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ORIGINAL ARTICLE

Important Role of Estrogen in Distinguishing Depression and Schizophrenia and Prognostic Judgment of MECT

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Abstract

OBJECTIVES: This study aimed to investigate the role of estrogen in the differential diagnosis of depression and schizophrenia and its relationship with the curative effects, adverse events.

METHODS: From 2017 to 2019, patients with depression or schizophrenia treated with modern electroconvulsive therapy (MECT) were studied retrospectively. Their serum estrogen levels, Hamilton Depression Scale, and Brief Psychiatric Rating Scale scores were collected. Differences in the estrogen levels between patients with depression and schizophrenia before and after treatment and the correlation of the estrogen level with curative effect and adverse events was evaluated. In total, 67 patients with depression and 61 with schizophrenia were included.

RESULTS: There were no significant differences in the baseline characteristics, except the estrogen level ($p < 0.001$). Serum estrogen levels increased in both groups after MECT (117 vs. 141 pmol/L, $p < 0.001$; 42 vs. 46 pmol/L, respectively; $p < 0.001$), and higher estrogen levels were positively correlated with better outcomes ($p < 0.001$).

CONCLUSION: Post-MECT estrogen levels were not associated with the incidence rate of adverse events of MECT. Estrogen plays a promising role in distinguishing depression and schizophrenia and evaluating the therapeutic efficacy of MECT.

INTRODUCTION

Mental illnesses, such as depression and schizophrenia, are often characterized by resistance to therapy and high relapse rates. These have also affected millions of people with increasing incidence rates (Substance Abuse and Mental Health Services Administration (SAMHSA) 2017). Fundamental sex differences have been discovered in the prevalence of mental illnesses, with anxiety, depression, and schizophrenia being more frequently diagnosed in women (Gender and women's mental health. Accessed June 12, 2018). It is noteworthy that reproductive women with frequent estrogen cycles may be more prone to mental disorders (Soares & Zitek 2008; Bratek *et al.* 2016). In general, estrogen is an important hormone that has a major impact on physiology and psychology by regulating emotion, body states, and cognition (Luine 2008; Rambhatla *et al.* 2016). Studies have found that estrogen can affect the response of the central nervous system's reward circuitry by regulating the synthesis and receptor concentration/trafficking (Sanchez *et al.* 2013; Krolick *et al.* 2018) of traditional neurotransmitters, including dopamine, serotonin, and gamma-aminobutyric acid (Dichter *et al.* 2012).

The perimenopausal (Gordon *et al.* 2018; Gordon *et al.* 2016) and early postmenopausal years (Campbell *et al.* 2015), which present with fluctuations and apparent declines in estrogen levels, are often associated with increased risk of depressive symptoms. A meta-analysis of 14 studies found that longer exposure to endogenous estrogen, especially among those with later menopause or longer childbearing age, decreases the risk of mental illnesses, such as depression or anxiety (Georgakis *et al.* 2016). A variety of studies have demonstrated that acute estrogen deprivation following ovariectomy might lead to depression-like symptoms (Lagunas *et al.* 2010; Daendee *et al.* 2013), which could be treated with estrogen replacement therapy (Heydarpour *et al.* 2013). On the other hand, studies have demonstrated that women who had recently given birth, had discontinued estrogen drugs, or are menopausal were more vulnerable to schizophrenia relapse due to decreased estrogen levels (Begemann *et al.* 2012). Kulkarni *et al.* conducted a large-scale randomized controlled clinical trial of premenopausal women with schizophrenia and found that both 100 and 200 μg estrogen therapy could effectively relieve the positive, general, and total symptoms, with the higher dose group presenting the most optimal clinical efficacy (Kulkarni *et al.* 2015). However, schizophrenia is a mental illness presenting with various emotional symptoms, including stupor and feeling down. As such, it should be carefully differentiated from depression. Above all, although estrogen levels were closely linked with depression and schizophrenia, it was not reported whether there is a significant difference in the estrogen levels between these two mental disorders. Therefore, further research is necessary.

