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ORIGINAL PAPER

Clinically favourable effects of ketamine as an anaesthetic for electroconvulsive therapy: a retrospective study

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Abstract In a retrospective chart review, we examined the effects of ketamine, an N-methyl-d-aspartate (NMDA) receptor antagonist, as electroconvulsive therapy (ECT) anaesthetic in patients suffering from therapy-resistant depression. We included 42 patients who received ECT treatment with either ketamine ($n = 16$) or the barbiturate thiopental ($n = 26$). We analysed the number of sessions until completion of ECT treatment (used as a surrogate parameter for outcome), psychopathology as assessed by pre- and post-ECT Mini-Mental State Examination (MMSE) and Hamilton Rating Scale for Depression (HAM-D) scores as well as ECT and seizure parameters (stimulation dose, seizure duration and concordance, urapidil dosage for post-seizure blood pressure management). The ketamine group needed significantly fewer ECT sessions and had significantly lower HAM-D and higher MMSE scores afterwards. As expected, the ketamine group needed more urapidil for blood pressure control. Taking into account the limits inherent in a retrospective study design and the rather small sample size, our results nonetheless point towards synergistic effects of ECT and ketamine anaesthesia, less cognitive side effects and good tolerability of ketamine.

Keywords ECT · Ketamine · Depression · Cognition

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Introduction

With its analgesic and anaesthetic properties, ketamine has been established in general anaesthesia for decades and was listed as a core medication in the World Health Organization's "Essential Drugs List" [1]. Unlike other anaesthetics, ketamine elevates blood pressure, which allows for its use in emergency contexts but is unwanted in other situations [2]. However, its ability to provoke dissociative symptoms at subanaesthetic doses is notorious because they are often perceived as aversive experiences [3].

Recently, the N-methyl-d-aspartate (NMDA) receptor antagonist ketamine has come into the focus of psychiatric research because of its purportedly inherent antidepressive properties. The substance has been shown to be fast-acting and effective in unipolar and bipolar depression [4, 5] and to exert rapid beneficial effects on suicidal cognition [6]. Additionally, it has also been successfully used as an augmentation strategy in treatment-resistant depression [7, 8]. The use of ketamine as an anaesthetic agent for electroconvulsive therapy (ECT) in patients suffering from depression is of particular interest in this respect because ketamine might act synergistically with ECT and thereby favourably influence the course of illness.

Although ketamine has already been used in ECT anaesthesia for a long time [9, 10], first-choice substances are usually barbiturate agents such as thiopental and methohexitone, or alternatively etomidate or propofol. These are considered as relatively safe but bear the risk of antagonizing the intended seizure since they are all known as potent anticonvulsives [11]. This might influence the quality or "adequacy" of the induced seizure and, as a

consequence, potentially hamper the effectiveness of treatment. Some authors consider switching to ketamine as narcotic agent in ECT as an augmentation strategy after failing to adequately induce seizures with narcotics possessing anticonvulsant properties [12, 13].

The comparison of different anaesthetic agents in ECT has already received some attention in the literature: recently, Okamoto et al. published an open-label trial comparing ketamine and propofol anaesthesia during ECT in treatment-resistant depression [14]. Patients in the ketamine group improved earlier in Hamilton Depression Rating Scale (HAM-D) scores but at the end of the study (4 weeks and 8 ECT sessions), response did not differ between the two groups. Krystal and colleagues compared seizure duration, ictal EEG and cognitive effects of ketamine and methohexital anaesthesia in ECT and observed improved seizure duration for ketamine [15]. Rapid and dramatic improvements in formerly treatment-resistant depressive patients were observed after the use of ketamine anaesthesia in ECT [16, 17].

The chosen anaesthetic might impact on cognitive deficits, which often occur during or after ECT treatment and usually are of a temporary and reversible nature. Existing data point towards fewer side effects when ketamine is used as an ECT narcotic: in a small study, ketamine and etomidate were compared with respect to ECT-associated impairment of short-term memory function [18], and ketamine was found to have a more favourable influence on short-term memory. The decision for ketamine was associated with less impairment in short-time memory. Interestingly, there were four patients who received etomidate in their first ECT course but then relapsed during the period of the study. All of them received ketamine in their second ECT course and experienced less memory loss with ketamine than with etomidate. In the aforementioned study by Krystal and colleagues, the ketamine group showed faster post-treatment reorientation.

