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Trends and Perspectives

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Ketamine or ECT? What Have We Learned From the KetECT and ELEKT-D Trials?

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Abstract

1. Two recent clinical trials, KetECT and ELEKT-D, compared the effectiveness of ketamine and electroconvulsive therapy (ECT) for major depressive disorder. Notably, these trials reported marked differences in ECT's clinical outcomes of, with remission rates of 63% for KetECT and a strikingly lower rate of 22% for ELEKT-D, while the remission rates for ketamine were 46% and 38%, respectively. Considering that the primary objective of both trials was to compare the standard treatment (ECT) with an experimental intervention (ketamine), it is crucial to highlight the pronounced disparities in ECT's clinical outcomes. This article offers a comprehensive comparison of these trials while also exploring how patient characteristics, treatment protocols, and study designs may contribute to such pronounced outcome discrepancies. These differences highlight the heterogeneous nature of depression and underscore the need for personalized treatments. These studies also provide valuable insights into identifying the most suitable candidates for ketamine and ECT.

Key Words: Major depressive disorder, electroconvulsive therapy, racemic ketamine, clinical trials

Introduction

Major depressive disorder (MDD) exhibits vast heterogeneity in its clinical manifestations, often leading to suboptimal effectiveness of current antidepressant treatments (Rush et al., 2006). Electroconvulsive therapy (ECT) is the gold standard treatment for severe depression, but its use is hampered by limited accessibility and the potential for cognitive side effects. Consequently, ECT is typically reserved for severely ill patients, including those with catatonic or psychotic features, or those responding poorly to pharmacological treatments. Ketamine has been shown to alleviate depression unresponsive to conventional treatments (Berman et al., 2000; Zarate et al., 2006), heightening interest in its potential therapeutic role.

So far, only 2 adequately powered pragmatic trials, KetECT (Ekstrand et al., 2022) and ELEKT-D (Anand et al., 2023), have been conducted. In the KetECT trial, among 186 hospitalized MDD patients, 46% of the participants treated with ketamine achieved remission, whereas 63% achieved remission with ECT (response rates 57% and 71%), showing that ECT was superior to ketamine. In the ELEKT-D, among 403 predominantly nonhospitalized MDD patients, 38% achieved remission with ketamine, and 22% achieved remission with ECT (response rates 55% and 41%), indicating that ketamine was noninferior to ECT.

Whereas efficacy studies examine treatments under ideal but somewhat artificial conditions, pragmatic or effectiveness trials assess them in real-world clinical settings. Thus, study populations should represent typical patients, treatments should mirror standard clinical procedures, and outcomes for control treatments should be aligned with routine clinical findings. Considering that KetECT and ELEKT-D had similar designs and the mutual objective to evaluate ketamine and ECT in populations typically treated with ECT—prioritizing real-world clinical scenarios over idealized conditions (effectiveness over efficacy)—the discrepancy in clinical outcomes raise important questions. This article addresses the essential distinctions between the studies using the aspects of the PICO (population-intervention-control-outcome) framework summarized in Table 1.

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Table 1. Comparison Between KetECT and ELEKT-D

Study PICO	KetECT	ELEKT-D
n; female (%)	186; 91 ECT, 95 KET (64%)	403; 203 ECT, 200 KET (51%)
Participants	100% inpatient No Referrals No Advertisement	89.1% outpatients Referral to a ECT service
Age, y[mean (SD)]	range:18–85 ECT: 50 (18) KET: 55 (18)	range:21–75 ECT: 47.1 (14.1) KET: 45.6 (4.8)
Psychotic depression	Included ECT: 15% KET: 19%	Excluded
Episode duration, month[median (IQR)]	ECT: 3.5 (2–3.5) KET: 3.5 (2–7)	ECT: 24 (10–72) KET: 24 (12–75)
Severity (MADRS)	ECT: 34.5 (5.7) KET: 33.1 (6.3)	ECT: 32.6 (6.0) KET: 32.3 (6.2)
Subtype of depression comorbidity	Mixed anxiety-depressive disorder, ECT 1%, KET 0% Additional psychiatric diagnosis, ECT 31%, KET 33%	Anxious features: ECT 54.2%, KET 55.5% GAD: ECT 55.7%, KET 56.5% Panic: ECT 20.7%, KET 16.5% PTSD: ECT 24.6%, KET 19.0% Social phobia: ECT 28.1%, KET 28.0%
Medications	Anticonvulsants: 6.45%[a] Benzodiazepines: 17, 2%[a]	Anticonvulsants: ECT 25.1%, KET 27.0% Benzodiazepines: ECT 31.0%, KET 30.0%
KET	0.5 mg/kg 3 infusion/wk. Up to 12 treatments	0.5 mg/kg or higher. 2 infusion/wk. Up to 6 treatments
ECT	1–12 sessions RUL or BT BP on age and gender	6–9 sessions RUL→ BL UBP at 6 times the ST
Remission rate	ECT 63% (57/91) vs KET 46% (44/95)	ECT 21.8% (37/170) vs KET 37.9% (74/195)
Response rate	ECT 71% (65/91) vs KET 57% (54/95)	ECT 41.1% (70/169) vs KET 50.8% (99/195)