In addition to antipsychotic drugs, modern electroconvulsive therapy (MECT) is commonly for physiotherapy at the Department of Psychiatry as it quickly relieves the psychiatric illnesses of patients through electrical seizure, though its therapeutic mechanism remains unclear (Tang *et al.* 2012). However, it has been confirmed that the electric seizure induced during MECT increases the level of neurotrophic factors in different areas of the brain (Gedge *et al.* 2012). Furthermore, MECT may correct the dysfunctional brain of patients with depression or schizophrenia by adjusting the neurotransmitters, neuron sensitivity, and electrical activity (Zhao *et al.* 2016). The waves of seizure induced by MECT, closely related to the therapeutic effect of MECT, can be observed in the electroencephalogram. Adverse cognitive effects and propensity for relapse has been considered as the two major attentions to limit the application of MECT historically, and these two limitations have been substantially improved in recent years (Sackeim 2017). Currently, MECT has become an increasingly widely used medical intervention (Jolivet & Grözinger 2021), especially for severe, psychotic or refractory depression, where it has become the most effective treatment (Kirov *et al.* 2021). However, detailed adverse events and the influence of MECT on sex hormone levels were imprecise, requiring more attention from psychiatrists.

Therefore, in this study, we utilized the internationally accepted Hamilton Depression Scale (HAMD) (Williams 1988; Zhu *et al.* 2017) and Brief Psychiatric Rating Scale (BRPS) (Overall & Beller 1984; Chon Park *et al.* 2018) scores to evaluate the clinical efficacy of MECT in patients with depression or schizophrenia. We focused on the fluctuating estrogen levels after MECT to explore the relationship between estrogen levels and therapeutic efficacy of MECT. Furthermore, according to the enrolled subjects' median estrogen level, the incidence rates of adverse events of illness management between the increasing and decreasing estrogen subpopulations were compared to discuss their potential relationships. Finally, we aimed to establish a new adjuvant diagnosis of estrogen levels to distinguish depression and schizophrenia and explore the predictive role of estrogen on the therapeutic efficacy of MECT.

MATERIAL AND METHODS

Study population

A total of 128 patients diagnosed with depression or schizophrenia in the general psychiatric department and open psychiatric department at Hospital between 2017 and 2019 were included in the present study. Patients who met the following criteria were enrolled: (1) diagnosis of depression or schizophrenia, based on the International Classification of Diseases, Tenth Edition; (2) age above 18 years; (3) received MECT 5–12 times; and (4) detected and recorded the serum

Tab. 1. Baseline characteristics of patients with depression and schizophrenia

Factors	Depression (n=67)	Schizophrenia (n=61)	χ^2/Z	*P* value†
Sex, n (%)			0.331	0.565
Male	16 (23.9%)	12 (19.7%)		
Female	51 (76.1%)	49 (80.3%)		
Age, years	30 (24, 40)*	29 (24.5, 35)*	-1.123	0.262
Periodicity of MECT, days	31 (24, 41)*	46 (33, 70)*	-4.197	<0.001
Times of MECT	7 (6, 9)*	9 (7, 10.5)*	-2.924	0.003
Duration of illness, month	1 (0.5, 3)*	2 (0.5, 12)*	-1.529	0.126
Serum estrogen	117 (46, 162)*	42 (22, 57)*	-4.552	<0.001

* median (interquartile range)
†: *p*-values are shown when the depression and schizophrenia groups were compared using the parametrical Mann-Whitney t-test. MECT, modern electroconvulsive therapy. Patients in the two groups showed no significant differences in terms of sex, age and duration of illness ($p > 0.05$). While patients in schizophrenia group showed lower serum estrogen level than that in depression group before MECT treatment ($p < 0.001$). The treatment times and periodicity of MECT significantly differed between the two groups due to the different therapy regimes.

estrogen level. Eventually, 67 patients with depression and 61 with schizophrenia were enrolled. This study was conducted in accordance with the 1983 revision of the Declaration of Helsinki. This retrospective study was approved and exempted from the requirement to obtain informed consent by the Committee on Medical Ethics of Huzhou Third People's Hospital (approval No. 2021-347).

