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The concentration of MMP-9 and the effects of intravenous anaesthetics on the efficacy of electroconvulsive therapy in patients with drug-resistant depression

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Abstract

Introduction: This study attempts to assess the concentration of intracellular matrix metalloproteinase (MMP-9) before and after the treatment of depressive episodes with ECT therapy and also to correlate the concentration of this enzyme with the use of commonly used general anaesthetics.

Materials and methods: The study group comprised of 37 patients hospitalized in the Department of Adult Psychiatry in Poznan, with a diagnosis of episodes of drug-resistant depression during the course of bipolar and unipolar affective disorders, and who were being treated using electroconvulsive therapy. For the purpose of inducing anaesthesia during the procedure propofol was used in 10 cases, thiopental in 9 cases. Propofol was alternated with ketamine in a further 10 cases and thiopental was alternated with ketamine in another 9 cases. In order to assess the intensity of depression symptoms, the 17 point Hamilton depression scale was used, immediately before commencing ECT therapy, and one day after its completion. The serum concentration of MMP-9 was determined before and after the series of ECT treatments. In order to assess the serum concentration of MMP-9, an ELISA immunoenzymatic method was applied.

Results: In this study, a significant reduction of MMP-9 concentration was noted after therapy, relative to the starting concentration, in the serum of patients suffering from depressive episodes resulting from either unipolar or bipolar affective disorders. These results correlated with improved psychiatric state, as assessed by the Hamilton scale. A significantly lower MMP-9 concentration was noted in the serum of patients given alternating thiopental and ketamine anaesthesia.

Conclusions: This study suggests the importance of the enzyme as a biological marker for the effective treatment of depression. Furthermore, the choice of general anaesthetic applied during ECT also plays a role.

Keywords: electroconvulsive therapy, ketamine, thiopental, propofol, matrix metalloproteinase - 9

Streszczenie

Wstęp: W pracy podjęto się oceny stężenia metaloproteinazy macierzy wewnątrzkomórkowej(MMP-9) przed i po leczeniu epizodów depresji za pomocą terapii zabiegowej EW , a także korelacji stężenia tego enzymu z zastosowanym do znieczulenia ogólnego rodzajem leku anestezjologicznego.

Materiał i metoda: Badaniem objęto 37 osób hospitalizowanych w Klinice Psychiatrii Dorosłych w Poznaniu z rozpoznaniem epizodu depresji lekoopornej , poddanych leczeniu elektrowstrząsowemu. Parametry prądu dobierano indywidualnie, zgodnie z oceną psychiatry. Do indukcji znieczulenia ogólnego podczas zabiegów stosowano propofol (10), tiopental (9), propofol zamienne z ketaminą w co drugim zabiegu(10) oraz tiopental zamiennie z ketamina także w co drugim zabiegu(9). Do oceny nasilenia objawów depresji u chorych bezpośrednio przed rozpoczęciem terapii EW i po dobie od jej zakończenia posłużono się skalą depresji Hamiltona (Hamilton Depression Rating Scale - HDRS). Oznaczenie stężenia MMP-9 w surowicy wykonano przed podjęciem terapii zabiegowej oraz po zakończeniu serii EW. Do oceny stężenia MMP-9 w surowicy krwi wykorzystano metodę immunoenzymatyczną ELISA.

Dyskusja: W pracy wykazano istotnie niższe stężenia MMP-9 po zakończeniu leczenia zabiegowego w porównaniu do stężeń wyjściowych w surowicy krwi osób badanych. Wyniki te korelowały z poprawą stanu psychicznego ocenianego za pomocą HDRS. Nie wykazano natomiast asocjacji stężeń MMP-9 w surowicy krwi z wiekiem, płcią, rozpoznaniem chorobowym i czasem trwania choroby. Istotnie niższe statystycznie stężenie MMP-9 zaobserwowano tylko u pacjentów znieczulanych tiopentalem i ketaminą w co drugim zabiegu.

Wnioski: Zmniejszenie się stężeń MMP-9 w surowicy krwi u pacjentów po zakończonej terapii EW korelujące z poprawą kliniczną u tych chorych może sugerować znaczenie tych enzymów jako markerów biologicznych skutecznego leczenia depresji metodą zabiegową.

Słowa kluczowe: terapia elektrowstrząsowa, ketamina, tiopental, propofol, metaloproteinaza macierzy zewnątrzkomórkowej

Introduction

The search for biomarkers correlating with the effective treatment of affective disorders is a serious challenge in psychiatry. In recent years, an increasing degree of interest has been shown in matrix metalloproteinases (MMP) as enzymes with potential roles in the pathogenesis of psychiatric diseases. MMPs are proteolytic enzymes belonging to the endopeptidase group, which have various roles in all the tissues of the body. They take part in both physiological processes, such as embryogenesis, angiogenesis or tissue regeneration, and in pathological processes such as cancer progression, inflammation [1,2] or neurodegeneration [3].

One of the better understood metalloproteinases of the central nervous system is MMP-9, produced both by the glial cells, and by the neurones [4,5]. Amongst its roles, MMP-9 takes part in long-term potentiation (LTP), a process known to be key to memory, learning, and neural plasticity [6]. NMDA receptors are involved with LTP and their activation is related to increased uptake of calcium by, and a cascade of changes within the neurones [7,8,9].

Extensive data from the literature in recent years led to the suspicion of a potential role of MMP-9 in the pathogenesis of psychiatric illnesses such as affective disorders or schizophrenia because the clinical manifestations of these diseases are reflected in irregularities within the neural circuits and synaptic connections, as well as in anatomopathological changes. In vitro studies of rat hippocampal cells showed that MMP-9 has morphological effects on the dendrites, dendritic spines, and on the number of AMPA and NMDA glutaminergic receptors in the synapses, which suggests that MMP-9 influences glutaminergic signalling [4,10]. Additionally, several studies have shown a relationship between the 20q11-13 region of chromosome 20, where the MMP-9 gene is located, and psychiatric illnesses such as bipolar affective disorder and schizophrenia [11,12].