In this conceptual framework, we present a retrospective study comparing ketamine to the barbiturate thiopental as narcotic for ECT anaesthesia in patients suffering from major depression. Based on the published data, we hypothesized higher tolerability and effectiveness with ketamine, i.e. less cognitive decline after an ECT course and fewer ECT sessions necessary to reach remission. Another focus of our evaluation was the general safety of ketamine for this indication.

Methods

In this retrospective single-centre study (Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Mannheim, Germany), we reviewed the charts of all inpatients treated with ECT for depression during the period from 02/2007 to 05/2010. Inclusion criteria were current major depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and ECT anaesthesia with either s-ketamine or thiopental (we use the term "ketamine" instead of "s-ketamine" throughout the manuscript, but s-ketamine was administered in all cases as stated in Table 2). Exclusion criteria were prior ECT treatment less than 6 months ago and additional severe psychiatric disorders (e.g. alcohol dependency or severe personality disorder) as well as lack of a documented depression rating and cognitive status evaluation.

The data from all included patients were used in the safety analysis, for the analysis of effectiveness, we included only patients who had no switch of anaesthesia. Additionally, we recorded side effects likely to have been caused by ketamine of all patients receiving at least one dose of ketamine in a descriptive way in order to evaluate the safety profile of ketamine in ECT more precisely.

Seizure threshold in all patients was titrated during the first treatment, and energy was subsequently increased if patients did not respond clinically or showed insufficient seizures during the ECT course (i.e. motor response time <20 s and EEG seizure activity <30 s). ECT was performed with a Thymatron® IV device (Somatics, LLC. Lake Bluff, IL, USA).

For each seizure, the following parameters were recorded: placement of electrodes (unilateral or bilateral), stimulation dose, dose of either ketamine or thiopental used, duration of the seizure determined from EEG and motor activity recordings, seizure concordance and urapidil dosage for post-seizure blood pressure management.

For each patient, the following parameters were additionally collected: number of seizures until completion of ECT treatment (used as a surrogate parameter for the outcome by assuming that a greater effectiveness is represented by a smaller number of ECT sessions needed), Hamilton Depression Rating Scale (HAM-D, 21 items) and Mini-Mental State Examination (MMSE) scores before and after the course of ECT (with differences in MMSE as a surrogate parameter for the influence on cognition of the ECT treatment), placement of electrodes and quantity of antihypertensive medication required during ECT. The decision to finish ECT was made by the treating physician when the patient either was in remission or did not improve for 2 weeks even after appropriate increase in stimulus dose and/or change of electrode placement. These outcomes were based on clinical impression. The regime of electrode placement was also based on clinical judgement. In general, we started with unipolar placement and only switched to bilateral in the absence of a treatment response after appropriate increase in stimulus dose for 2 weeks.

Only in cases with severe suicidality or other life-threatening symptoms, treatment was initiated using a bilateral electrode placement.

Statistical analysis

The comparison between the two groups was performed with one- or two-sided t-tests, depending on appropriate prior hypotheses. For the evaluation of concordance and urapidil dosage, uncollapsed data entered statistical analysis, i.e. data were derived from all individual ECT sessions. For all other variables, collapsed data, i.e. mean data of each individual patient, were used. An ANOVA was used for testing the influence of independent variables such as psychotic symptoms or electrode placement on the differences of the two groups of anaesthesia. All statistics were performed using STATA® (StataCorp, Texas 77845, USA, version 11) at a significance level of 0.05.

Results

We included 16 patients from the ketamine group and 26 patients from the thiopental group in the analysis of effectiveness. Demographic data as shown in Table 1 revealed no significant between-group differences. Clinical outcome parameters are listed in Table 2. Patients in the ketamine group needed significantly fewer ECT sessions until course completion ($P = 0.015$, one sided, Fig. 1) and had significantly lower HAM-D scores ($P = 0.015$, one sided, Fig. 2), indicating a notable improvement in psychopathology. These outcome parameters were not significantly influenced by the presence of psychotic symptoms ($F = 0.46$, $P = 0.50$) or electrode placement ($F = 1.92$, $P = 0.17$). Overall, there was a significant difference between the changes of the MMSE scores taken at baseline and upon treatment completion in the ketamine group (+1.2, $N = 9$, SD: 1.3) compared to the thiopental group (−0.5, $N = 12$, SD: 2.1) ($P = 0.025$, one-sided, Fig. 3), which resulted partly from a slight decline of MMSE scores in the thiopental group—indicative of worsened cognitive functioning—as well as a slight cognitive improvement in the ketamine group.