Clinical and pathological characteristics

Patients' demographic information and treatment history were retrospectively reviewed from our depression and schizophrenia database, including age, sex, age at onset, duration of illness, treatment times and periodicity of MECT, serum estrogen level, serum prolactin level and comorbidities. MECT was administered thrice weekly for 5–12 times, according to the standard protocols. First, routine nursing was administered, and intravenous access was prepared. Patients were deprived of food and water 6 h before MECT. Succinylcholine (1.0 mg/kg) was used as a muscle relaxant, while atropine sulfate (0.5 mg) and propofol (1.5 mg/kg) were used to induce and maintain anesthesia. About 1 min after patients stopped breathing and had relaxed muscles, a MECT instrument (SOMATIC, USA) was charged, set according to the age, sex, or antipsychotic therapy, and applied to the patients. The static resistance was 100–3000 Ω. Generally, MECT is administered three times weekly every other day, but for patients in the acute phase, it should be started as once daily in the first three to six sessions. Lastly, low-flow oxygen with positive pressure was delivered to patients with hypoxemia. After MECT, food and water deprivation should be continued for 2 h, combined with monitoring of the vital signs.

Clinical scales

HAMD was used to evaluate the depression severity. We ranked the total score between 7 and 17, 17 and 24, and >24 as mild, moderate, and severe depression, respectively. Usually, the 24-items tool includes seven parts with a 5-point scale ranging from "not present"

Tab. 2. Change in serum estrogen levels in patients with depression and schizophrenia who underwent MECT

Factors	Before MECT	After MECT	Z	*P* value†
Depression	n=67	n=67		
HAMD	30 (28, 34)*	7 (6, 10)*	-7.12	<0.001
Estrogen	117 (46, 162)*	141 (48, 207)*	-4.631	<0.001
Schizophrenia	n=61	n=61		
BPRS	108±13	41±9	443635	<0.001
Estrogen	42 (22, 57)*	46 (31, 74)*	-4.194	<0.001

*median (interquartile range)
†: *p*-values are shown when the estrogen level, HAMD score, or BRPS score before and after MECT were compared using parametric t-tests.
MECT, modern electroconvulsive therapy; HAMD, Hamilton Depression Scale; BRPS, Brief Psychiatric Rating Scale. After MECT, the HAMD score for depression patients and BRPS score for schizophrenia patients significantly decreased; while estrogen level increased.

to "very severe," including anxiety/somatization, weight loss, mental disorders, diurnal variation, retardation symptoms, sleep disturbances, and hopelessness symptoms. It is a well-validated, universally accepted clinical checklist for quantifying the symptoms of depression (Williams 1988). The remission criteria of HAMD included the following conditions: no response (NR) was defined as a < 25% reduction, early response (ER) was defined as a <50% reduction, ultimately response (UR) was defined as a <75% reduction, and complete recovery (CR) was defined as a 75% reduction in the HAMD baseline score.

In addition, the 18-item BPRS was used to evaluate psychiatric symptoms, such as somatic concern, anxiety, emotional withdrawal, conceptual disorganization, feelings of guilt, tension, mannerism and posturing, grandiosity, depressive mood, hostility, suspiciousness, hallucinatory behavior, motor retardation, uncooperativeness, unusual thought content, blunted affect, excitement, and disorientation. All the BPRS items are scored on a 7-point scale, ranging from "not present" to "very severe." A total score of ≥36 indicates the presence of a possible illness. Many studies have validated the BPRS for its excellent applicability and generality (Leucht *et al.* 2005). The remission criteria of BRPS included the following conditions: NR was defined as a <30% reduction, ER was defined as a <50% reduction, UR was defined as a <90% reduction, and CR was defined as a 90% reduction in BPRS baseline score.

For the 67 subjects with depression and 61 subjects with schizophrenia who completed the study, the HAMD or BPRS scores were measured before and after MECT to detect the changes.

Adverse events and serum estrogen monitoring

Adverse effects were recorded using the Adverse Symptom Checklist by the patients themselves, including nausea, headaches, increased saliva, and sexual dysfunction. On the other hand, the safety analysis probed on the frequency of adverse events, relapse of disease, and the dropout rate of subjects, which was recorded within 1 month after MECT.

