Xiang Yu-Tao (Orcid ID: 0000-0002-2906-0029)

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Electroconvulsive therapy for older adult patients with major depressive disorder: a systematic review of randomized controlled trials

Running Head: ECT for older depressed patients

[1#]Min Dong, MD,
[2#]Xiao-Min Zhu, MD, PhD;
[3#]Wei Zheng, MD;
[4#.]Xiao-Hong Li, MD, PhD
[5]Chee H. Ng, MBBS, MD
[6,7]Gabor S. Ungvari, MD, PhD
[2*]Yu-Tao Xiang, MD, PhD

1. Unit of Psychiatry, Faculty of Health Sciences, University of Macau, Macao SAR, China;
2. Institute of Mental Health, Suzhou Psychiatric Hospital, The Affiliated Guangji Hospital of Soochow University, Jiangsu, China;
3. The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, China;
4. The National Clinical Research Center for Mental Disorders & Beijing Key Laboratory of Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, China;
5. Department of Psychiatry, University of Melbourne, Melbourne, Victoria, Australia
6. University of Notre Dame Australia / Graylands Hospital, Perth, Australia;
7. Division of Psychiatry, Medical School, University of Western Australia, Perth, Australia

[#] These authors contributed equally to the paper.

*Address correspondence to Dr. Yu-Tao Xiang, 3/F, Building E12, Faculty of Health Sciences, University of Macau, Avenida da Universidade, Taipa, Macau SAR, China. Fax: +853-2288-2314;

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Phone: +853-8822-4223; E-mail: xyutly@gmail.com

ABSTRACT

Background: Electroconvulsive therapy (ECT) has been widely used in treating older adult patients with major depressive disorder (MDD). The results of randomized controlled trials (RCTs) are mixed. This study systematically examined the efficacy and safety of ECT versus antidepressants (ADs) in older adult patients with MDD.

Methods: Literature search was conducted independently by two reviewers examining the PubMed, Embase, PsycINFO, Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang and SinoMed databases from their inceptions until May 17, 2017. The Cochrane risk of bias and Jadad scale were used to assess the quality of RCTs included in the systematic review.

Results: Five RCTs (n=374; mean age of 66.0-66.4 years; males: 36.4%-58.3%) all conducted in China were identified including 3 RCTs (n=203) with ECT alone and 2 RTCs (n=171) with ECT-ADs co-treatment. In 2 of the 3 RCTs, ECT alone was superior to ADs monotherapy in improving depressive symptoms assessed with the Hamilton Depression Scale (HAMD) and clinical judgment at the conclusion of the course of ECT. Both RCTs of AD-ECT co-treatment showed significant reduction of the HAMD total score at post-ECT compared with ADs monotherapy. The response rate ranged from 80% to 97.5% in the ECT groups and 63.4% to 73.3% in ADs groups. No group differences were found in terms of adverse reactions (ARs). Only one RCT reported the discontinuation rate without significant group difference.

Conclusions: This systematic review showed that ECT appears to be an

effective and safe treatment of older adult patients with MDD. Further high quality studies with extended follow-up are warranted.

Key words: older adults, electroconvulsive therapy, major depressive disorder

INTRODUCTION

Late-life depression is a common psychiatric disorder [1] which has more complications than early-onset or adult depression. For instance, late-life depression is often associated with more chronic course, worse prognosis, higher recurrence rate, and greater likelihood of cognitive impairment, psychotic symptoms, medical morbidities and mortality. [2-5] Up to one third of depressed patients do not remit after acute pharmacological treatment, [6] particularly older patients. [7] As comorbid physical diseases are common, there is a high likelihood of antidepressant-induced side effects occurring in older adult. [8] For this reason, electroconvulsive therapy (ECT) is an alternative treatment for late-life depression. ECT yields higher remission rate in middle-aged and older adult patients than younger ones, [9-11] but the findings have been inconsistent.

ECT is widely used for older MDD patients in many countries. [12] In a survey 43.6% of older hospitalized patients with MDD received ECT. [13] However, the use of ECT in treating psychiatric disorders remains controversial. Some experts argued that ECT could rapidly improve psychiatric symptoms and shorten hospital stay, [14] but others contended that ECT should be strictly controlled due to the risk of cognitive effects. [15] Therefore, the efficacy and safety of ECT in late-life depression needs to be examined, with particular attention paid to

randomized controlled trials (RCTs). The findings of RCTs of ECT in late-life depression conducted have been mixed. The response rates of ECT range from 80% to 97.5%, [16,17] which is partly due to different patients mixed and study design across studies. Many studies were reported in non-English journals, therefore not readily accessible to the international readership.