Abbreviations: BL, biletaral; BT, bitemporal; BP, brief pulse; ECT, electroconvulsive therapy; IQR, interquartile range; KET, ketamine; MADRS, Montgomery Åsberg Depression Rating Scale; PICO (population-intervention-control-outcome); RUL, right unilateral; ST, seizure threshold; UBP, ultra brief pulse.
[a]Unpublished data.
The primary outcome of the KetECT was remission rate measured by MADRS, while that of the ELEKT-D trial was response rate measured by a self-reporting Quick Inventory of Depressive Symptomatology scale. However, for the comparison between the trials, common outcomes such as remission/response rate based on MADRS scores are reported.

Population

Both studies claim to have recruited real-world patients, implying high generalizability. However, disparities in recruitment processes, clinical characteristics, and medication usage exist. Firstly, in the KetECT study, only hospitalized patients about to receive ECT were included, without the utilization of advertisements or referrals from psychiatric outpatient care colleagues. In contrast, the ELECT-D trial included both outpatients (89%) and inpatients referred for ECT. The study protocol (Mathew et al., 2019) highlighted concerns about recruitment bias due to widespread promotion of ketamine therapy, which became evident in an almost 20% (38/203) dropout rate before ECT treatment initiation compared with only 5/200 allocated to ketamine. This raises questions about the extent to which the study population may have been positively biased towards and hoped to be randomized to ketamine treatment. It is worth noting that at least 1 participating site solicited participants online, offering complimentary study treatments and associated care. https://web.archive.org/web/20211026211551; https://www.bcm.edu/healthcare/clinical-trials/h-40701

Secondly, clinical characteristics entail both current states and enduring traits of individuals within the study population, significantly impacting clinical outcomes. This differed between the studies. Notably, a shorter median duration of the current depressive episode (KetECT 3.5 vs ELEKT-D: 24 months), inclusion of patients with psychotic depression (KetECT 17% vs ELECT-D: 0%), older mean age (KetECT 52 vs ELEKT-D: 46 years), and larger proportion of hospitalized patients (KetECT 100 vs ELEKT-D: 11%) are factors associated with a positive ECT outcome (Haq et al., 2015; van Diermen et al., 2019; Nakajima et al., 2022). Another clinical characteristic concerns comorbid anxiety conditions. In the KetECT trial, 11% of patients had 1 or 2 concurrent anxiety disorders, including posttraumatic stress disorder, generalized anxiety disorder, social phobia and obsessive-compulsive disorder. In contrast, the ELEKT-D trial reported higher comorbidity rates for anxiety conditions: depression with anxious features (55%), generalized anxiety disorder (56%), panic disorder (16%), posttraumatic stress disorder (19%), and social phobia (28%). Given the possibility of diagnostic overlap, accurate diagnosis can be challenging when symptoms of depression and anxiety coincide. Therefore, a comprehensive assessment considering various factors, such as episodicity, beyond just the DSM criteria is essential. Furthermore, the concept of treatment-resistant depression used in ELEKT-D is not a diagnosis but a self-referential concept, potentially complicating and hampering reassessment of the diagnosis (Malhi et al., 2019). ECT can benefit patients with depression with comorbid anxiety disorders but is not recommended for primary anxiety disorders because it may result in partial or temporary improvement or exacerbate existing issues due to potential side effects, leading to a low remission rate (Steinholtz et al., 2021; Goegan et al., 2022). Rigorous effectiveness clinical trials with ECT as the control treatment require a study population that accurately represents real-world demographics and aligns with the actual clinical outcomes of the control treatment. This entails the need for precise diagnosis, patient selection, and evaluation of ECT's suitability for specific cases.