Serum estrogen levels in all patients were also collected before and after MECT. Estradiol levels were measured using a chemiluminescent assay in our hospital, with a coefficient of variation ranging between 2-8 pmol/L.

Statistical analysis

SPSS software (version 19.0; IBM, Armonk, NY, USA) for Windows was used to analyze the data. Statistical significance was set at $P < 0.05$. To identify the normal distribution of all continuous variables, the Kolmogorov-Smirnov Z test was used. In terms of normal distribution data, mean ± standard deviation was analyzed using parametric t-tests or Mann-Whitney t-test. Otherwise, data are presented as median (interquartile range) and were analyzed using the Wilcoxon rank-sum test, while categorical data were compared using the chi-square test or Fisher's exact test.

RESULTS

Serum estrogen level is distinct between patients with depression and schizophrenia

In this study, we enrolled 67 patients with depression and 61 with schizophrenia, and all had increased serum estrogen levels. To compare differences in the serum estrogen levels, we first compared the subjects' baseline characteristics (Table 1). The percentage of male patients was approximately 20% in both groups. The patients' median age (30 years for the depression group and 29 years for the schizophrenia group) and duration of illness (1 month for the depression group and 2 months for the schizophrenia group) were well matched between the two groups. However, due to their different therapy regimes, the treatment times and periodicity of MECT significantly differed between the two groups ($p < 0.05$). Comparing the baseline levels before MECT, the serum estrogen level in the schizophrenia group was significantly lower than that in the depression group (117 vs. 42 pmol/L, $p < 0.001$), indicating that serum estrogen might be an adjuvant factor for distinguishing between depression and schizophrenia.

Tab. 3. Serum estrogen levels in patients with depression and schizophrenia with different therapeutic efficacy of MECT

Factors	ER	UR	CR	χ^2	*P* value‡
Depression	n=14	n=6	n=47		
Estrogen	34 (25, 76)*	98 (46, 180)*	176 (63, 235) *,†	18.651	0.001
Schizophrenia	n=42	n=8	n=11		
Estrogen	39 (27, 51)*	52 (36, 115)*	181 (150, 222) *,†	28.509	<0.001

*median (interquartile range)
†: When compared with the ER subgroup, $p<0.05$.
‡: *p*-values are shown when the ER, UR, and CR subgroups were compared using the chi-square test.
ER, early response; UR, ultimate response; CR, complete recovery; MECT, modern electroconvulsive therapy. After MECT, the patients were divided into ER, UR and CR groups, and the median serum estrogen levels gradually increased, with highest serum estrogen levels in CR group.

Tab. 4. The incidence rates of adverse events in patients with depression according to serum estrogen levels after MECT

Factors	<141 pmol/L (n=33)	≥141 pmol/L (n=34)	χ^2	*p* value*
Headache, n (%)			0.001	0.975
No	31 (93.9)	32 (94.1)		
Yes	2 (6.1)	2 (5.9)		
Short-term memory impairment, n (%)			0.003	0.954
No	27 (81.8)	28 (82.4)		
Yes	6 (18.2)	6 (17.6)		
Dizzy, n (%)			2.421	0.12
No	32 (97.0)	28 (82.4)		
Yes	1 (3.0)	6 (17.6)		
Nausea, n (%)			NA	NA
Yes	33 (100.0)	34 (100.0)		
Fatigue, n (%)			1.371	0.242
No	33 (100.0)	33 (97.1)		
Yes	0 (0.0)	1 (2.9)		
Relapse, n (%)			0.005	0.945
No	25 (75.8)	26 (76.5)		
Yes	8 (24.2)	8 (23.5)		
Dropout, n (%)	0 (0)	0 (0)	NA	NA

*: *p*-values are shown when the <141 pmol/L and ≥141 pmol/L subgroups were compared using the chi-square test.
MECT, modern electroconvulsive therapy. The depression patients were divided into high (≥141 pmol/L) and low (<141 pmol/L) serum estrogen levels based on median value. The adverse events between high (≥141 pmol/L) and low (<141 pmol/L) serum estrogen level groups were compared, and no differences were found.