For these reasons, this study systematically examined the efficacy and safety of ECT versus antidepressants (ADs) in older adult patients with MDD.

METHODS

Search strategy and study selection

Both English (PubMed, Embase, PsycINFO and Cochrane Library) and Chinese (Chinese National Knowledge Infrastructure, Wanfang and SinoMed) databases were searched from their inception until May 17, 2017. The following search terms were used: (random*) AND (older adults OR elderly OR aged OR aging) AND (electroconvulsive shock OR electroconvulsive therapy OR ECT OR MECT) AND (depression OR depressive OR depressed). Moreover, reference lists from relevant review were manually searched in order to avoid missing any studies.

Inclusion and exclusion criteria

Studies that fulfilled the following criteria according to the *PICOS* strategy of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [18] were included in this review: (1) ***P***articipants: older patients with MDD defined by respective studies; (2) ***I***ntervention: real ECT alone or real ECT

plus ADs; (3) ***C***omparison: ADs monotherapy or sham ECT plus ADs; (4) ***O***utcomes: primary outcome was the improvement of depressive symptoms as measured by standardized rating scales (such as the Hamilton Depression Scale; HAMD) [19] or clinical judgement by psychiatrists; secondary outcomes were dropout rate and adverse reactions (ARs); (5) ***S***tudy design: RCTs with relevant data. Review articles, case series and those without accessible full texts were excluded.

Data extraction

Two authors (DM and ZXM) independently searched the literature and extracted relevant data. Any disagreement was resolved by a discussion with a third author (ZW).

Quality assessment

The quality of studies including method of random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias was assessed by the Cochrane risk of bias. [20] In addition, the Jadad scale [21] was used to evaluate the quality of studies; the total score <3 indicated low quality; otherwise, studies were considered as high quality.

RESULTS

Literature search

The flow chart of study is shown in Figure 1. A total of 1,654 potentially relevant studies were identified, but only 5 RCTs, [16,17,22-24] all conducted in China, which fulfilled the inclusion criteria were analyzed.

Study characteristics

Table 1 presents the characteristics of the five RCTs involving 374 patients, including 3 RCTs (n=203) with ECT alone and 2 RCTs (n=171) with ADs-ECT co-treatment. The proportion of male patients varied from 36.4% to 58.3%, the mean age ranged from 66.0 to 66.4 years in the whole sample. The number of ECT sessions ranged from 6 to 12, while the length of the ECT course ranged from 2 to 8 weeks.

The improvement after the treatment with ECT

ECT alone vs. ADs

Of the 3 RCTs comparing ECT alone and ADs, in 2 RCTs ECT alone was superior to ADs improving depressive symptoms assessed with the HAMD [24] and clinical judgment [17] at post-ECT assessment (Table 1). Furthermore, the post-ECT response rate (reduction of HAMD total score >50%) was 96.7% in the ECT group and 73.3% in the ADs group ($p<0.05$) [24] while the corresponding figures were 97.5% and 63.4% ($p<0.05$) in the other study. [17] However, the third RCT did not find significant improvement in post-ECT depressive symptoms measured with the HAMD. [16]

Adjunctive ECT+ADs vs. ADs

Patients in the ECT groups received ECT and ADs concurrently. In one study the post-ECT HAMD total score was reduced significantly in the ECT group compared to the ADs group. [22] Another study found a significantly higher response rate (85.3%) in the ECT group than in the AD group (64.9%) measured with the HAMD. [23] The discontinuation rate of 17.1% was reported only in one study [23] (Table 2).

ARs

ECT alone vs. ADs

The most common ARs reported in the three studies were memory impairment (19.4%-30.0%, 3 RCTs), headache or dizziness (6.7%-16.1%, 2 RCTs), nausea or vomiting (9.7%, 2 RCTs), muscle pain (1 RCTs) in the ECT group, while thirst or dry mouth (6.7%, 3 RCTs), headache or dizziness (10.0%-20.0%, 2 RCTs), constipation (2 RCTs), nausea or vomiting (13.3%, 1 RCTs), drowsiness (1 RCTs), insomnia (6.7%, 1 RCTs), and dysuria (16.7%, 1 RCTs) in the ADs group (Table 2).