One of the earliest findings on the subject of MMP-9 in depression was published by Garvin et al. in 2009. Their work involved the testing of 402 randomly selected people, aged between 45 and 59 years, and with symptoms of depression as measured by the CES-D questionnaire (Centre for Epidemiologic Studies Depression Scale). The study revealed an independent relationship between raised MMP-9 concentration in the blood serum and the results of the CES-D questionnaire [13]. In 2010, Domenici et al. demonstrated raised MMP-9 concentrations in 245 patients diagnosed with episodes of depression in unipolar affective disorder (at least 2 documented episodes of major depression) compared to a control group. In a study of the Japanese population in 2012, a positive correlation was found between the concentration of MMP-9 and the severity of depression symptoms in 69 of the subjects that matched the criteria for an episode of depression according to DSM-IV [14]. In 2013, Polish researchers in Poznan showed that MMP-9 concentration is raised in young people (<45 years) with a diagnosis of bipolar affective disorder, either during an episode of depression or during remission, in comparison to a control group. [15] The majority of studies carried out so far have, however, related to the pharmacological treatment of the patients. It was not until the work of Chiyo Shibasaki was published in 2016 that the possible impact of MMP levels on the effectiveness of depression treatment by electroconvulsive therapy (ECT), being the most effective approach in drug-resistant disease, was explored. The concentration of MMPs 9 and 2 was assessed before and after ECT treatment and the results were compared with the enzyme levels in a healthy control group. A statistically significant reduction in MMP levels after treatment, was associated with reduced risk of relapse. Among patients who did not experience a relapse of depression symptoms after treatment, a significantly lower MMP concentration was determined in comparison to the level prior to treatment. Patients who suffered a relapse of depression symptoms showed no significant difference in MMP levels before or after treatment (2016, 2017). [16,17]

Electrotherapy in psychiatric disorders is used when it is necessary to bring about a rapid therapeutic effect because of the worsening symptoms of mental illness, a serious somatic state, or if pharmacotherapy is ineffective or contraindicated. Despite extensive documentation in

the literature regarding its efficacy, it is only recently that the underlying biological mechanisms of electrotherapy have begun to be explored, with a view to documenting and explaining the phenomena and its functioning.

Among the mechanisms directly resulting from electroconvulsive treatment there are: increased seizure threshold, inhibition of kindling of the limbic system, strengthening of long-term potentiation (LTP), improved blood-flow to the brain, increased permeability of the blood-brain barrier, increased secretion of neuropeptides and hypothalamic hormones, and normalization of the hypothalamic-pituitary-adrenal axis (HPA). Therapeutic effects are also brought about by the indirect and remote outcomes of ECT. Among these there are the significant influence on noradrenaline (synthesis and metabolism) and on serotonin (synthesis and metabolism), and on the adrenergic and noradrenergic systems (changes to receptor sensitivity), on calcium metabolism and signal transduction in cells, protein synthesis in brain cells, and on nonspecific functioning of the immune system. The molecular mechanism behind ECT has not been fully explained (Permoda-Osip "Depression in the young") which is why the search for biological markers, whose presence in varying concentrations in the blood of patients and which correlate with the effectiveness of treatment, and with remission time, continues to be of value. The choice of general anaesthetic used during electrotherapy is also of some importance. An ideal intravenous anaesthetic would be characterized by the rapid onset of its effect and by the quick but gentle recovery of the patient. The rapid return of consciousness is important, together with minimal side effects and interactions with other drugs.

In the Clinic of Psychiatry in Poznan, the drug originally used as an anaesthetic during ECT was thiopental, a derivative of barbituric acid which, owing to its high solubility in lipids, has a rapid depressive effect on the CNS. After intravenous administration, it begins to work after only 30 to 40 seconds and lasts for up to 30 minutes. The anaesthetic effect is accompanied by depressive effects on the circulatory and respiratory systems. It also has antiseizure properties. To induce a general anaesthetic effect, it is usually used in doses of 1.5 to 5mg/kg. Since 2016, Propofol has also been used as a general anaesthetic for ECT in Poznan and, owing to its parameters, has now fully replaced thiopental. [18]

Propofol is an organic compound of the phenol group which is ideally soluble in lipids and has depressive effects on the respiratory and circulatory systems, though this effect is minimal when using the dosages appropriate to ECT. The patient wakes after around 5 minutes and is sometimes affected by slight disturbances to consciousness [19]. Many workers have pointed out the neuroprotective properties of propofol which arise from the inhibition of glucose metabolism in nerve cells, decreased electrical activity of the brain, reduced oxygen consumption by the neurones and decreased perfusion of the brain [20,21]. Propofol shows both structural and functional similarities to vitamin E, and has similar antioxidant properties [22,23]. From the literature on this subject it is worth drawing attention to a few studies which compare the mode of action of thiopental and propofol during ECT procedures. In 2007, Ingram et al. compared the clinical effects, cognitive functions, and duration of seizures,. Thiopental, caused greater and longer lasting seizures and a worse clinical effect, measured by the HDRS, whilst no differences in cognitive functions were determined amongst groups [24]. In their 2009 study, Bauer showed no difference in the clinical effects among patients, despite using higher electrical charges to induce seizures in patients given propofol as an anaesthetic [25]. In 2012 Kumar et al., and in 2013 Purtuloglu demonstrated the greater efficacy of propofol during ECT [26,27]. In 2016 Jarineshin also compared the efficacy of thiopental and propofol in patients treated with ECT for periods of depression, schizophrenia, and OCD [28]. The duration of seizures was shorter when using propofol, though no difference in the energy used to induce seizures was reported. Propofol also resulted in smaller haemodynamic changes, which may be of significance in patients with cardio-vascular diseases. Inspired by research into the antidepressant effects of ketamine, the Poznan centre also undertook research using ketamine as a general anaesthetic during ECT procedures. Ketamine is a chemical derivative of phencyclidine that causes so-called dissociation anaesthesia and analgesia. After intravenous administration, loss of consciousness occurs after around 30 to 40 seconds, and its return after 15 to 60 minutes. Ketamine is an anaesthetic which shows no depressive effects on the respiratory system, but which has a stimulatory effect on circulation through increased activity of the heart and increased arterial pressure, resulting in greater oxygen requirements of the cardiac muscle. Ketamine affects many receptors, including high-affinity non-competitive antagonist of NMDA (N-methyl-D-aspartate) receptors. When ketamine blocks NMDA receptors on GABA interneurons of the prefrontal cortex, it results in inhibition of glutamate release, which in turn activates postsynaptic AMPA receptors, resulting in fast stimulatory transmission. AMPA stimulation initially triggers the ERK and AKT signal transduction cascade, finally activating mTOR, resulting in synthesis of synaptic proteins and increasing the density of dendritic spines [29]. Various studies have appeared in the literature comparing the clinical effects, neuroprotective properties, and the influence on cognitive functions that different anaesthetics have during ECT procedures. In 2012, Loo

