Ketamine vs Electroconvulsive Therapy in the Management of Treatment-Resistant Depression:

Do We Need More Data?

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Depression is one of the most common, debilitating psychiatric disorders, especially for treatment-resistant patients who do not receive an adequate response after 2 or more first-line treatments.[1] While electroconvulsive therapy (ECT) has been the gold standard for treatment-resistant depression (TRD) for many decades,[2] ketamine has recently gained traction among patients and providers as a possible alternative.[3]

A previous meta-analysis suggested that ECT is likely superior to ketamine for patients in the acute phase[4]; however, this finding was based on a small number of studies with low sample sizes. Recently, the largest study to date directly compared ECT and intravenous (IV) ketamine.[5] To better understand whether ECT or ketamine are better initial treatments for patients with TRD, we re-evaluated our previous meta-analysis with these newer data to determine if ECT or ketamine was associated with better outcomes (ie, improvement in depressive symptoms and response and remission rates).

Methods

We performed an updated systematic review and meta-analysis that compared ECT with IV ketamine.[4] The study protocol was registered in PROSPERO database (#CRD42022338045). In this analysis, we included data from a large, newer trial that directly compared ECT to IV ketamine.[5] We calculated Hedges *g* standardized mean difference (SMDs) to determine relative effectiveness of ECT and IV ketamine in treating depressive symptoms as well as on response and remission rates. Detailed methodologic strategies and analytical plans were reported in the earlier study.[4]

Results

In total, 7 clinical trials comprising 600 patients (n = 285 for ECT and n = 315 for IV ketamine) were included in the meta-analysis.[5–11] The overall pooled SMD for depression severity for ECT when compared with ketamine was −0.23 (95% CI, −1.39 to 0.94), suggesting that no statistical difference was found between ECT and ketamine in treating depression (Figure 1). In addition, we did not find any statistical differences in response and remission rates between ECT and ketamine (Figure 2).

Discussion

The present meta-analysis includes effect sizes for depression severity as well as response and remission rates from 7 studies that enrolled a total of 600 patients and is the most comprehensive meta-analysis comparing the efficacy of ECT to that of IV ketamine. Results here suggest that the difference between these treatment modalities may be smaller than previously thought. While this analysis suggests therapeutic advantage, albeit slight, in favor of ECT, the largest and most recent trial found an advantage of IV ketamine over ECT in a TRD study population.[5] Of the trials included in this meta-analysis, only 2 are well-powered, head-to-head comparisons.[5,6] While the most recent study[4] has suggested that ketamine may even be superior to ECT, the trial was not designed nor sufficiently powered to assess this potential outcome.

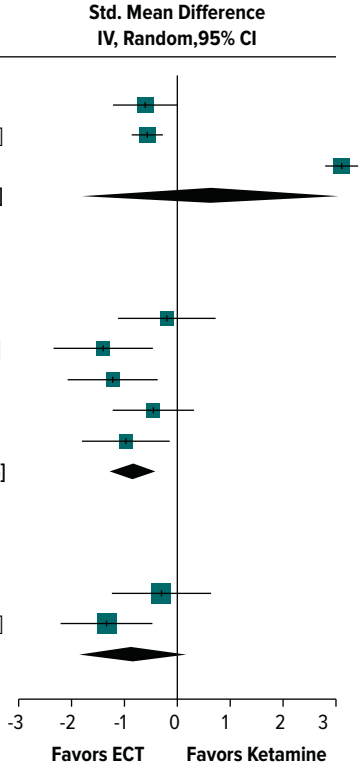
Additionally, TRD is associated with increased suicide risk.[12–15] Both ECT and ketamine may provide substantial reductions in suicidal ideation for patients with TRD. However, acute increases in suicidality during initial treatment remain a concern, especially for ketamine. Notably, one of the recent large head-to-head trials examined suicidality as a secondary outcome via the clinician-administered Columbia-Suicide Severity Rating Scale.[5] In that study, patients reported a similar decrease in suicide risk when treated with ECT or ketamine. Consistent with this effect, 4 of 195 patients in the ketamine group and 2 of 170 patients in the ECT group reported suicidal ideation, with 1 person in the ketamine group attempting suicide. Similarly, in the other large head-to-head trial,[6] 4 of 95 ketamine patients attempted suicide as did 5 of 91 patients in the ECT group, with 1 ECT patient dying by suicide 3 months after achieving remission during the trial. These data cumulatively suggest that ketamine and ECT carry similar risks in terms of acutely increasing suicidality.

Figure 1.

