Abdallah CG, Adams TG, Kelmendi B, et al. Ketamine's mechanism of action: a path to rapid-acting antidepressants. *Depress Anxiety*. 2016; 33:689–697.
14. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000;47:351–354.
15. DiazGranados N, Ibrahim LA, Brutsche NE, et al. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2010;71:1605–1611.
16. Thakurta RG, Ray P, Kanji D, et al. Rapid antidepressant response with ketamine: is it the solution to resistant depression? *Indian J Psychol Med*. 2012;34:56–60.
17. Shiroma PR, Johns B, Kuskowski M, et al. Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. *J Affect Disord*. 2014;155:123–129.
18. Domany Y, Shelton RC, McCullumsmith CB. Ketamine for acute suicidal ideation. An emergency department intervention: a randomized, double-blind, placebo-controlled, proof-of-concept trial. *Depress Anxiety*. 2020;37:224–233.
19. Witt K, Potts J, Hubers A, et al. Ketamine for suicidal ideation in adults with psychiatric disorders: a systematic review and meta-analysis of treatment trials. *Aust N Z J Psychiatry*. 2020;54:29–45.
20. Phillips JL, Norris S, Talbot J, et al. Single, repeated, and maintenance ketamine infusions for treatment-resistant depression: a randomized controlled trial. *Am J Psychiatry*. 2019;176:401–409.
21. Harihar C, Dasari P, Srinivas JS. Intramuscular ketamine in acute depression: a report on two cases. *Indian J Psychiatry*. 2013;55:186–188.
22. Zanicotti CG, Perez D, Glue P. Mood and pain responses to repeat dose intramuscular ketamine in a depressed patient with advanced cancer. *J Palliat Med*. 2012;15:400–403.
23. Loo CK, Gálvez V, O'Keefe E, et al. Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression. *Acta Psychiatr Scand*. 2016;134:48–56.
24. Chilukuri H, Reddy NP, Pathapati RM, et al. Acute antidepressant effects of intramuscular versus intravenous ketamine. *Indian J Psychol Med*. 2014; 36:71–76.
25. Swiatek KM, Jordan K, Coffman J. New use for an old drug: oral ketamine for treatment-resistant depression. *BMJ Case Rep*. 2016; 2016:bcr2016216088.
26. Irwin SA, Iglewicz A. Oral ketamine for the rapid treatment of depression and anxiety in patients receiving hospice care. *J Palliat Med*. 2010; 13:903–908.
27. Irwin SA, Iglewicz A, Nelesen RA, et al. Daily oral ketamine for the treatment of depression and anxiety in patients receiving hospice care: a 28-day open-label proof-of-concept trial. *J Palliat Med*. 2013;16:958–965.
28. McNulty JP, Hahn K. Compounded oral ketamine. *Int J Pharm Compd*. 2012;16:364–368.
29. Broadley KE, Kurowska A, Tookman A. Ketamine injection used orally. *Palliat Med*. 1996;10:247–250.
30. Bonnet U. Long-term ketamine self-injections in major depressive disorder: focus on tolerance in ketamine's antidepressant response and the development of ketamine addiction. *J Psychoactive Drugs*. 2015; 47:276–285.
31. Caddy C, Amit BH, McCloud TL, et al. Ketamine and other glutamate receptor modulators for depression in adults. *Cochrane Database Syst Rev*. 2015:CD011612.
32. Rosenblat JD, Carvalho AF, Li M, et al. Oral ketamine for depression: a systematic review. *J Clin Psychiatry*. 2019;80:18r12475.
33. Ghasemi M, Kazemi MH, Yoosefi A, et al. Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder. *Psychiatry Res*. 2014; 215:355–361.

34. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56–62.

35. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967;6:278–296.

36. Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the scale for suicide ideation. *J Consult Clin Psychol*. 1979; 47:343–352.

37. Trullas R, Skolnick P. Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. *Eur J Pharmacol*. 1990;185:1–10.

38. Murrough JW, Perez AM, Mathew SJ, et al. A case of sustained remission following an acute course of ketamine in treatment-resistant depression. *J Clin Psychiatry*. 2011;72:414–415.

39. Ionescu DF, Bentley KH, Eikermann M, et al. Repeat-dose ketamine augmentation for treatment-resistant depression with chronic suicidal ideation: a randomized, double blind, placebo controlled trial. *J Affect Disord*. 2019;243:516–524.

40. Domany Y, Bleich-Cohen M, Tarrasch R, et al. Repeated oral ketamine for out-patient treatment of resistant depression: randomised, double-blind, placebo-controlled, proof-of-concept study. *Br J Psychiatry*. 2019;214:20–26.