Considering that patients with schizophrenia are more likely to take antipsychotic medications which block dopamine and raise prolactin and hyperprolactinaemia may interfere with estrogen productions. Spearman correlation analysis was used to investigate the correlation between prolactin and estrogen levels. For all included patients, the prolactin level and estrogen level before MECT treatment were 13.6 (10.4, 19.3) and 49.0 (32.0, 141.5), respectively. Spearman analysis revealed that there was no correlations between prolactin level and estrogen level (r = -0.025, $p = 0.777$). The prolactin level and estrogen level after MECT treatment were 24.0 (17.4, 36.6) and 60.5 (39.3, 176.0), respectively. Spearman analysis revealed that there was weak positive correlations between prolactin level and estrogen level (r = 0.268, $p = 0.002$). Similar results were observed for depression patients (r = -0.101, $p = 0.415$ before MECT treatment; r = 0.259, $p = 0.034$ after MECT treatment). For schizophrenia patients, there were no correlations between prolactin level and estrogen level (r = 0.180, $p = 0.172$ before MECT treatment; r = 0.088, $p = 0.508$ after MECT treatment). These data suggested that the lower serum estrogen in schizophrenia group might not be caused by antipsychotic usage.

Serum estrogen elevation in patients with depression and schizophrenia after MECT

MECT employs anesthesia during treatment to avoid painful experiences and undue injury induced by the ECT, which has been widely accepted by patients. In this study, patients with depression and schizophrenia received MECT according to the standard protocol, and the HAMD and BRPS scores were determined before and after MECT. Statistical results showed that the HAMD scores in patients with depression and the BPRS score in patients with schizophrenia significantly decreased (both $p < 0.001$, Table 2), indicating the therapeutic efficacy of MECT. Contrary to the HAMD or BRPS scores, the serum estrogen level increased significantly after MECT (117 vs. 141 pmol/L, $p < 0.001$ and 42 vs. 46 pmol/L, $p < 0.001$, respectively; Table 2).

Estrogen is an important hormone in females. In contrast, the estrogen level in males is lower than in females. On comparing the changes in the HAMD or BPRS scores between female and male patients administered with MECT, data showed that the therapeutic efficacy of MECT was equivalent in female and male patients with depression or schizophrenia. However, the degree of estrogen elevation in female patients with depression who underwent MECT was more

Tab. 5. The incidence rates of adverse events in patients with schizophrenia according to serum estrogen levels after MECT

Factors	<46 pmol/L (n=30)	≥46 pmol/L (n=31)	χ^2	*p* value*
Headache, n (%)			0.223	0.637
No	29 (93.5)	26 (86.7)		
Yes	2 (6.5)	4 (13.3)		
Short-term memory impairment, n (%)			0.184	0.668
No	28 (90.3)	25 (83.3)		
Yes	3 (9.7)	5 (16.7)		
Dizzy, n (%)			0.001	0.973
No	29 (93.5)	28 (93.3)		
Yes	2 (6.5)	2 (6.7)		
Nausea, n (%)			0.552	0.458
No	31 (100.0)	28 (93.3)		
Yes	0 (0.0)	2 (6.7)		
Fatigue, n (%)			0.127	0.722
No	27 (87.1)	27 (90.0)		
Yes	4 (12.9)	3 (10.0)		
Relapse, n (%)			0.882	0.348
No	24 (77.4)	26 (86.7)		
Yes	7 (22.6)	4 (13.3)		
Dropout, n (%)	0 (0)	0 (0)	NA	NA

*: *p*-values are shown when the <46 pmol/L and ≥46 pmol/L subgroups were compared using the chi-square test.
MECT, modern electroconvulsive therapy. The schizophrenia patients were divided into high (≥46 pmol/L) and low (<46 pmol/L) serum estrogen levels based on median value. The adverse events between high (≥46 pmol/L) and low (<46 pmol/L) serum estrogen level groups were compared, and no differences were found.

significant than that in male patients (35.4% vs. 2.2%, Table S1), while this did not occur in patients with schizophrenia (slightly elevated in both female and male patients, Table S2). To some extent, it has been suggested that estrogen plays a distinct role in depression and schizophrenia.