Furthermore, patient characteristics, such as gender distribution and average age, offer valuable insights into cohort representativeness, regardless of their direct impact on the outcome. Notably, ECT appears equally effective in both genders and more effective in older individuals (Zorumski et al., 1986; O'Connor et al., 2001; Brus et al., 2017; Ekstrand et al., 2022; Blanken et al., 2023). The community-based ECT study of Prudic et al. revealed an average age of 57 years, with 63% female patients (Prudic et al., 2004). Clinical data from 20 independent international sites also showed an average age of 55 years and 59% women (Blanken et al., 2023). Typically, depression is more prevalent in women, resulting in women constituting about two-thirds of ECT recipients as seen by previously reported studies (Slade et al., 2017; Wilkinson et al., 2018; Luccarelli et al., 2020; Kaster et al., 2021). In the KetECT study, the average age was 53 years, with 64% of participants being female. Conversely, in the ELEKT-D study, the mean age was 46 years and 51% of participants were female, indicating a potential bias toward an atypical cohort.

Additionally, as highlighted by the authors of ELEKT-D, the study excluded patients with psychotic depression, a factor that may have contributed to the lower rates of remission. However, we acknowledge that this factor alone had limited impact, as given that the prevalence of psychotic depression in naturalistic cohorts typically ranges between 15% and 20% (Johnson et al., 1991; Ohayon and Schatzberg, 2002; Ekstrand et al., 2022). Importantly, when patients with psychotic depression were excluded from KetECT, the remission rates were still 60% (46/77) for ECT and 45% (35/77) for ketamine. Additionally, it is worth noting that in KetECT, the remission rate for ketamine-treated patients with psychotic depression was 50% (9/18). This rate surpasses the 38% Montgomery Åsberg Depression Rating Scale(MADRS)–based remission rate observed in the ketamine arm of ELEKT-D for patients without psychotic features. Therefore, there may remain an opportunity to further explore the efficacy/effectiveness of ketamine for this patient population.

Thirdly, concurrent medications should be acknowledged. In the KetECT trial, 6% of the patients were using anticonvulsant medications and 17% were taking benzodiazepines (Ekstrand et al., unpublished data). Among those taking benzodiazepine, 50% had oxazepam (short half-life) administered if needed no later than the day before ECT as recommended. In the ELEKT-D trial, 25% of the patients were taking anticonvulsant medications, and 31% were prescribed benzodiazepines. Although concerns about their potential impact on ECT efficacy have been raised (Cinderella et al., 2022), the evidence regarding anticonvulsants' influence on ECT's efficacy in depression remains limited (Stromgren et al., 1980; Zolezzi, 2016; Brus et al., 2017). Most studies in this area have primarily focused on patients with schizophrenia and mania (Jahangard et al., 2012; Haghighi et al., 2013; Kaster et al., 2017; Rakesh et al., 2017). However, although there have been suggestions that benzodiazepines might influence ECT efficacy, especially in the context of right unilateral (RUL) ECT (Auriacombe and Tignol, 1991; Jha and Stein, 1996; Tang et al., 2017), contradictory data are also present (Delamarre et al., 2019).

Intervention/Control Treatment

Ketamine administration differed between the trials. In the KetECT trial, hospitalized patients received ketamine thrice weekly for up to 12 sessions over 4 weeks at a fixed dose of 0.5 mg/kg, mirroring the ECT protocols, including fasting and medication adjustments. ELEKT-D, however, allowed up to 6 ketamine infusions twice weekly over 3 weeks using the dose of 0.5 mg/kg, with potential dosage adjustments. Despite limited evidence, a dose-response relationship with ketamine is plausible. The utilization of a fixed ketamine dosage in KetECT could have played a role in reducing the remission rate despite the higher number of treatments administered compared with ELEKT-D.

