Clinical and Practical **Psychopharmacology**

Important Insights for the Use of Ketamine From Randomized Controlled Trials That Compared Ketamine With Electroconvulsive Therapy in Severe Depression

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

Five randomized controlled trials (RCTs) have compared racemic ketamine, mostly administered intravenously in the dose of 0.5 mg/kg across 40–45 minutes, with right unilateral or bilateral electroconvulsive therapy (ECT). These RCTs were conducted in samples of severely ill patients with mostly unipolar depression (with or without psychotic features) who were referred for ECT. Of these, 2 RCTs were of reasonably adequate quality to inform clinical practice; one, in fact, was large (n = 186) and had a 1-year post-treatment follow-up. In these RCTs, ECT emerged as a clearly superior treatment with regard to response rate, remission rate, time to response, time to remission, and magnitude of improvement at treatment endpoint; however, relapse rate and time to relapse did not differ between ECT and ketamine groups. ECT appeared superior in older patients and in those with psychotic depression, as well. These findings notwithstanding, response and remission rates with ketamine appeared sufficiently impressive for ketamine to be viewed as a viable alternative to ECT in severely depressed patients who are referred for ECT. Notably, in such patients ketamine does not appear to have dramatic antidepressant action; rather, the benefits evolve across a course of 6 or more alternate day, thrice weekly sessions, validating the concept of a course of ketamine treatment that is administered much as ECT is. Finally, whereas the high relapse rates after successful remission encourage the use of ECT and ketamine as continuation therapy, continuation ketamine must be carefully supervised in patients who are prone to substance abuse.

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Intranasal esketamine has been approved for treatment-resistant depression and for depression with suicidal ideation or behavior. The benefits observed are dramatic. For example, in a randomized controlled trial (RCT) of intranasal ketamine vs placebo, esketamine outperformed placebo on the Montgomery-Asberg Depression Rating Scale (MADRS) as early as 4 hours after treatment administration; MADRS ratings dropped by half in 2–3 days, and this improvement was maintained by repeated dosing to a 25-day treatment endpoint.[1]

Racemic ketamine does not have a label for the treatment of depression. Nevertheless, a large number of placebo- and active-controlled clinical trials have established the efficacy of racemic ketamine in depression. For example, in a systematic review and meta-analysis[2] of 7 RCTs conducted in patients with treatment-resistant depression, the antidepressant effect of intravenous (IV) ketamine was found to be superior to that of placebo at 24 hours; the effect size (ES) was 0.77, which is at the threshold of being deemed as large. The benefits of ketamine persisted at 1 week (3 RCTs; ES, 0.49). The odds ratio (OR) for treatment response was 7.39 (95% confidence interval [CI], 2.50–21.83) at 24 hours and 5.09 (95% CI, 1.88–13.76) at 1 week.[2]

There has been speculation about whether or not ketamine is as effective as electroconvulsive therapy (ECT) and whether ketamine can replace ECT in clinical practice.[3] In this context, many open-label and rater-blinded RCTs have compared ketamine and ECT head to head in depressed adults.[4–8] These RCTs are examined in chronological order and instructive findings are highlighted. Other clinical trials that also compared ketamine and ECT[9–11] are not considered because patients in those studies were not randomized to their respective treatments.

Studies From Iran

In a small rater-blinded RCT,[4] patients with major depressive disorder (MDD) who were referred for ECT were randomized to receive either IV ketamine (n = 9) or bilateral ECT (n = 9) in 3 alternate-day sessions. Ketamine was administered in the dose of 0.5 mg/kg across 45 minutes. ECT was administered at 2.5× seizure threshold. Ongoing psychotropic medications were continued during the trial. Patients were followed for a week after treatment endpoint. Both groups improved in parallel, with a small advantage for ketamine after the first session.