Adjunctive ECT+ADs vs. ADs

Patients reported nausea or vomiting (14.7%, 2 RCTs), muscle pain (1 RCTs), memory impairment (1 RCTs), headache or dizziness (41.2%, 1 RCTs), thirst or

dry mouth (14.7%, 1 RCTs), and sleepiness (8.8%, 1 RCTs) in the ECT+ADs group, and nausea or vomiting (27%, 2 RCTs), thirst or dry mouth (16.2%, 2 RCTs), constipation (1 RCTs), headache or dizziness (10.8%, 2 RCTs) in the ADs group (Table 2).

Quality assessment

All RCTs mentioned "randomized allocation", while only one detailed its method (Table 3). All RCTs were open label trials and were rated as high risk regarding allocation concealment. Incomplete outcome data were addressed, thus selective reporting were rated as low risk. The mean JADAD score was 2.2, and its range was from 2 to 3 (Table 1).

DISCUSSION

This was the first systematic review that examined the efficacy and safety of ECT in older adult patients with MDD. The extracted data were not meta-analyzable, therefore only a systematic review was performed.

According to this review, ECT appears to be effective in treating older adults with MDD although its long-term efficacy was not reported. The mechanism of ECT for depression is still unclear. ECT could alter the sensitivity of certain neurotransmitters, including dopamine, serotonin, adrenaline and GABA. [25-27] Further, the serum level of brain-derived neurotrophic factor (BDNF) was significantly lower in depressed patients than in healthy controls, which could

increase after ECT. [28] Because of its effectiveness treating late-life depression, ECT has been considered as the "gold standard" treatment for older adults with antidepressant-resistant depression. [29-31]

A recent review found that the response rate of ECT in late-life depression ranged from 60% to 80%, [32] considerably lower than the figures (80% to 97.5%) found in this systematic review. The reason for this discrepancy is not clear. Treatment response to ECT is dependent on a host of factors including the severity of depressive symptoms at baseline and other patient characteristics, such as medical co-morbidity, the mode of delivery of ECT (unilateral vs. bitemporal electrode placement, type of anesthesia, etc.), and assessment instruments. In addition, treatment-resistant depression is common in older patients. [33] ECT is recommended for antidepressant-resistant patients or who cannot tolerate pharmacotherapy. [34] Antidepressant-resistant patients had a response rate of up to 71% to ECT. [35] However, no RCT in this study included medication-resistant depressed patients.

In terms of safety, 4 studies reported transient memory impairment in the ECT group, with the rate ranging from 19.4% to 30.0%. Memory impairment is associated with abnormal electrical activities in the hippocampus and the change of memory encode process related to ECT. [36-38] ECT-induced cognitive impairment is more obvious in the first 3 days after ECT, but working memory, anterograde memory and part of executive functions are significantly improve after 15 days. [39] The possible reasons for different type and percentage of cognitive changes across studies include comorbidities, such as cardiovascular,

metabolic and neurodegenerative diseases, different methods of the cognitive assessments and a characteristics of the delivery of ECT. [40] In this review, nausea and headache were common side effects of ECT, comparable to the rates of 23% and 48%, respectively, reported earlier. [41] Thirst or dry mouth were reported in the ADs group of all studies, while sleepiness was only reported in the ECT group in one study. As found previously, [42] most side effects were transient. [16,24] The discontinuation rate was reported only in one study [16] without observing group difference. Apart from one patient who dropped out due to arrhythmia, [23] no other severe side effects of ECT were reported in any of the studies.

There are several limitations in this review. First, the data of the RCTs were not meta-analyzable due to the small number of studies, the diverse delivery methods and the length of ECT course. Second, further important methodological shortcomings included the lack of blinding and standardized assessment of treatment response and complications that may have reduced the power to detect minor changes. Third, the long-term effect of ECT were not examined. Finally, all RCTs included in the review included only Chinese patients. Studies targeting different ethnic populations are warranted.

In conclusion, this systematic review confirmed that ECT appears to be effective and safe in the treatment of older Chinese adults with MDD. High quality RCTs of extended duration in other settings are warranted.

Competing financial interests

There is no conflict of financial interest concerning the authors in conducting this

study and preparing the manuscript.