Severity of Depressive Symptoms Between Electroconvulsive Therapy (ECT) and Ketamine in ECT-Eligible Patients With Major Depressive Episode

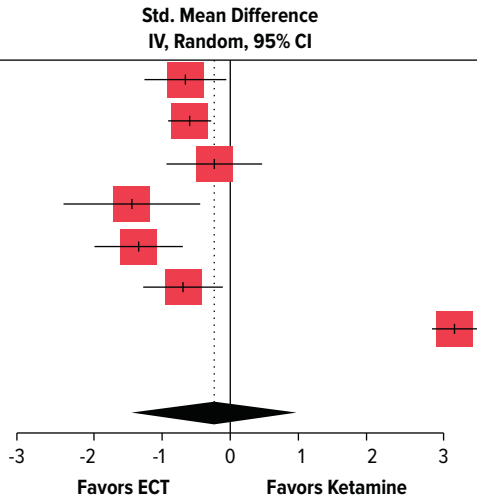
A. Severity of depressive symptoms by measure

Study or Subgroup	ECT Total	ECT Mean	ECT SD	Ketamine Total	Ketamine Mean	Ketamine SD	SMD	95% CI
MADRS								
Basso (2020)	24	-17.420	7.4900	25	-13.000	6.1500	-0.636	[-1.211; -0.061]
Ekstrand (2021)	91	-22.300	9.6100	95	-16.200	11.3500	-0.577	[-0.870; -0.283]
Anand (2023)	170	-13.100	0.7000	195	-15.300	0.7000	3.136	[2.829; 3.444]
Total (95% CI)	**285**			**315**			**0.647**	**[-1.804; 3.097]**
Heterogeneity: Tau^2 = 4.6445; Chi^2 = 327.18, df = 2 (P < .01); I^2 = 99%								
HDRS								
Ghasemi (2013)	9	-21.880	5.8500	9	-20.670	5.4200	-0.204	[-1.131; 0.723]
Kheirabadi (2019)	12	-12.500	3.5000	10	-7.700	2.9500	-1.415	[-2.371; -0.458]
Sharma (2020)	13	-21.190	5.8400	12	-14.500	4.3800	-1.246	[-2.115; -0.376]
Kheirabadi (2020)_IM	12	-12.330	5.0300	15	-10.140	4.4400	-0.451	[-1.221; 0.319]
Kheirabadi (2020)_Oral	12	-12.330	5.0300	12	-8.170	2.9800	-0.972	[-1.826; -0.117]
Total (95% CI)	**58**			**58**			**-0.838**	**[-1.272; -0.404]**
Heterogeneity; Tau^2 = 0.0478; Chi^2 = 5.1, df = 4 (P = .28); I^2 = 22%								
BDI								
Ghasemi (2013)	9	-26.780	8.7000	9	-23.780	9.5100	-0.313	[-1.245; 0.618]
Sharma (2020)	13	-30.650	5.7700	12	-20.450	8.6800	-1.350	[-2.233; -0.466]
Total (95% CI)	**22**			**21**			**-0.842**	**[-1.858; 0.173]**
Heterogeneity; Tau^2 = 0.3225; Chi^2 = 2.5, df = 1 (P = .11); I^2 = 60%								



B. Overall effect size for severity of depressive symptoms

Study	N	SMD	95% CI
Basso (2020)	50	-0.636	[-1.211; -0.061]
Ekstrand (2021)	186	-0.577	[-0.870; -0.283]
Ghasemi (2013)	18	-0.259	[-0.916; 0.398]
Kheirabadi (2019)	22	-1.415	[-2.371; -0.458]
Sharma (2020)	25	-1.297	[-1.916; -0.677]
Kheirabadi (2020)	39	-0.684	[-1.256; -0.112]
Anand (2023)	365	3.136	[2.829; 3.443]
Total (95% CI)		**-0.226**	**[-1.392; 0.941]**
Heterogeneity; Tau^2 = 2.3858; Chi^2 = 418.25, df = 6 (P < .01); I^2 = 99%			