In a slightly larger rater-blinded study,[5] patients with MDD who were referred for ECT were randomized to receive either IV ketamine (n = 16) or bitemporal ECT (n = 16) twice weekly for 6 sessions. Ketamine was administered in the dose of 0.5 mg/kg across 40 minutes; the dosing strategy for ECT, expressed in the unit of joules, was unclear. Six patients dropped out of treatment

Table 1. Important Findings From the Study by Ekstrand et al[8]

1. More ketamine (22%) than ECT (4%) patients dropped out before reaching the 6-session assessment threshold; most of the dropouts were due to the experience of adverse events.
2. At the 6-session threshold, a further 16% vs 11% of patients were discontinued from the study in the ketamine vs ECT groups, respectively, because they had improved by < 25%.
3. Given the higher dropout rate in the ketamine group, ketamine patients expectedly received fewer treatment sessions than ECT patients (mean, 7 vs 8).
4. At treatment endpoint, the remission rate was significantly higher with ECT than with ketamine (63% vs 46%, respectively). Rapid remission was rare; most patients required at least 6 sessions to remit.
5. At treatment endpoint, the response rate was also significantly higher with ECT than with ketamine (71% vs 57%, respectively).
6. Endpoint MADRS scores were significantly lower with ECT than with ketamine (means, 12 vs 17, respectively).
7. There was a significant interaction between treatment and age: older patients were more likely to remit with ECT but younger patients remitted comparably with the 2 treatments. Here, age 50 years was used as the cutoff to separate older from younger patients.
8. In patients with psychotic symptoms, mean MADRS improvement scores were 27 vs 18 in ECT vs ketamine groups; the advantage for ECT narrowly missed statistical significance ($P = .069$). In patients with psychotic symptoms, the remission rate was 79% vs 50% ($P = .15$). In logistic regression, the interaction between treatment and psychotic symptoms did not reach statistical significance. These analyses in patients with psychotic symptoms were almost certainly underpowered.
9. Adverse effects during the treatment course largely corresponded to the known profile of these 2 treatments.
10. Among patients who remitted, 70% vs 63% relapsed in the ketamine vs ECT groups, respectively; median time to relapse was 57 vs 61 days, respectively.

Abbreviations: ECT = electroconvulsive therapy, MADRS = Montgomery-Asberg Depression Rating Scale.

Table 2. Take Home Messages From the Studies of Sharma et al[7] and Ekstrand et al[8]

1. In severely depressed unipolar depression patients who are referred for and who agree to receive ECT, thrice-weekly suprathreshold right unilateral ECT is superior to thrice-weekly intravenous ketamine (0.5 mg/kg, administered across 40 min) on a range of antidepressant outcomes: response rate, remission rate, time to response, time to remission, and magnitude of improvement at treatment endpoint. Some of these advantages for ECT may apply to patients with psychotic depression, as well, but data are insufficient to inform clinicians about the relative merits of these treatments in patients with bipolar depression.
2. Older patients respond better to ECT than to ketamine; younger patients respond comparably to the 2 treatments.
3. Although the antidepressant benefits with ketamine do not match those with ECT, the benefits are nonetheless sufficiently substantial for ketamine to be considered a potential alternative in patients, especially younger patients, considered for or referred for ECT.
4. In depressed patients referred for ECT, the antidepressant benefits of ketamine are not as dramatic as those commonly reported in literature; rather, they appear to evolve progressively across a course of 6 or more treatment sessions, administered on alternate days, thrice weekly. This validates the concept of administering ketamine in a course, much as is done with ECT.
5. Strategies are required to reduce the dropout rate in patients receiving a course of ketamine.
6. After a course of treatment, relapse rates and time to relapse are similar with ketamine and ECT. This indicates that the benefits after a course of ketamine are similarly sustained by maintenance psychotropic medications, much as they are after ECT. However, the high relapse rates suggest that a comparison of continuation ketamine vs continuation ECT is warranted in patients who remit after an acute course of treatment. Continuation ketamine must be carefully supervised in patients who are prone to substance abuse.
7. The findings described above cannot be generalized to populations of patients other than severely ill unipolar depressed patients referred for ECT.

Abbreviation: ECT = electroconvulsive therapy.

from the ketamine group and 4 from the ECT group. The 2 groups did not differ significantly in either antidepressant or memory outcomes. The validity of the study findings is in question because completer and not intent to treat analyses were performed.