et al. could not confirm earlier suggestions that ketamine has a protective effect against cognitive deficits among patients, although patients anaesthetized in this way were found to recover from depression symptoms faster – within the first week after treatment [30]. Similar results were published by Yoosefi in 2014. In that study, it was observed that, among patients anaesthetized by ketamine, the symptoms of depression were reduced faster, after longer lasting seizures (according to EEG) and with improved results in MMSE. Additionally, ketamine anaesthesia was well tolerated [31] In the Clinic of Adult Psychiatry in Poznan, a study was carried out to determine the effects of ketamine on the efficacy of ECT and on cognitive function. A group of 45 patients with diagnoses of drug-resistant depression was divided into three groups anaesthetized with thiopental alone, thiopental and ketamine during the second and third treatments, or with thiopental alternated with ketamine for the second, fourth, sixth, eighth and tenth treatments. The results of verbal memory tests were worse for groups anaesthetized through ketamine than among patients where thiopental had been used alone [32].

Several studies also compared the effectiveness and tolerability of ketamine and propofol as anaesthetics during ECT procedures. In Wang's study, patients were anesthetized with propofol 1.5mg / kg, ketamine 0.8mg / kg, and both anaesthetics simultaneously. Patients anaesthetized with ketamine or with both ketamine and propofol simultaneously obtained earlier and greater reduction of depressive symptoms than those in the group treated with propofol alone. In the summary of the study it was suggested that the combination of both anaesthetics could be a first-line method in the induction of anaesthesia for ECT [33]. In a double-blind trial with 40 participants suffering from drug resistant depression, Fernie was not able to confirm the antidepressant effects of ketamine or its possible neuroprotective effects on cognitive functions [34].

Methods

The study group comprised of 37 patients hospitalized in the Clinic of Adult Psychiatry in Poznan, with diagnosed episodes of depression resulting from unipolar or bipolar affective disorder and treated by electroconvulsive therapy. The basic qualifying criteria for treatment were a lack of response to pharmacological treatment and a detailed assessment of general health (including consultations with a cardiologist and an anaesthetist). Signed consent for electroconvulsive therapy was obtained from all patients. Electrical parameters were chosen individually, based on the observations of the psychiatrist running the treatment session. In order to monitor the effects of treatment, the HDRS was used to assess the state of the patients immediately before beginning ECT, and again after its completion. Serum MMP-9 concentration was tested twice; once before the treatment, and again a day after completing the treatment series. Approximately 5ml of fasting blood was drawn into clotting tubes from the basilic vein. After incubation, the samples were centrifuged to obtain the serum which was stored in appropriate tubes in a freezer at -70°C. For the assessment of MMP-9 concentration in the serum, an ELISA immunoenzymatic method was used.

Electroconvulsive treatments were carried out three times a week, using a Thymatron System IV instrument. In each case, patients were treated bilaterally, using the same arrangement of electrodes to cover the fronto-temporal areas while brain activity was monitored by electroencephalogram (EEG). The electrical charge selected varied between 100 and 300 mC, the parameters being selected by the psychiatrist performing the procedure. For 10 patients, the general anaesthetic applied was propofol (dose 100-150mg), in 9 patients' thiopental was used. In a further 10 patients, anaesthesia was by thiopental and ketamine, and in 9 cases propofol and ketamine. For statistical calculations the program Statistica 10 was used.

Results

The study included 37 people (27 coded 1 for sex and 10 coded 2 for sex) aged between 28 and 68 years. The average age of the study group was 51.1±10.0 years. The average age of sex-code 1 patients was 51.3±10.4 years and for sex-code 2 patients the average age was 50.6±9.4 years. The difference was not statistically significant ($p>0.05$). Half the patients were aged less than 50 years and half were aged over 50.

Qualitative variables were described in terms of abundance (n) and frequency (%). Measurable variables were described using basic parameters including the arithmetic mean, standard deviation, median, and both minimum and maximum values.

When testing for the significance of differences in measurable variables between two groups, the parametric Student's t-test was used. Where normal distribution conditions could not be met, nonparametric tests were used:

- the Wilcoxon signed rank test – to test the significance of differences between two dependant variables (at the beginning and end points),
- the Mann-Whitney U test – to test the significance of differences between two groups,
- the Kruskal-Wallis test – to test for the significance of differences between at least three groups.

Correlations between measurable variables was tested using Spearman's rank coefficient correlation.

In order to test for relationships between qualitative variables, owing to the low numbers expected, the chi-square test (maximal reliability) was used.

Statistical significance was accepted at $p<0.05$. All calculations were carried out using the statistics package, Statistica 10 PL.

Table 1. Descriptive statistics – age of studied patients according to student's t-test

Sex	n	Age [years]					Student's t-test	
		Average	Std. deviation	Median	Min.	Max.	t	p
1	27	51.3	10.4	50.00	28	68	018	0.8618
2	10	50.6	9.4	50.5	33	63		
Total	37	51.1	10.0	50.0	28	68		

Table 2. Descriptive statistics – duration of sickness and episodes among the tested patients

Variable	n	Average	Std. deviation	Median	Min.	Max.
Duration of illness (years)	37	14.8	10.2	13.0	0	42
Duration of episodes (months)	37	6.9	7.1	4.0	1	34

Patients were ill for an average period of 14.8±10.2 years (from 0 to 42 years), and the average duration of episodes was 6.9±7.1 months (from 1 to 34 months).

1. Comparison of MMP-9 concentrations at two points in time – starting (Point 0) and ending (Point E).

Table 3. Descriptive statistics – Concentration of MMP-9 among tested patients at two points in time and the results of the Wilcoxon Signed Rank test.

Measurement	n	ng/ml					Wilcoxon Signed Rank test	
		Average	Std. deviation	Median	Min.	Max.	Z	p
Point 0	37	454.1	224.7	388.0	148	991	2.20	0.0282*
Point E	37	360.1	154.3	333.0	112	698		

** - statistically significant (p<0.05)*

Metalloproteinase concentration fell in 25 patients (19 of sex-code 1 and 6 of sex-code 2), whilst an increase in concentration was observed in 12 people (8 of sex-code 1 and 4 of sex-code 2). Average concentration levels were higher at the beginning of the study period than at the end. This difference was statistically significant (p=0.0282).