For safety and seizure parameters, we analysed 176 seizures with ketamine anaesthesia and 321 seizures with thiopental anaesthesia. All parameters are listed in Table 3. As expected, the use of urapidil was higher in the ketamine group ($P = 0.030$, one-sided, collapsed data, Fig. 4). There were no group differences in the stimulation doses used and in the percentage of unilateral stimulation. The motor response time as well as the duration of EEG activity did not differ between groups. Concordance as a parameter of

Table 1 Demographic data of both groups

	Ketamine	Thiopental	*P* (two sided)
N	16	26	–
Sex (f/m)	0.81 (SD 0.40)	0.54 (SD 0.51)	NS (0.08)
Age in years	65.4 (SD 14.8)	63.8 (SD: 12.4)	NS (0.70)
HAM-D before ECT	29.1 ($N = 12$) (SD: 7.4)	30.0 ($N = 16$) (SD: 6.1)	NS (0.72)
MMST before ECT	25.9 ($N = 13$) (SD: 4.3)	26.3 ($N = 19$) (SD: 4.3)	NS (0.79)
Psychotic symptoms (in %)	69.0 (SD: 48)	54.0 (SD: 51)	NS (0.35)
First depressive episode (in %)	0.0 (SD: 0.0)	11.5 (SD: 33)	NS (0.17)
Diagnosis (unipolar in %)	87.5 (SD: 34)	91.7 (SD: 28)	NS (0.68)

Presented as means with standard deviation (SD)

NS not significant

Table 2 Clinical outcome data of both groups

	Ketamine	Thiopental	*P* (one sided)
N	16	26	–
Number of ECT needed	8.9 (SD 3.9)	11.9 (4.4)	0.015
HAM-D final	3.6 ($N = 5$) (SD 1.8)	9.7 ($N = 14$) (SD 5.6)	0.015
HAM-D difference	−22.2 ($N = 5$) (SD 4.76)	−21.8 ($N = 12$) (SD 10.5)	NS
MMSE difference	1.2 ($N = 9$) (SD 1.3)	−0.5 ($N = 12$) (SD 2.1)	0.025

Presented as means with standard deviation (SD)

NS not significant

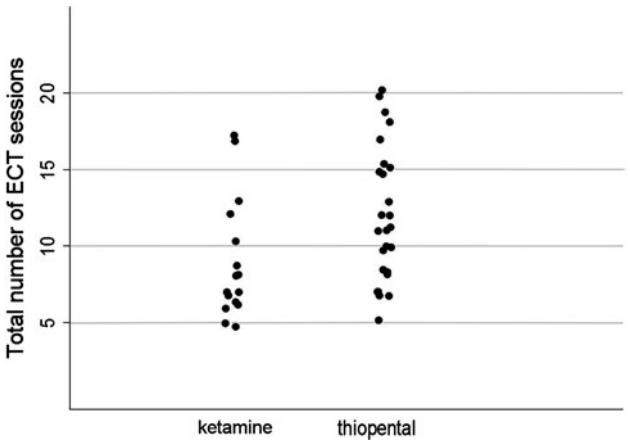

Fig. 1 Total number of ECT sessions of each individual patient in the ketamine (8.9, SD: 3.9) and thiopental (11.9, SD: 4.4) group ($P = 0.015$, one sided) point towards a better antidepressant effectiveness of ketamine

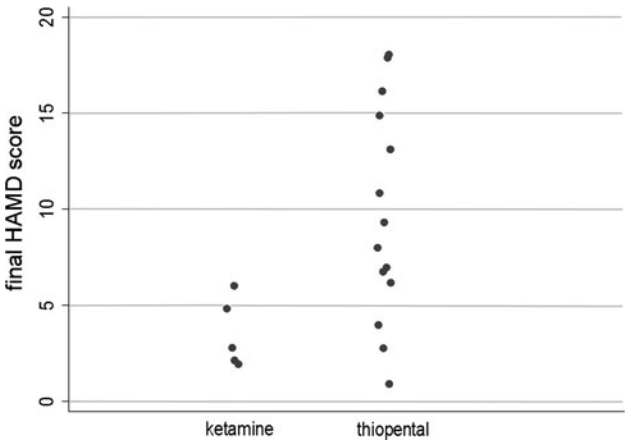

Fig. 2 Final HAM-D_{21} score after ECT of each individual patient in the ketamine (3.6, SD: 1.8, $N = 5$) and thiopental (9.7, SD: 5.6, $N = 14$) group ($P = 0.015$, one sided) indicate a better antidepressant response in the ketamine group

seizure quality was significantly higher in the ketamine group ($P = 0.045$, one-sided, Fig. 5).