In a completely unblinded study,[6] patients with MDD who were referred for ECT were randomized to receive intramuscular (IM) ketamine (n = 15), oral ketamine (n = 15), or bilateral ECT (n = 15). Intramuscular ketamine was dosed at 0.5 mg/kg and oral ketamine at 1 mg/kg; the dosing strategy for ECT, expressed in joules, was unclear. Ongoing psychotropic medications were continued during the trial. Treatments were administered for a total of 6–9 sessions across 3 weeks. Three patients dropped out of treatment from the oral ketamine group and 3 from the ECT group. The authors concluded in the text of their paper that "oral and IM ketamine both probably have equal antidepressant and antisuicidal effects compared with ECT." Oral ketamine, which has only 20%–30% bioavailability,[12] was probably underdosed in this study. ECT, which was administered twice rather than thrice weekly, was probably administered at suboptimal frequency.[13] The validity of the study findings is in question because completer and not intent to treat analyses were performed.

These 3 RCTs were poorly reported and contained incomplete details and even contradictions. For example, Ghasemi et al[4] stated that they recruited patients with MDD, but, in a table, they presented bipolar disorder (BD) among the additional diagnoses that patients had. Kheirabadi et al[5] stated that patients and raters were blinded but did not explain how patients were blinded; given how different the treatment procedures are, patient blinding would have been almost impossible to implement. These authors also did not state whether or not patients in the trial were continued on psychotropic medications during the trial. Kheirabadi et al[6] stated in their CONSORT diagram that no patients were excluded from analysis but excluded the treatment dropouts from the data that they presented. They suggested that there was a significant interaction term in each of their efficacy analyses but did not explain the interaction, and in different places in their abstract and text, they offered different conclusions about the relative efficacy of ketamine and ECT.

A Study From India

In a small rater-blinded RCT,[7] patients with MDD or BD who were referred for ECT were randomized to receive either IV ketamine (n = 12) or ECT (n = 14). The sample was young; the mean age was 34 years in the ketamine group and 41 years in the ECT group. Nine patients (35% of the sample) had psychotic symptoms associated with depression, 5 of whom received ketamine, and 9 patients (35% of the sample) had bipolar depression, 3 of whom received ketamine.

Ketamine was administered in the dose of 0.5 mg/kg across 45 minutes. ECT electrode placement was either bifrontal (n = 9) at 1.5× to 2× seizure threshold or right unilateral (RUL) at 6× seizure threshold (n = 4). Treatments were administered on alternate days, thrice weekly, for 2 weeks; that is, for a total of 6 sessions. Ongoing psychotropic medications were continued during the trial and were not controlled. Three patients dropped out of the ketamine arm but were included in the intent to treat analysis. No patient dropped out of the ECT arm, but 1 was excluded from analysis because of a change in diagnosis.

Ratings on both Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI) attenuated significantly faster and to a greater extent in the ECT group than in the ketamine group; improvement with ketamine was gradual rather than dramatic. Response, defined as at least 50% attenuation in depression ratings, was significantly greater in the ECT group than in the ketamine group (100% vs 67%). Remission, defined as a final HDRS score of 7 or lower, was also significantly greater in the ECT group (92% vs 50%). Time to response and time to remission for both HDRS and BDI were each less with ECT than with ketamine. Response was also obtained in 4 of 5 ketamine-treated patients who had had psychotic symptoms (J. Thirthalli, MD, personal communication). Whereas data on cognitive outcomes were presented, patient numbers for whom these data were available were too small for meaningful interpretations to be possible.

An important limitation of this study is that there was no follow-up, so we do not know for how long the benefits persisted after treatment was stopped.

A Study From Sweden

Ekstrand et al[8] described a large, 6-center, randomized, non-blind comparison of ketamine (n = 95) and ECT (n = 91) in severely ill unipolar depression patients who had been referred for ECT and who had agreed to receive ECT (screened n = 622). Reasons for referral for ECT were not described. Suicidal patients and patients with psychiatric comorbidities were not excluded.

The mean age of the sample was about 53 years. The sample was 64% female. The average patient was overweight. A third of the sample had psychiatric comorbidities. Nearly 40% of patients had previous experience of ECT, and treatment response had been good in nearly 70% of these patients.

The mean duration of the current depressive episode was 14 weeks. Psychotic symptoms were present in 19% of ketamine patients and in 15% of ECT patients. About 82% of patients were receiving antidepressants and about 65% were receiving anxiolytics; however, very few were receiving benzodiazepines (P. R. Rad, MD, PhD, personal communication). About 20% of patients were also receiving antipsychotic drugs.