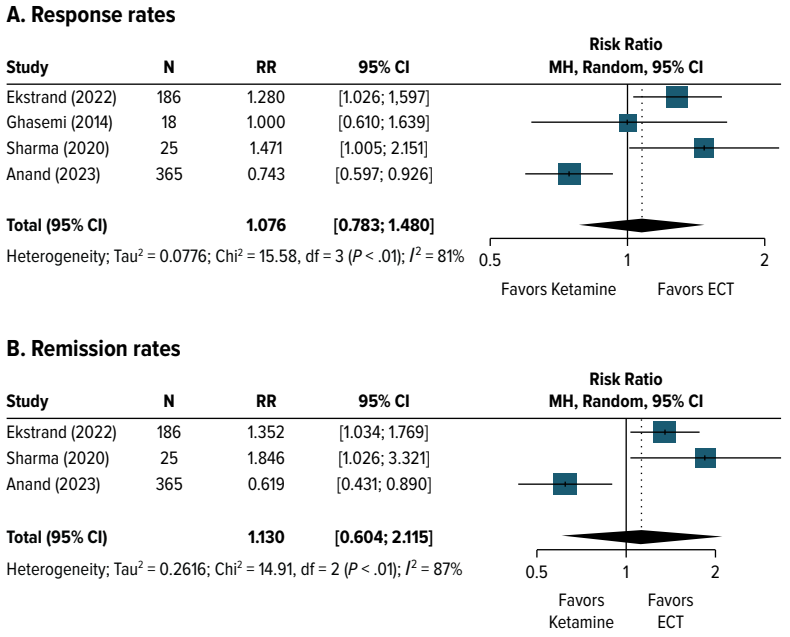


Abbreviations: BDI = Beck Depression Inventory, HDRS = Hamilton Depression Rating Scale, IV = inverse variance, MADRS = Montgomery-Asberg Depression Rating Scale, SMD = standardized mean difference.

Other differences in study design, setting, and TRD patient characteristics may further challenge direct comparisons on outcomes. Both large studies[5,6] enrolled patients with moderate to severe depressive symptoms (ie, Montgomery-Asberg Depression Rating Scale [MADRS] >20) who had tried multiple other treatments (including potentially ECT or ketamine) while excluding those who were living with psychotic symptoms. The 2 studies similarly provide the greatest insight to patients with cumbersome, persistent

Figure 2.

Response and Remission Rates Between Electroconvulsive Therapy (ECT) and Ketamine in ECT-Eligible Patients With Major Depressive Episode



Abbreviations: MH = Mantel-Haenszel, RR = risk ratio.

depression with no history of psychoses and may be less valuable to clinicians treating initial presentation of depression.

However, the ketamine-ECT (KetECT) trial[6] utilized only hospitalized patients while the ketamine in patients with treatment-resistant depression (ELEKT-D) trial[5] utilized a predominately outpatient (89%) over inpatient (11%) population. Thus, the noninferiority of ketamine to ECT may also be most useful for clinicians treating major depressive disorder in the outpatient setting. Additionally, the ELEKT-D trial[5] only utilized bilateral ECT if response was inadequate halfway through the treatment period to unipolar stimulation, which may decrease the apparent effectiveness of ECT.

Both studies found similar adverse events for both treatments that are consistent with prior clinical trials as well as reports from community practice. For ECT, cognitive impairment and musculoskeletal adverse events were more common than in ketamine treatment, which had higher rates of dissociation. While these disparate adverse events should and will likely inform clinical practice, it is notable that by the end of the primary follow-up phase, both groups returned to similar levels for all measures. For clinicians and patients choosing between treatments, it may be worthwhile to consider if avoiding acute cognitive impairment or dissociation is more desirable when deciding on treatment modality.

Unfortunately, these 2 studies[5,6] represent the only well-powered studies to date, pointing to the need for studies comparing ketamine (in different formulations) and ECT (in different applications) across comparable populations and settings. Future trials comparing ECT and ketamine alongside placebo are crucially needed as well as increased follow-up periods to evaluate the long-term efficacy of these different treatment modalities. Psychiatric trials, particularly for mood disorders, are dramatically altered by placebo and expectation effects. While ECT has been a mainstay of depression treatment with much bad publicity in the lay media, ketamine has enjoyed a conversely warm welcoming by many patients suffering with depression due in no small part to its popularity as a recreational drug. Such different baseline expectations for potential treatments may additionally make ketamine extremely effective. Understanding patients' predisposition toward these treatments before randomization would help shed light on such expectancy effects. Increased follow-up of patient outcomes for year(s) will also help clinicians guide clinical practice.

Future studies should focus on specific illness characteristics, symptom profiles, longer range outcomes, and patient populations. For example, separating patients based on age is appropriate since studies suggest ECT tends to be more efficacious in older populations than in younger ones. Conversely, younger and more anxious populations may respond better to ketamine than ECT. Lastly, given that ECT requires anesthesia, a natural question is: Does the use of ketamine as an anesthetic during ECT produce synergistic effects? A recent meta-analysis suggests that while ketamine may provide greater antidepressant effect than another common anesthetic (propofol), this effect is tempered by greater cognitive side effects.[16] Clearly, studies are needed to better understand the unique applications of ECT and ketamine in the appropriate patient populations, clinical settings, and course of illness.

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