The following patients were excluded from the efficacy analysis: one female patient was switched from thiopental to ketamine after the fourth session due to an allergic reaction to thiopental. She went in full remission after an additional set of 12 sessions with ketamine. Another female patient was transferred to our hospital after seven ECT sessions with different narcotics because seizure durations had been insufficient. We continued ECT with ketamine for five sessions; with sufficiently long seizures, a full remission was achieved. Another female patient developed feelings of derealization, which she attributed to ketamine and was switched to thiopental (for details, see section *Safety issues*). One male patient was initially treated with

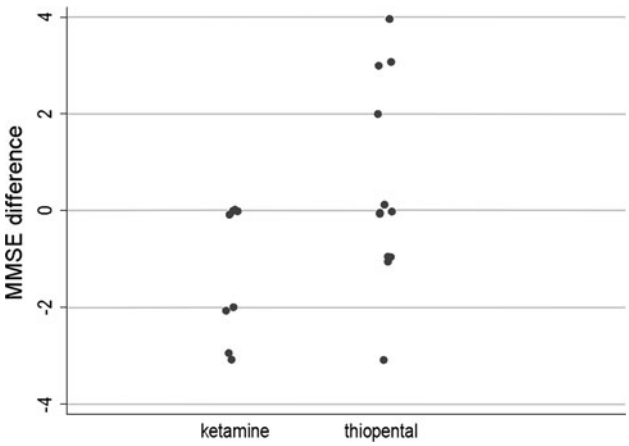

Fig. 3 Differences of the MMSE score before and after ECT of each individual patient in the ketamine (1.2, SD: 1.3, $N = 9$) and thiopental (−0.5, SD: 2.1, $N = 12$) group ($P = 0.025$, one sided) demonstrate a better cognitive outcome after ECT in the ketamine group

ECT and thiopental as anaesthetic agent but because of a pronounced decline in cognition, ketamine was used from session nine onwards. Finally, an elderly patient showed no response to ECT and ketamine anaesthesia after six sessions; a diagnosis of early-onset dementia and adjustment disorder was suspected, and the patient was later indeed diagnosed with Alzheimer's disease.

Safety issues

One female patient who had been suffering from derealization during previous major depression episodes—without receiving ketamine then—reported derealization and nightmares (without recall of their content) after the beginning of ECT with ketamine as narcotic. Feelings of derealization persisted after switching to thiopental and disappeared after remission from depression.

Two patients in the ketamine group had cardiac side effects: one patient developed intermittent atrial fibrillation and the other had a single salve of ventricular extrasystoles after the first ECT session while suffering from a pre-existing partial cardial decompensation and pre-existing intermittent ventricular extrasystoles. Both patients recovered fully from these singular incidents, and no further problems were reported during the following ECT sessions. We found one case of a cardiac side effect in a patient treated with thiopental with a longer lasting tachycardia (up to 160 bpm for several hours) after the initial session. More than mild post-ECT headache was observed in one case per group. In the thiopental group, postictal agitation occurred in four patients (15.4%) but was completely absent in the ketamine group.

Table 3 Seizure data of both groups

	Ketamine	Thiopental	*P* (one sided)
N total	176	321	–
S-ketamine (mg)	46.7 ($N = 173$) (SD 12.0)	–	–
Thiopental (mg)	–	236.0 ($N = 320$) (SD 64.3)	–
Stimulation dose (%)	36.9 ($N = 175$) (SD 28.6)	39.5 ($N = 320$) (SD 27.9)	NS
Unilateral stimulation (%)	73 ($N = 175$) (SD 45)	82 (SD 39)	NS (0.7139)
Seizure duration (motor) (s)	31.1 ($N = 175$) (SD 23.6)	29.8 ($N = 315$) (SD 14.1)	NS
Seizure duration (EEG) (s)	49.5 ($N = 174$) (SD 17.7)	50.2 ($N = 317$) (SD 22.8)	NS
Concordance	0.64 ($N = 174$) (SD 0.15)	0.61 ($N = 315$) (SD 0.21)	0.045
Urapidil (mg)	9.5 (SD 13.1)	6.9 (SD 10.5)	0.030