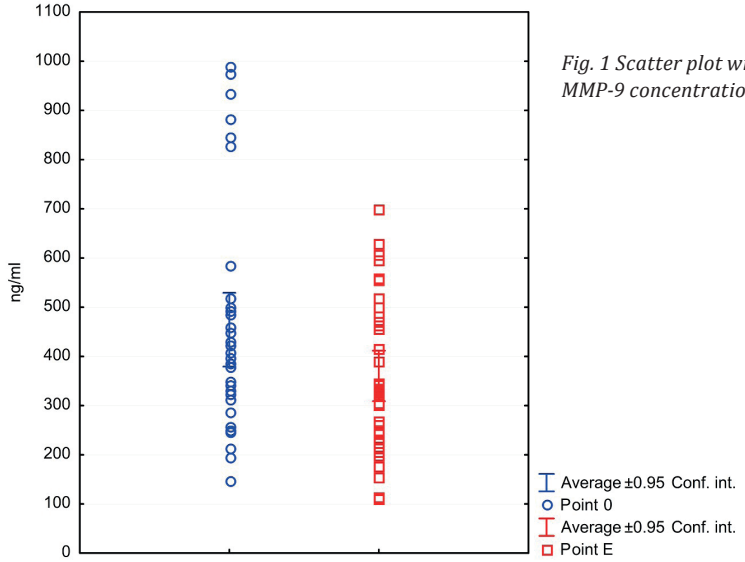

Fig. 1 Scatter plot with 95% confidence interval showing the average MMP-9 concentration among patients at two points in time

Table 4. Descriptive statistics – MMP-9 concentration in men and women at two points in time and the results of a Wilcoxon Signed Rank test

Sex	Measurement	n	ng/ml					Wilcoxon Signed Rank Test	
			Average	Std. deviation	Median	Min.	Max.	T/Z	p
1	Point 0	27	484.9	251.1	397.0	148	991	2.20	0.0306*
	Point E	27	357.5	158.5	333.0	112	629		
2	Point 0	10	371.1	96.5	384.0	214	499	22.0	0.5751
	Point E	10	367.1	150.1	320.0	200	698		

** - statistically significant (p<0.05)*

In both men and women, the average concentration of metalloproteinase was higher at the beginning of the treatment than at the end. However, the difference was only statistically significant for sex-code 1 (p=0.0306).

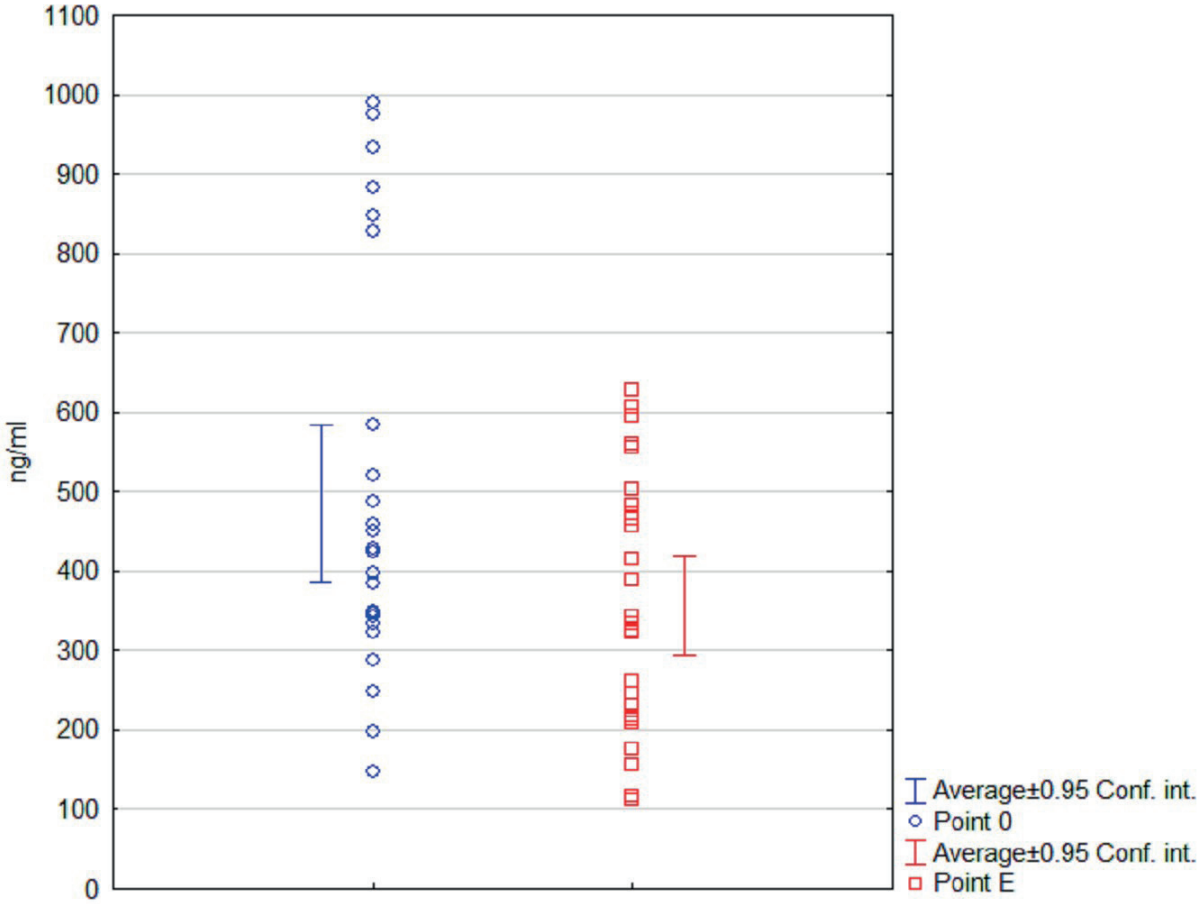

Fig. 2 Scatter plot with 95% confidence interval showing the average concentration of MMP-9 among sex-code 1 patients at two points in time.