Ketamine was dosed at 0.5 mg/kg IV across 40 minutes. ECT was administered with RUL electrode placement to all patients, but 9% also received bilateral treatments. ECT dosing took into consideration patient age and sex; the initial dose ranged from 154 to 759 millicoulombs (mC) and the range across the course was 67–1,025 mC.

Patients were treated in thrice-weekly sessions to remission or to maximum antidepressant benefit, subject to the receipt of a minimum of 6 sessions of treatment before declaring treatment failure, and a maximum of 12 sessions of treatment in patients who appeared to benefit. Treatment response was defined as at least 50% reduction from baseline in MADRS scores, and remission as a MADRS score of 10 or lower, persisting across at least 2 treatment sessions or for at least 5 days. Ongoing psychotropic medications were continued during the trial and were not controlled. Patients were followed up at 1 week and at 3, 6, and 12 months post-treatment. Relapse was defined as once again meeting diagnostic criteria for depression.

Important findings from the study[8] are presented in Table 1. In summary, there were fewer dropouts and treatment failures with ECT than with ketamine. More patients responded to and remitted with ECT than with ketamine. Endpoint depression scores were lower with ECT than with ketamine. Older patients were more likely to remit with ECT; younger patients remitted comparably with the 2 treatments. Patients with psychotic symptoms improved more with ECT than with ketamine, but the analyses were underpowered and narrowly missed statistical significance. Among remitters, relapse rates and time to relapse were comparable in the 2 groups.

An important limitation of this study[8] is that neither patients nor raters were blind to treatment allocation, so individual biases may have influenced the treatment ratings; however, the authors did find that patients in the treatment groups did not differ with regard to expectations from treatment or fear of negative outcomes, based on visual analog scale ratings. Curiously, the groups were compared cross-sectionally using *t* tests rather than longitudinally using analysis of covariance or repeated-measures analysis of variance. Important strengths of the study are the large sample size and the 1-year follow-up.

General Comments

Impressions are drawn only from the small RCT by Sharma et al[7] and the large, partly naturalistic RCT by Ekstrand et al[8] because, as described earlier, there were important concerns about the methodological and reporting qualities of the earlier 3 RCTs.[4–6]

Take home messages from the 2 recent RCTs[7,8] are presented in Table 2. These apply almost exclusively to patients with MDD because only Sharma et al[7] included

patients with BD and because only 3 of their BD patients received ketamine; the concern here is that prior literature suggests that the benefits of ketamine, if any, wear off earlier in BD patients than in MDD patients.[14] The take home messages also apply primarily if not exclusively to depressed patients who are referred for ECT, the population from which the samples of the 2 studies were drawn; the issue here is that patients are referred for ECT for many reasons beyond medication-refractoriness, and few of such patients are treated in the community. And, because neither Sharma et al[7] nor Ekstrand et al[8] described medication-refractoriness in the sample, it is uncertain to what extent their findings regarding ketamine apply specifically to medication-refractory patients with MDD.

Gradual, not dramatic, onset of response with ketamine contrasts with literature[15] and validates the need for a "course" of ketamine. Perhaps the more gradual response in the 2 studies[7,8] is because both samples were drawn from patients who were referred for ECT and who may therefore have been more treatment-resistant and more severely ill. Importantly, and for the first time in literature, the safe and effective administration of ketamine was documented in patients with psychotic depression; however, it was not clear from the descriptions whether these patients were "protected" by antipsychotic drugs coadministered with antidepressant drugs. In both Indian[7] and Swedish[8] studies, few patients received benzodiazepines; these drugs may compromise benefits with ketamine.[16] The findings of the studies, therefore, cannot be generalized to patients who are receiving benzodiazepines.

The advantage for ECT over ketamine is potentially larger than that presented by Ekstrand et al.[8] For one, many of the patients whom they screened declined to participate in the study because they had previously responded well to ECT. For another, 96% of the ECT sessions in their study were administered using right unilateral electrode placement at an unknown multiple of the seizure threshold; RUL ECT that is so dosed may be therapeutically inferior to bilateral ECT.

Parting Notes

Ekstrand et al[8] speculated that administration of ECT and ketamine as continuation therapy might have attenuated the relapse rates in their patients who relapsed after remitting. This possibility merits examination in future research. To some extent, continuation treatment has been validated in the intranasal esketamine clinical trials.[17,18] Careful supervision is however necessary in patients with addiction liabilities who may be prone to abuse ketamine.

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