In addition, 22% of patients in KetECT randomized to ketamine (4% in the ECT arm) dropped out early in the treatment course (before reaching the sixth treatment). This high dropout rate was primarily due to patient discomfort from dissociative symptoms and might have been exacerbated by patients knowing that ECT would be available after declining additional ketamine infusions, whereas ketamine treatment was not available for dropouts from the ECT arm. Given that remission required multiple infusions, higher remission with ketamine might have been reached by better preparation of the patients and more experienced staff. Nonetheless, the remission rate for ketamine in KetECT was higher at 46% compared with 38% in the ELEKT-D study. This may imply that with the appropriate patient selection, ketamine has the potential to yield even higher remission rates.

It is pertinent to highlight the ECT techniques utilized in the 2 trials given their potential impact on clinical outcomes. Both trials administered ECT 3 times per week for a maximum of 4 (KetECT) or 3 weeks (ELEKT-D) using different stimulation parameters. The KetECT study employed right unilateral (RUL) brief pulse (BP) ECT, adjusting energy delivery based on age and gender. Approximately 9% of patients received bilateral (BL) ECT as part of their treatment. In contrast, the ELEKT-D study utilized RUL ultra-brief pulse (UBP) ECT, with the option to switch to BL electrode placement (with PB 0,5), if necessary. The seizure threshold (ST) was determined with empirical dose titration, with subsequent treatments set at 5 to 6 times ST. The decision to limit the number of ECT sessions to a maximum of 9 over a 3-week period was based on research indicating that approximately 9 treatments, on average, were required to achieve remission.

Notably, 1 of these efficacy trials found that 25% of remitted patients required more than 9 treatments (Kellner et al., 2016), and the other trial used a minimum of 8 or 10 ECT treatments (Sackeim et al., 2008). We argue that it is inherently suboptimal to limit the number of treatments that patients receive in a pragmatic trial based on the mean of previous efficacy trials, as it disregards the significant proportion of patients requiring more sessions to respond or remit.

Furthermore, there are trials investigating UBP ECT that have shown an equivalent antidepressant effect compared with BP ECT, even though UBP ECT required more treatment sessions (Niemantsverdriet et al., 2011; Magid et al., 2013). All in all, a 2015 meta-analysis concluded that UBP stimulation was linked to fewer cognitive side effects, but it also had lower remission rates and required a greater number of treatments (Tor et al., 2015).

Retrospective real-world data corroborate reduced remission rates in cohorts primarily treated with UBP ECT: 21% in Hart et al 2023, 21% in Luccarelli et al 2022, and 27% in Galletly et al 2014, compared with 39% for BP RUL (Galletly et al., 2014; Luccarelli et al., 2022; Hart et al., 2023).

Given all the evidence, we attribute the ELEKT-D study's low remission rate partially to the combination of a maximum of 9 and ultra-brief pulse sessions.

Outcome

Ensuring the selection of appropriate study outcomes is a critical aspect of research design. In the KetECT study, the primary

outcome chosen for evaluation by clinicians was remission, measured using the MADRS. This decision was in line with a patient-centered approach and Swedish treatment guidelines that prioritize remission as the primary objective due to its lower relapse risk following ECT compared with a mere response (Sackeim et al., 2001). The choice of a maximum of 12 sessions was informed by evidence suggesting an average of 6 to 10 brief pulse ECT sessions may be necessary to achieve remission. On the other hand, the primary outcome in the ELEKT-D trial was response rate, defined as a 50% reduction in depression scores utilizing the Quick Inventory of Depressive Symptomatology–Self-Report, as directed by the funding agency "consistent with the effectiveness (and not efficacy) aim of this trial" as stated in the protocol Mathew et al., (2019).