Table 5. Descriptive statistics – Concentration of MMP-9 in patients treated using different anaesthetics at two points in time and the results of a Wilcoxon Signed Rank test

Anaesthetic	Measurement	n	ng/ml					Wilcoxon Signed Rank test	
			Average	Std. deviation	Median	Min.	Max.	T	p
Propofol	Point 0	17	392.1	171.0	349.0	214	991	52.0	0.2461
	Point E	17	339.8	149.5	305.0	112	698		
propofol +ketamine	Point 0	20	506.9	254.2	449.5	148	974	53.0	0.0522
	Point E	20	377.4	159.9	361.0	116	629		

The average concentration of MMP-9 was higher at the beginning of treatment than at the end, for both propofol and propofol with ketamine groups. The difference was not, however, statistically significant (p>0.05).

In the group of patients where propofol and ketamine were used as anaesthetic, the probability level was p=0.0522, very close to the limit of statistical significance.

Table 6. Descriptive statistics - Concentration of MMP-9 in patients treated using different anaesthetics at two points in time and the results of a Wilcoxon Signed Rank test

Anaesthetic	Measurement	n	ng/ml					Wilcoxon Signed Rank test	
			Average	Std. deviation	Median	Min.	Max.	T	p
propofol	Point 0	9	384.1	62.4	380.0	312	499	9.0	0.1097
	Point E	9	332.8	126.6	335.0	208	595		
pro+ket	Point 0	10	462.5	251.5	423.5	148	934	27.0	0.9594
	Point E	10	443.4	165.0	487.0	116	629		
thiopental	Point 0	8	401.0	249.5	340.5	214	991	18.0	1.0000
	Point E	8	347.6	180.7	283.5	112	698		
thio+ket	Point 0	10	551.3	262.2	484.5	197	974	2.0	0.0093*
	Point E	10	311.3	130.7	311.5	155	555		

** - statistically significant (p<0.05)*

The average concentration of MMP-9 was higher at the beginning of the treatment than at the end. The difference was, however, statistically significant only for the group of patients where thiopental and ketamine were used together (p=0.0093).

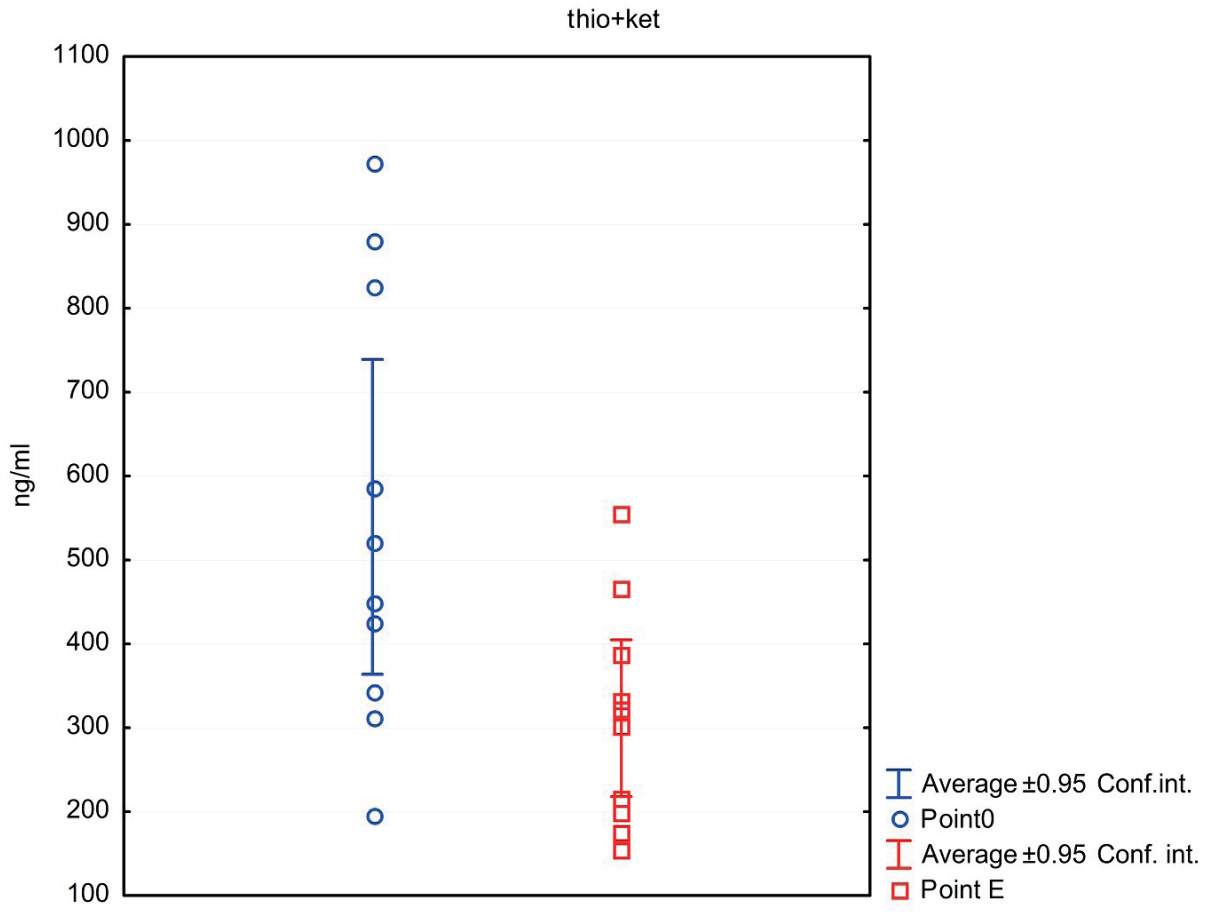

Fig. 3 Scatter plot with 95% confidence interval showing average concentrations of MMP-9 in patients where thiopental and ketamine were used as an anaesthetic at two points in time

Table 7. Descriptive statistics – Concentration of MMP-9 in patients with differing diagnosis at two points in time and the results of a Wilcoxon Signed Rank test

Diagnosis	Measurement	n	ng/ml					Wilcoxon Signed Rank test	
			Average	Std. deviation	Median	Min.	Max.	Z/T	p
1	Point 0	27	437.1	210.6	385.0	197	974	1.44	0.1494
	Point E	27	365.3	167.6	333.0	112	698		
2	Point 0	10	500.1	265.5	436.5	148	991	11.0	0.0926
	Point E	10	346.0	117.4	323.5	200	519		

The concentration of metalloproteinase was higher at the beginning than at the end of the treatment in patients with different diagnoses. The difference was not, however, statistically significant (p>0.05).