Higher serum estrogen levels were related to improved therapeutic efficacy of MECT

Based on the improvement in the HAMD or BPRS scores after MECT, patients with depression and schizophrenia were divided into ER (14 patients with depression and 42 with schizophrenia), UR (six patients with depression and eight with schizophrenia), and CR (47 patients with depression and 11 with schizophrenia). The median serum estrogen levels in these three subgroups gradually increased in patients with depression and schizophrenia ($p = 0.001$ and $p < 0.001$, respectively), and the difference between the ER and CR subgroups was significant (both $p < 0.05$, Table 3). Therefore, we can conclude that a higher serum estrogen level might also be an effective predictor of improved therapeutic efficacy of MECT in patients with depression and schizophrenia.

The relationship between serum estrogen and adverse events of MECT

According to the abovementioned median serum estrogen levels in patients with depression, we recorded the adverse events of MECT in the serum estrogen < 141 (33 patients) and > 141 pmol/L (34 patients) populations. The incidence rates of headache, short-term memory impairment, dizziness, nausea, fatigue, relapse, and dropout in both populations were not significantly different (Table 4). We also analyzed the incidence rates of adverse events in patients with schizophrenia and found no significant difference between serum estrogen < 46 (31 patients) and > 46 (30 patients) pmol/L populations (Table 5).

DISCUSSION

With respect to economic development and heavy pressure of modern lifestyles, the prevalence rates of depression and schizophrenia have been rising over the recent decades due to the combination of mental, biological, and societal factors (Burns *et al.* 2014; Shorey *et al.* 2018). Many previous studies have concluded that the diagnosis of depression and schizophrenia increases in

Tab. S1. Change of serum estrogen levels in female and male patients with depression who underwent MECT

Factors	Male (n=16)	Female (n=51)	Z	*p* value†
Estrogen before MECT	46 (28, 48) *	130 (83, 171)*	-4.325	<0.001
Estrogen after MECT	45 (24, 53) *	176 (114, 235)*	-4.361	0.001
HAMD before MECT	31 (27, 33) *	30 (28, 34)*	-0.178	0.859
HAMD after MECT	6 (5, 8) *	7 (6, 10)*	-1.486	0.137

* median (interquartile range)
†: *p*-values are shown when the male and female subgroups were compared using the Mann-Whitney t-test.
MECT, modern electroconvulsive therapy; HAMD, Hamilton Depression Scale. For depression patients, the HAMD score showed no differences between males and females before or after MECT. Female patients showed higher estrogen level than male patients before or after MECT.

Tab. S2. Change in serum estrogen levels in female and male patients with schizophrenia who underwent MECT

Factors	Male (n=16)	Female (n=51)	Z	*p* value†
Estrogen before MECT	18 (15, 23)*	46 (32, 125)*	-4.284	<0.001
Estrogen after MECT	29 (24, 39)*	52 (34, 130)*	-3.53	<0.001
BRPS before MECT	120 ± 11*	105 ± 12*	3.802	<0.001
BRPS after MECT	50 ± 8*	39 ± 8*	3.774	<0.001

* median (interquartile range)
†: *p*-values are shown when the male and female subgroups were compared using the Mann-Whitney t-test.
MECT, modern electroconvulsive therapy; BRPS, Brief Psychiatric Rating Scale. For schizophrenia patients, female patients showed lower BRPS score than male patients before or after MECT. Female patients showed higher estrogen level than male patients before or after MECT.

women after birth or menopause, and estrogen replacement could be beneficial for controlling these diseases as these women are vulnerable to relapse (Begemann *et al.* 2012; Heydarpour *et al.* 2013; Kulkarni *et al.* 2015; Marsh *et al.* 2017; Tantipongpiradet *et al.* 2019). Therefore, we focused on the relationship between the estrogen level, the most important sex hormone in women, and depression or schizophrenia. Statistical results indicated that serum estrogen levels in patients with schizophrenia were dramatically lower than those in patients with depression, offering us a promising adjuvant diagnosis to avoid delayed diagnosis and inappropriate therapy.