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Figure legend

Figure 1. Flowchart for study selection

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Table 1. Summary of studies included in the systematic review

Study (courtry)	N	Design -Blinding -Setting	Participants -Criteria -Illness duration	Sex[a]: % of males in whole sample, ECT and ADs groups	Age[a] (yrs) in whole sample, ECT and ADs groups	ECT [a]: sessions (range); ADs dosages[a]: mg/day (range); Number of recruited patients/analyzed patients (n/n_A); Analysis: ITT/PP	Trial or ECT duration (wks)	Bilateral or unilateral	Main findings	Jadad score
ECT vs. ADs monotherapy										
Zhang 2014 (China)	82	-Open label -Inpatients	-NR -NR	31 (37.8%); NR; NR	66.0; NR; NR (63-79)	1. ECT (M=NR, R=6-12); n/n_A =41/41; 2. Paroxetine (M=40, R=40); n/n_A=41/41; ITT	NR or 2-4	NR	The superiority in the improvement of post-ECT depressive symptoms and mean shorter hospitalization in ECT group than in control group. Response rate: 97.5% in ECT group vs. 63.4% in ADs group (Rating scale: NA).	2
Chen 2013 (China)	61	- Open label -Inpatients	-CCMD-3 -NR	28 (45.9%); NR; NR	NR; NR; NR (62-75)	1. ECT (M=NR, R=6-12); n/n_A =31/31; 2. ADs[b] (M=NR, R=NR); n/n_A =30/30; ITT	NR or 2-4	Bilateral	Rating scale: HAMD. ECT group was associated with higher response rate than ADs group. Response rate: 96.7% (30/31) in ECT group vs. 73.3% (22/30) in ADs group (HAMD reduction⩾50%).	2
Wang 2012 (China)	60	- Open label -Inpatients	-ICD-10 -15 to 46	35 (58.3%);	66.2; 66.5;	1. ECT (M=NR, R=NR); n/n_A =30/30;	8 or 8	NR	Rating scale: HAMD. ECT group had significant improvement in early depressive	2

Study (courtry)	N	Design -Blinding -Setting	Participants -Criteria -Illness duration	Sex[a]: % of males in whole sample, ECT and ADs groups	Age[a] (yrs) in whole sample, ECT and ADs groups	ECT [a]: sessions (range); ADs dosages[a]: mg/day (range); Number of recruited patients/analyzed patients (n/n_A); Analysis: ITT/PP	Trial or ECT duration (wks)	Bilateral or unilateral	Main findings	Jadad score
ECT vs. ADs monotherapy										
			d	18 (60%); 17 (56.7%)	65.8; (60-78)	2. Venlafaxine (M=68.3, R=12.5-150); n/n_A =30/30; ITT			symptoms than control group, but there was no group difference in the post-ECT assessment. Response rate: 80% (24/30) in ECT group vs. 73.3% (22/30) in ADs group (HAMD reduction⩾50%).	
ECT + AD vs. ADs monotherapy										
Ma 2016 (China)	88	- Open label -Inpatients	-ICD-10 -NR	32 (36.4%); NR; NR	66.0; NR; NR; (63-79)	1. Escitalopram (M=NR, R=5-10) + ECT (M=10, R=10); n/n_A =44/44; 2. Escitalopram (M=NR, R=5-10); n/n_A =44/44; ITT	6 or 6	NR	Rating scale: HAMD. ECT group had significant improvement in depressive symptoms in both the early and post-ECT assessments compared to the control group. Change of mean score of HAMD: from 32.0-to 7.64 in ECT group vs. from 31.6 to 10.09 in ADs group.	2
Jiang 2014	83	- Open label	-ICD-10	41	66.1;	1. Sertraline (M=NR,	8 or 8	NR	Rating scale: HAMD. ECT group had	3

Study (courtry)	N	Design -Blinding -Setting	Participants -Criteria -Illness duration	Sex[a]: % of males in whole sample, ECT and ADs groups	Age[a] (yrs) in whole sample, ECT and ADs groups	ECT [a]: sessions (range); ADs dosages[a]: mg/day (range); Number of recruited patients/analyzed patients (n/n_A); Analysis: ITT/PP	Trial or ECT duration (wks)	Bilateral or unilateral	Main findings	Jadad score
ECT vs. ADs monotherapy										
(China)		-in- and outpatients	-NR	(57.7%); 19 (50%); 22 (59.5%)	65.3; 66.9; (60-79)	R=50-100) + ECT (M=NR, R=NR); n/n_A =41/34; 2. Sertraline (M=NR, R=50-100); n/n_A =42/37; PP			significant improvement in depressive symptoms in both the early and post-ECT assessments compared to the control group. Response rate: 85.29% (29/34) in ECT group vs. 64.86% (24/37) in ADs group (HAMD reduction⩾50%).	