Table 8. Descriptive statistics – Concentration of MMP-9 in patients with differing intensities of symptoms according to the HDRS at two points in time and the results of a Wilcoxon Signed Rank test

Intensity of symptoms according to the Hamilton scale	Measurement	n	ng/ml					Wilcoxon Signed Rank test	
			Average	Std. deviation	Median	Min.	Max.	Z/T	p
2	Point 0	25	443.8	217.5	385.0	148	991	1.68	0.0926
	Point E	25	353.2	134.8	326.0	116	607		
3	Point 0	12	475.8	247.4	418.5	197	974	23.0	0.2094
	Point E	12	374.3	194.8	338.0	112	698		

Amongst patients with different intensity of depression symptoms according to the HDRS, the concentration of MMP-9 was higher at the beginning of the treatment than at the end. This difference was not, however, statistically significant (p>0.05).

Table 9. Descriptive statistics – Concentration of MMP-9 in patients at different stages of remission according to the HDRS at two points in time and the results of a Wilcoxon Signed Rank test.

Remission according to the Hamilton scale	Measurement	n	ng/ml					Wilcoxon Signed Rank test	
			Average	Std. deviation	Median	Min.	Max.	Z/T	p
1	Point 0	21	436.0	189.8	385.0	248	991	2.03	0.0420*
	Point E	21	345.3	136.4	326.0	116	595		
2	Point 0	16	477.9	268.4	408.5	148	974	49.0	0.3259
	Point E	16	379.5	177.8	339.5	112	698		

** - statistically significant (p<0.05)*

Among patients with different degrees of remission according to the HDRS, the average concentration of metalloproteinase was higher at the start of the treatment than at the end. The difference was not, however, statistically significant (p>0.05). Statistical significance was only observed for patients where the remission code was 1 (p=0.0420).

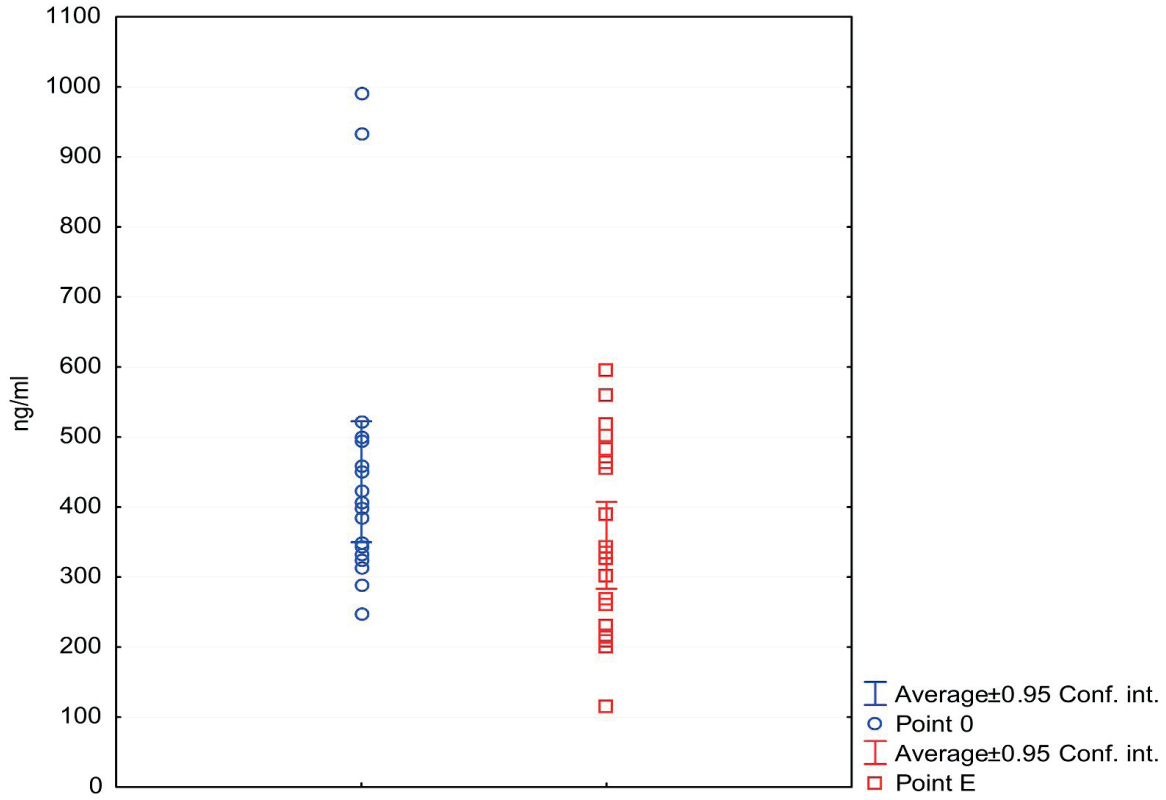

Fig. 4 Scatter plot with 95% confidence interval showing the average concentration of MMP-9 in patients with remission code 1 at two points in time

The following correlations were determined for differences in the concentration of MMP-9 between the start and end points.

Table 10. The results of the Spearman rank correlation coefficients between age, duration of the disease, duration of episodes, differences in the severity of depression symptoms according to the HDRS, and differences in the concentration of MMP-9 between the initial and end point tests

Pair of variables	n	R	t(n-2)	p
Age & Δ ng/ml	37	-0.033	-0.20	0.8452
Length of disease (years) & Δ ng/ml	37	0.284	1.75	0.0889
Duration of episodes (months) & Δ ng/ml	37	0.160	0.96	0.3436
Δ Hamilton & Δ ng/ml	37	0.284	1.75	0.0890

No statistically significant correlations were found between age, duration of disease or episodes, severity of symptoms according to the HDRS, and the concentration of metalloproteinase (p>0.05).

2. Comparison of the severity of depression according to the HDRS at two points in time – start time (Point 0) and end time (Point E).

Table 11. Descriptive statistics – Severity of depression amongst the tested patients, according to the HDRS, at two points in time and the results of a Wilcoxon Signed Rank test.

Measurement	n	Hamilton depression scale					Wilcoxon Signed Rank test	
		Average	Std. deviation	Median	Min.	Max.	Z	p
Point 0	37	27.4	5.4	26.0	18	38	5.30	0.0000*
Point E	37	7.3	6.0	5.0	0	25		

** - statistically significant (p<0.05)*

In all patients there was a decrease in the severity of symptoms according to the HDRS. The average depression score was higher at the start of the treatment than at the end. The difference was found to be statistically significant ($p<0.0001$).