Presented as means with standard deviation (SD)

NS not significant

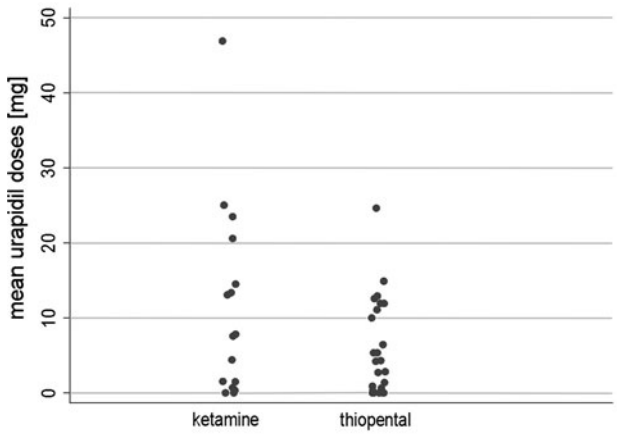

Fig. 4 Mean doses of urapidil (in milligrams) of each individual patient in the ketamine (9.5, SD: 13.1) and thiopental (6.9, SD: 10.5) group ($P = 0.030$, one sided). The difference reflects the activation of the sympathetic system by ketamine, thereby causing higher postictal blood pressure

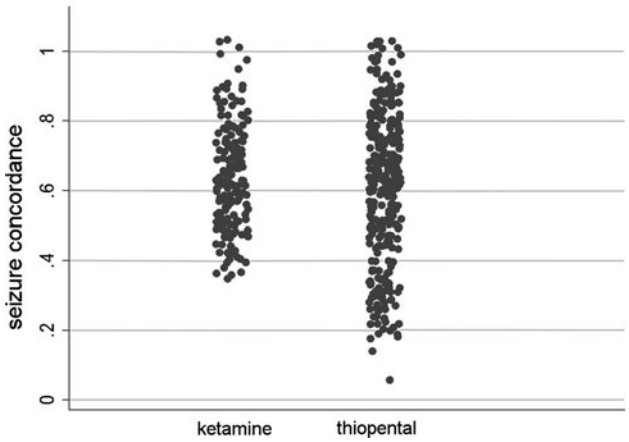

Fig. 5 Individual concordance (ratio of motor response time over EEG seizure duration) of each seizure in the ketamine (0.64, SD: 0.15, $N = 174$) and thiopental (0.61, SD: 0.21, $N = 315$) group ($P = 0.045$, one sided). Ketamine enhances the concordance and thus seizure quality

Discussion

In a retrospective study, we evaluated the safety and efficacy of ketamine as an ECT anaesthetic in patients suffering from treatment-resistant depression. We found that in the ketamine group, fewer ECT sessions than in the thiopental group were required until completion. The total number of sessions can be used as surrogate parameter representing the clinical response to the treatment [19]. Additionally, the severity of depression prior to ECT was similar in both groups; after the ECT course, HAM-D scores in the ketamine group were significantly lower, pointing towards the validity of our surrogate marker.

Our results demonstrate for the first time synergistic antidepressant effects of ECT and the ketamine anaesthesia. This finding corroborates reports about inherent antidepressant properties of ketamine [4, 5] and the anticonvulsive properties of thiopental, the latter of which are known to exert a relevant influence on seizure quality and treatment outcome [11, 19]. In our study, the ketamine group needed fewer sessions, so it is compelling to propose a rapid antidepressant effect of ketamine, as had already been claimed by Okamoto et al. in a comparison of ketamine and propofol [14]. However, we were able to show not only a faster but significantly better response at the end of treatment. It was not the scope of the study to detect and evaluate very rapid antidepressant responses (within hours or days) to ketamine [5, 16, 17]. In line with Krystal [15], seizure parameters in the ketamine group were overall more favourable, e.g. with respect to seizure duration.

Transient and reversible—but nonetheless sometimes clinically relevant—cognitive impairment is another important issue in ECT practical application and research. Patients from the ketamine group did not display any

decline in MMSE scores. A generally better cognitive outcome with ketamine anaesthesia was also observed in a study comparing ketamine with barbiturates [15] in that patients of the ketamine group had a shorter post-seizure reorientation time than those of the barbiturate group. Shorter reorientation time is known to be associated with less cognitive deficits during and after ECT [20].