[a] Weighted mean of patients who were analyzed in each group; [b] Including paroxetine OR sertraline OR buspirone;

$_A$ number of patients who were analyzed;

ADs = antidepressants; CLZ = clozapine; CCMD-3 = China's mental disorder classification and diagnosis standard 3th edition; d = days; ECT = electroconvulsive therapy; HAMD = Hamilton Depression Scale; ICD-10 = International Classification of Diseases 10th Revision; ITT = Intent-to-treat analysis; M =mean; MADRS: Montgomery and Asberg Depression Rating Scale (Montgomery and Asberg, 1979); NR = not reported; PP = Per-protocol analysis; R= range; wks = weeks; yrs = years.

Table 2. ADs and discontinuation rate

Study	ECT vs. ADs monotherapy			ECT + ADs vs. ADs monotherapy	
	Zhang 2014	Chen 2013	Wang 2012	Ma 2016	Jiang 2014

	ECT (N=41)	ADs (N=41)	ECT (N=31)	ADs (N=30)	ECT (N=30)	ADs (N=30)	ECT (N=44)	ADs (N=44)	ECT (N=34)	ADs (N=37)
ARs										
All	24.4	26.8	NR	NR	NR	NR	24.5	26.0	/	/
Nausea/vomiting (n, %)	NA	/	3 (9.7%)	/	/	4 (13.3%)	NA	NA	5 (14.7%)	10 (27.0%)
Muscle soreness (n, %)	NA	/	/	/	/	/	NA	/	/	/
Memory impairment (n, %)	NA	/	6 (19.4%)	/	9 (30.0%)	/	NA	/	/	/
Drowsiness (n, %)	/	NA	/	/	/	/	/	/	/	/
Thirst/dry mouth (n, %)	/	NA	/	NA[a]	/	2 (6.7%)	/	NA	5 (14.7%)	6 (16.2%)
Headache or dizziness (n, %)	/	/	5 (16.1%)	6 (20.0%)	2 (6.7%)	3 (10.0%)	/	NA	14[b] (41.2%)	4 (10.8%)
Insomnia (n, %)	/	/	/	/	/	2 (6.7%)	/	/	/	/
Sleepiness (n, %)	/	/	/	/	/	/	/	/	3 (8.8%)	/
Dysuria (n, %)	/	/	/	5 (16.7%)	/	/	/	/	/	/
Constipation (n, %)	/	NA	/	NA[a]	/	/	/	NA	/	/
Night sweat (n, %)	/	/	/	/	/	/	/	/	/	3 (8.1%)
Discontinuation rate										
All causes (n, %)	/	/	/	/	/	/	/	/	7 (17.1%)	5 (11.9%)
ARs (n, %)	/	/	/	/	/	/	/	/	7 (17.1%)	2 (4.8%)
Inefficacy (n, %)	/	/	/	/	/	/	/	/	/	3 (7.1%)

[a]This trial failed to separately report the number of patients with dry mouth and constipation (n=10).

[b]This data were extracted from the total number of patients with headache (n=6) and dizziness (n=8).

NA: This was reported in the study but the number was not applicable. /: This was not reported in the study.

Table 3. Cochrane Risk of bias

	Random sequence generation (selection bias)	***Allocation concealment (selection bias)***	***Blinding of participants and personnel***	***Blinding of outcome assessment (Symptom reduction, response)***	***Incomplete outcome data addressed (attrition bias)***	***Selective reporting (reporting bias)***	***Other sources of bias***
Zhang 2014	?	-	-	-	+	+	?
Chen 2013	?	-	-	-	+	+	?
Wang 2012	?	-	-	-	+	+	?
Ma 2016	?	-	-	-	+	+	?
Jiang 2014	+	-	-	-	+	+	?

+ :Low risk of bias, - : High risk of bias, ? : Unclear risk of bias

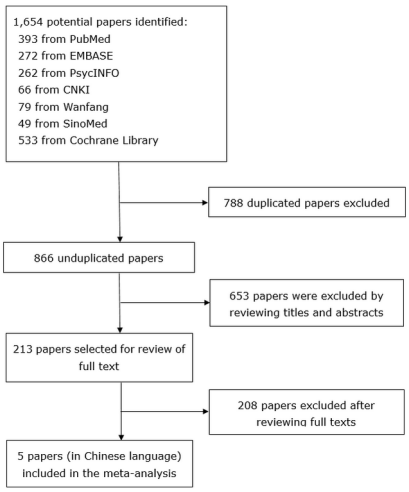

Figure 1.tif