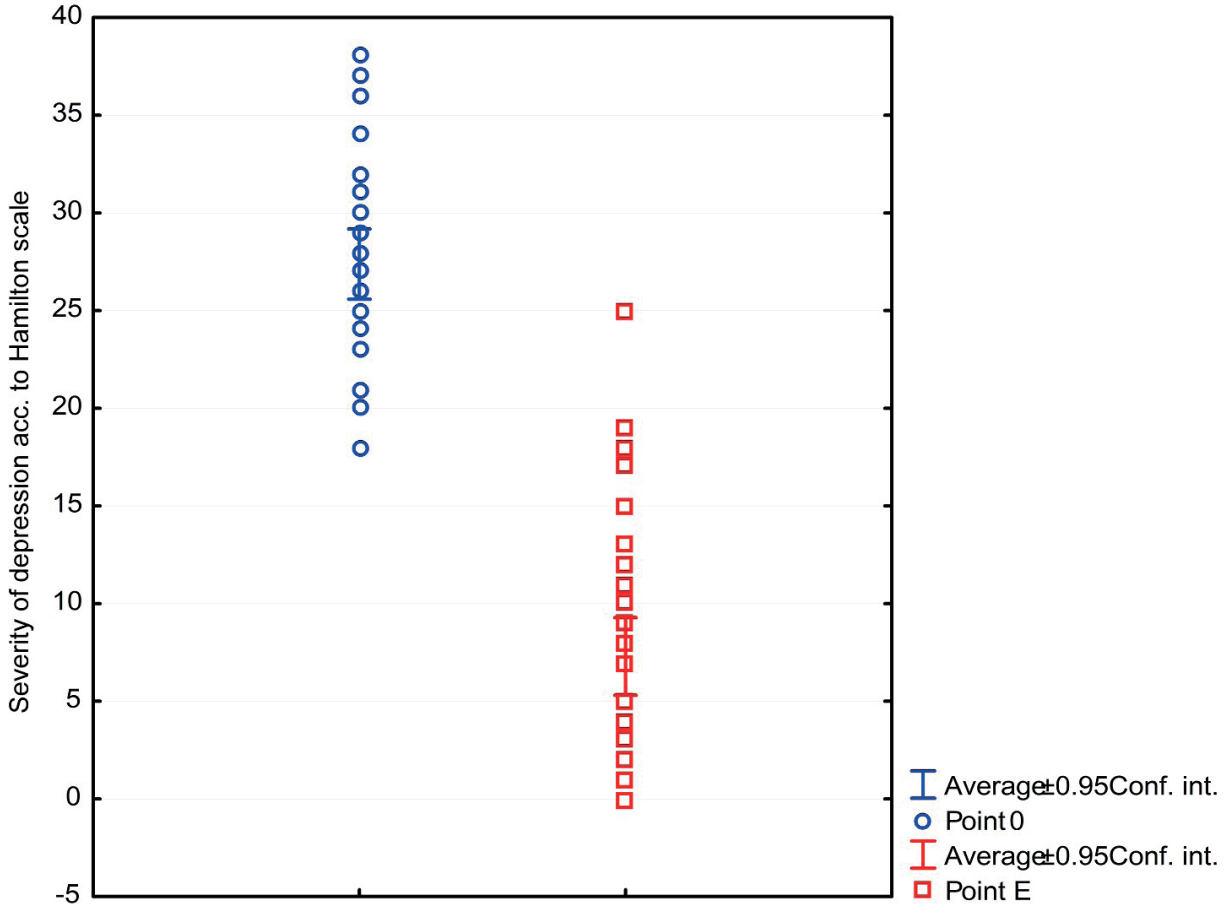

Fig. 5 Scatter plot with 95% confidence interval showing the severity of depression according to the Hamilton scale at two points in time.

3. Concentration levels of MMP-9 at the end of the study

Table 12. Descriptive statistics – The concentration of MMP-9 at the end of the study in both men and women and the results of a Mann-Whitney U test

Sex	n	Point E ng/ml					Mann-Whitney U test	
		Average	Std. deviation	Median	Min.	Max.	U	p
1	27	357.5	158.5	333.0	112	629	130.0	0.8777
2	10	367.1	150.1	320.0	200	698		

At the end of the study, the average metalloproteinase level was higher in patients of sex-code 2 than in patients of sex-code 1. The difference was not statistically significant ($p>0.05$).

Table 13. Spearman Rank correlations between age and the concentration of MMP-9 at the end point of the test.

Pair of variables	n	R	t(n-2)	P
Age & Point E ng/ml	37	-0.122	-0.73	0.4706

There was no statistically significant correlation between age and MMP-9 concentration at the end point of the experiment ($p>0.05$).

Table 14. Descriptive statistics – The concentration of MMP-9 at the end point among patients treated with different anaesthetics and the result of a Mann-Whitney U test

Anaesthetic	n	Point E ng/ml					Mann-Whitney U test	
		Average	Std. deviation	Median	Min.	Max.	U	p
Propofol	17	339.8	149.5	305.0	112	698	147.0	0.4929
propofol +ketamine	20	377.4	159.9	361.0	116	629		

At the end of the study, the average concentration of metalloproteinase was higher in patients in whom the applied anaesthetic was propofol and ketamine than among patients treated with propofol alone. The difference was not statistically significant (p>0.05).

Table 15. Descriptive statistics – Concentration of MMP-9 at the end point of the study among patients treated with different anaesthetics and the result of a Kruskal-Wallis test

Anaesthetic	n	Point E ng/ml					Kruskal-Wallis test	
		Average	Std. deviation	Median	Min.	Max.	H	p
Propofol	9	332.8	126.6	335.0	208	595	4.51	0.2116
pro+ket	10	443.4	165.0	487.0	116	629		
thiopental	8	347.6	180.7	283.5	112	698		
thio+ket	10	311.3	130.7	311.5	155	555		

At the end of the study, the average concentration of MMP-9 was the highest among patients whose anaesthetic had been propofol and ketamine, and lowest in those to whom the anaesthetic had been thiopental and ketamine. The Kruskal-Wallis test showed no statistically significant differences in the concentration levels of patients treated with different anaesthetics (p>0.05).