Other Considerations

Both the KetECT and ELEKT-D trials assessed the comparative effectiveness of ketamine and ECT in treating depression. Whereas KetECT deemed ECT superior, ELEKT-D found the 2 treatments equally effective. Both studies adopted a non-inferiority design but differed in their assumptions. KetECT assumed a 60% ECT remission with a non-inferiority limit of 40%. In contrast, ELEKT-D set a 10% difference threshold and concluded ketamine's non-inferiority based on a presumed 50% ECT response rate. The 60% assumption in the KetECT study was grounded in data from a previous study (Kellner et al., 2010), and the Swedish national ECT registry, while it seems that the presumed 50% ECT response rate in ELEKT-D was based on historical data, likely derived from the participating sites. In KetECT, ECT achieved a 63% remission rate, contrasting sharply with the 22% of ELEKT-D. Such a low remission rate is a clear outlier, whether community based or not (Kirov et al., 2021; Espinoza and Kellner, 2022). In a letter to the editor, the authors of ELEKT-D cited a study to underscore their low ECT response (Prudic et al., 2004). However, it is important to note that the cited study highlights factors like prolonged episode duration, comorbid personality disorders, and schizoaffective disorder, which are linked to less favorable outcomes, underscoring the importance of optimal patient selection for ECT.

The term "community-based" in the ELEKT-D trial suggests that it captures real-world data quality. Consequently, it is essential not only to provide an accurate representation of real-world patients but also to ensure clinical outcomes are consistent with daily practice. For instance, 1 study site, the Cleveland Clinic, based on 51 participants, reported a 27.5% response rate to ECT, with a remission rate likely approaching zero. At least to us, they appear to belong to a group for whom ECT would not be recommended.

Conclusion

When considering ECT, it is imperative to use existing evidence and clinical experience to select patients with a high likelihood of achieving remission. This includes older individuals with depression and those with psychotic features, suicidality, shorter episode durations, episodic disease patterns, and family histories of severe mental illnesses.

In contrast, our current understanding of ketamine's use is limited, and the question of ketamine's superiority over alternatives like repetitive transcranial magnetic stimulation or tricyclic antidepressants remains unresolved for patients unresponsive to prior antidepressant treatments who are not suitable for ECT. This necessitates further research before any broader recommendation can be made. Nevertheless, in some cases, patients are referred for ECT without clear predictors of its effectiveness, making it challenging to find suitable alternatives. In such instances, ketamine may be considered as an option, including for high-risk patients with severe medical conditions or those who have not responded to ECT.

Furthermore, caution is crucial. In Sweden and comparable European countries, strict hospital-based regulation applies to the administration of intranasal esketamine and i.v. ketamine, primarily for safety. Conversely, in the United States, over 500 ketamine clinics advertise extensively for various mental disorders, chronic pain, and migraines. One concerning observation is that some patients request additional treatments despite limited relief and no discernible improvement in functioning. Consequently, future research should focus on functional improvements, not just on subjective experiences possibly influenced by drug cravings.

Our in-depth comparison of KetECT and ELEKT-D highlights substantial disparities in patient characteristics and treatment protocols as key contributors to different ECT outcomes. Although the exclusion of patients with psychotic depression in ELEKT-D influenced remission rates, it does not fully account for the substantial differences observed. Other contributing factors include variations in patient recruitment, episode duration, comorbid anxiety disorders, and hospitalization requirements. Additionally, the limited treatment sessions and use of UBP ECT in ELEKT-D may have contributed to suboptimal outcomes. The higher dropout rate in KetECT's ketamine arm may have masked its full therapeutic potential. Future research must address these biases and improve patient selection for ECT as the standard treatment.

Interest Statement

A.N., J.E., and P.M.R. received lecturer honoraria from Lundbeck.

J.E. is currently employed as a consultant by IQVIA in a clinical trial sponsored by Boehringer Ingelheim. C.K. receives fees from UpToDate for ECT topics, royalties from Cambridge University Press for *Handbook of ECT*, and honoraria from Northwell Health for teaching in an ECT course.

Data Availability

There are no new data associated with this article.

Author Contributions

Joakim Ekstrand (Writing—review and editing [Equal]), Akihiro Takamiya (Writing—review and editing [Equal]), Axel Nordenskjöld (Writing—review and editing [Supporting]), George Kirov (Writing—review and editing [Supporting]), Charles Kellner (Writing—review and editing [Supporting]), Pascal Sienaert (Writing—review and editing [Supporting]), and Pouya Movahed Rad (Writing—original draft [Lead], Writing—review and editing [Equal]).

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