Despite its unclear mechanism, MECT is a quick and effective therapy frequently used for depression and schizophrenia (Tang *et al.* 2012), the predictors of therapeutic efficacy and adverse events of MECT should be studied through clinical trials. Out study observed a significant increase in the estrogen levels after MECT and constructed a connection between higher estrogen levels and improved therapeutic efficacy. This provided the newest evidence on the promising role of estrogen as a predictor of a satisfactory prognosis following MECT in patients with depression and schizophrenia. In addition, it corresponded with increasing incidences of depression and schizophrenia in females with lower estrogen levels and the better curative effect of higher doses of estrogen drugs. Our results offered an innovative perspective of the underlying relationship between the MECT mechanism and estrogen level. The network of signal pathways among MECT, estrogen, and neurotrophic factors deserves further research.

However, this trial enrolled approximately 20% male patients to study sex-based differences. Interestingly, the results showed that sex differences existed only in patients with depression after undergoing MECT but not in those with schizophrenia. Similarly, Riedel-Heller *et al.* found that increased estrogen levels could be associated with depression in males (Stanikova *et al.* 2018), and Bratek *et al.* demonstrated its equally important role in schizophrenia in both males and females (Bratek *et al.* 2016). Contrary to depression in females, the prevalence of depression in males increases with a drop in plasma testosterone levels (Khera 2013), the major male sex hormone that promotes the development of male reproductive tissues, muscle and bone mass, and well-being (Bassil *et al.* 2009). A low testosterone level in males has also been associated with numerous non-specific symptoms, including depression and anxiety (Khera 2013; Alkamel *et al.* 2014). In addition to estrogen, the essential role of testosterone in males with depression is also worthy of attention. However, no published literature has focused on the relationship between testosterone and the curative effect of MECT for depression. Although our results were suggestive of the proper administration of MECT between sexes in patients with depression and schizophrenia, another trial with a larger sample size of male patients is needed.

Furthermore, the safety profile of MECT in this study was good, with the main adverse events being

nausea and short-term memory impairment, similar to previous reports (Baghai & Moller 2008; Nakatake *et al.* 2010). By dividing the patients with depression or schizophrenia according to the median serum estrogen level, we found that the estrogen level after MECT did not evidently affect the incidence rate of adverse events. As the adverse events of MECT vary according to sex and history of antipsychotic drugs, the univariate factor analysis of estrogen level might not be sufficient.

There were also limitations in this study. The participants include ones in very early phase of their illnesses in that their median duration of illness was only a few months, which might be a source of confounding. Besides, since the amount and role of estrogen would be different between genders, it may not be best to interpret hormone levels of all the participants. It would be better to interpret all the results separately by the gender. This is partially addressed in the supplementary tables (Table S1-2), but only to compare estrogen levels between male and female patients, not before and after treatment.

CONCLUSION

In conclusion, the observation or detection of estrogen levels plays a promising role in distinguishing between depression and schizophrenia and evaluating the therapeutic efficacy of MECT. However, our data in this study came from a single cohort center and were reviewed retrospectively. As such, a prospective, multicenter, randomized clinical trial should be conducted to further validate the impact of estrogen on these two mental illnesses.

DECLARATIONS

Ethics approval and consent to participate

This retrospective study was approved and exempted from the requirement to obtain informed consent by the Committee on Medical Ethics of Huzhou Third People's Hospital (approval No. 2021-347).

Consent for publication

Not applicable.

Availability of data and materials

Not applicable. This study was only the primary research, and further study has been in progress.

Competing Interests

The authors declare that they have no competing interests.

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Authors' contributions

Jin and Huang conceived and designed the research, and Bao-hua Song and Min Feng participated in the acquisition of data. Zhao and Song carried out the analysis and interpretation of data. Min Feng and Gang Song participated in the design of the study and performed the statistical analyses. Guangbiao Huang and Xi-long Jin conceived the study, participated in its design and coordination and helped draft and revise the manuscript for important intellectual content. All authors read and approved the final manuscript.

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