Considering the general safety of ketamine, potential cardiac side effects deserve attention. Ketamine causes a systemic release of catecholamines and inhibition of norepinephrine re-uptake at peripheral nerves and non-neuronal tissues such as the myocardium [21]. Although desirable in emergency context, such an activation of the sympathetic system is unwanted in ECT anaesthesia or management of acute or chronic pain. In our study, there were two cardiovascular events in the ketamine group, and higher dosages of antihypertensive medication immediately after the seizures were required. For example, in chronic pain management, where ketamine could be used as low-dose infusion or taken orally over several months, effects on the cardiovascular system seem moderate and well tolerated [22, 23]. Oral ketamine was given as add-on to antidepressants in patients with major depression for 2 weeks in a case series and was very well tolerated without cardiovascular side effects [8]. However, the cardiovascular events in our study should be considered as a warning that caution is always required in patients with cardiovascular disease (e.g. patients with ischaemic heart disease or hypertension).

Even though our results have relevant and meaningful ramifications for the treatment of severe cases of major depressive disorder with ECT, there are several disadvantages. Our study is retrospective in design, and sample size is modest. Thus, quality of evidence is restricted, and the future should see randomized, well-controlled studies investigating a larger number of patients. In addition, a retrospective study does not guarantee a complete data set, and missing data reduce the scope of some of our analyses. Considering the number of ECT sessions required until full remission, i.e. HAM-D score of 7 or below, there were not enough complete data sets in both groups to allow for a meaningful statistical analysis. Although it was not statistically significant, a slightly unbalanced distribution of patients suffering from psychotic symptoms or unbalanced distribution of unilateral and bilateral treatments may have influenced the outcome. Bilateral stimulation leads to a more rapid response or remission of major depression, but is generally associated with a higher rate of cognitive side effects [24]. However, this pattern was not observed in our ketamine group. Finally, the decision to end a patient's ECT treatment course was based solely on the clinical impression and not defined in terms of a specific reduction in HAM-D scores. Another limitation is that the relatively "rough" MMSE is not the ideal instrument to evaluate cognitive function particularly since many variables can confound test performance, e.g. depression and low socioeconomic levels [25, 26].

Several explanations can be invoked to account for our observations. Recently, Li et al. proposed that the rapid antidepressant action is modulated by the mammalian target of rapamycin (mTOR) pathway [27], and this may be a contributing factor for the smaller number of ECT sessions required by patients in the ketamine group. Additional factors already associated with antidepressant action of ketamine are increased activity in the anterior cingulate cortex [28], AMPA [29] and sigma [30] receptors and neurotrophic substances (vascular endothelial growth factor und brain-derived neurotrophic factor) [31, 32].

Cognitive side effects might be due to seizure activity elicited during ECT, which in turn may give rise to reversible excitotoxic damage. Excitotoxic neuronal damage is mediated by glutamate acting on NMDA receptors [33], and thus, ketamine as an NMDA antagonist could act as a neuroprotector. Other clinically used NMDA antagonists such as memantine have extensively been demonstrated to act protectively in the treatment of dementia [34]. Second, several studies have shown that repeated electroconvulsive shocks (ECS) in rats lead to mossy fibre sprouting in the hippocampus. While the functional significance of this change is still unclear, its time course corresponds to that of ECT-induced memory impairment. Interestingly, ketamine administration during ECS blocks the development of mossy fibre sprouting [35, 36]. Another mechanism to preserve memory function could be the blocking capabilities of excessive long-term potentiation (LTP), which is necessary for memory coding, by ketamine. ECS in rats leads to LTP-like changes, potentially consuming all resources for further LTP, which facilitates memory impairment [37]. It has been demonstrated that an NMDA antagonist blocking LTP induction during ECS also improved memory outcomes [38].

Treatment resistance in major depression disorder continues to pose a challenge for clinicians. This is why this interesting and relevant issue deserves further investigation with prospective, high-quality studies seeking to investigate the interaction between ECT and ketamine. On the basis of our—as yet preliminary—findings, ketamine seems to be an appropriate alternative to barbiturate anaesthesia when cognitive decline, insufficient seizure induction or clinical non-response are limiting factors in ECT.

Conflict of interest The authors declare that they have no conflict of interest.

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