Table 16. Descriptive statistics – Concentration of MMP-9 at the end point of the study in patients with different diagnoses and the result of a Mann-Whitney U test

Diagnosis	n	Point E ng/ml					Mann-Whitney U test	
		Average	Std. deviation	Median	Min.	Max.	U	p
1	27	365.3	167.6	333.0	112	698	130.0	0.8777
2	10	346.0	117.4	323.5	200	519		

At the end of the study, the average MMP-9 concentration was higher in patients with diagnosis code 1 than in patients with diagnosis code 2. The difference was not statistically significant (p>0.05).

Table 17. Spearman Rank correlations between duration of sickness and the duration of episodes and the concentration of MMP-9.

Pair of variables	n	R	t(n-2)	p
Duration of sickness (years) & Point E ng/ml	37	0.232	1.41	0.1670
Duration of episodes (months) & Point E ng/ml	37	0.008	0.05	0.9608

No statistically significant correlations were found between the duration of sickness or the duration of episodes and the concentration of metalloproteinase (p>0.05).

Table 18. Descriptive statistics – Concentration of MMP-9 at the end point of the test in patients with different severity of depression symptoms according to the Hamilton scale and the results of a Mann-Whitney U test

Severity of depression according to the Hamilton scale	n	Point E ng/ml					Mann-Whitney U test	
		Average	Std. deviation	Median	Min.	Max.	U	p
2	25	353.2	134.8	326.0	116.0	607.0	144.0	0.8584
3	12	374.3	194.8	338.0	112.0	698.0		

At the end of the study, the average concentration of MMP-9 was higher in patients with depression 3 than in those with depression code 2. The difference was not statistically significant (p>0.05).

Table 19. Descriptive statistics – Concentration of MMP-9 at the end point of the study in patients in different states of remission according to the HDRS and the results of a Mann-Whitney U test.

Remission status according to Hamilton scale	n	Point E ng/ml					Mann-Whitney U test	
		Average	Std. deviation	Median	Min.	Max.	U	p
1	21	345.3	136.4	326.0	116	595	151.0	0.6130
2	16	379.5	177.8	339.5	112	698		

At the end of the study, the average concentration of metalloproteinase was higher in patients with remission code 2 than in patients with remission code 1. The difference was not statistically significant (p>0.05).

4. 4. The type of anaesthetic and increasing or decreasing MMP-9 concentration

When testing whether the concentration of MMP-9 rose or fell during the test, the patients could be divided into two groups:

- those with increased concentration – 12 people showed increased metalloproteinase concentration at Point E in comparison to Point 0, among whom 8 were of sex-code 1 and 4 were of sex-code 2.
- those with decreased concentration – 25 people showed decreased metalloproteinase concentration at Point E in comparison to Point 0, among whom 19 were of sex-code 1 and 6 were of sex-code 2.

Table 20. Type of anaesthetic used and increased or decreased metalloproteinase concentration in comparison to the starting point and the result of a chi-square (maximal reliability)

Anaesthetic	Increased conc. n=12		Decreased conc. n=25		Chi-square test (m. r.)		
	n	%	n	%	χ^2	df	p
Propofol	1	8.3	8	32.0	9.30	3	0.0256*
pro+ket	6	50.0	4	16.0			
Thiopental	4	33.3	4	16.0			
thio+ket	1	8.3	9	36.0			

** - statistically significant (p<0.05)*

The type of anaesthetic used and whether there was an increase or decrease in concentration of MMP-9, in comparison to the concentration at starting point showed changes of statistical significance (p=0.0256).

Among subjects anaesthetized with propofol alone or with thiopental and ketamine, the percentage of people with a decreased MMP-9 concentration was higher.

Among subjects anaesthetized using propofol and ketamine or with thiopental alone, the proportion of patients with increased MMP-9 concentration was higher.

No statistically significant relationships were found between sex, age, duration of illness, duration of episodes, type of anaesthetic, severity of depression symptoms according to the Hamilton scale, remission status according to the Hamilton scale and individuals with increased or decreased MMP-9 concentration (p>0.05).

Discussion

Studies of the efficacy of treatment during episodes of depression have shown that only 25-35% of patients achieve remission on the basis of pharmacological treatment using antidepressant medicines [35]. Amongst others, the STAR*D study showed that around 33% of patients with depression do not achieve remission, even after 4 antidepressant treatments [36]. Other sources show that 60-70% of those treated for depression do not achieve remission status, around 30-40% fail to react as expected to their first course of antidepressants, 20% do not return to health within 2 years, and 10% suffer from

chronic depression despite numerous pharmacological interventions [37]. For these reasons it is important to find treatments for patients with drug-resistant disease. Drug-resistant depression, according to the definition proposed by Helmchen in 1991, is characterized by episodes of depression with unsatisfactory reaction to treatment (meaning that symptoms persist or are not substantially reduced) despite at least two consecutive treatment regimens using antidepressant drugs of different classes and used in appropriate doses, and for the appropriate length of time, for the treatment. Scientific interest is therefore focussed on methods of treatment for drug-resistant depression which, according to some studies, can achieve remission in around 50% of cases [38].

In popular opinion, and even among some professionals working in the field, treatment by electroconvulsive therapy, which was introduced as a treatment method more than 70 years ago, still suffers from misconceptions about quality, often related to alleged irreversible personality changes, memory disorders or permanent brain damage. It must be assumed that this results from insufficient knowledge of the subject, even though since the 1990s increasing numbers of publications have been showing that ECT is associated with lower risk of complications than conventional pharmacotherapy [40]. It is worth mentioning that current therapeutic methods involve a multidisciplinary medical team of not only psychiatrists, but also cardiologists, anaesthetists, and neurologists who work together to ensure complete safety for the patient undergoing treatment.

The authors of this study wished to draw attention to the role that the choice of anaesthetic drugs may have on the results of ECT, both in terms of reduction of side effects and in terms of improved efficacy. The choice of anaesthetic affects many parameters of the induced seizures, on how long they last and on their clinical effects, on haemodynamics, and on cognitive functions. There are no recommendations regarding the choice of anaesthetic drugs. The selected drug is chosen based on individual risk factors such as coexisting disease and possible interactions with other drugs being taken by the patient [29].

There is the perspective that it may be possible to associate markers for the efficacy of ECT treatment with the choice of anaesthetic drugs used in the procedure. This study was limited by the rather low number of patients enrolled as study subjects and by a lack of precise information regarding the duration of remission after completion of ECT therapy. Issues remain regarding the efficacy of treatment and the duration of its effects. These issues will require constant observation and further testing involving significantly larger groups of patients.

Conflict of interest

The authors have declared no conflict of interest.

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