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The Effectiveness of Electroconvulsive Therapy on Major Depressive Disorder

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List of Abbreviations and Acronyms

Abbreviations / Acronyms	**Full Forms**
5-hydroxytryptamine	5-HT
cAMP	Cyclic guanosine monophosphate
Cre	Creatine
dACC	Dorsal anterior cingulate cortex
DLPFC	Dorsolaterla prefrontal cortical region
ECS	Electroconvulsive shock
ECT	Electroconvulsive therapy
Glx	Glutamate/glutamine
HAMD	Hamilton rating scale for depression
MDD	Major depressive disorder
MWSAS	Modified work and social adjustment scale
NAA	*N*-acetylaspartate
NICE	National Collaborating Centre for Mental Health
PI	Phosphatidylinositol
QALY	Quality-adjusted life years
rTMS	Repetitive transcranial magnetic stimulation
sgACC	Subgenual anterior cingulate cortex

The Effectiveness of Electroconvulsive Therapy on Major Depressive Disorder

Abstract

ECT is the last line of intervention in curing treatment-resistant MDD, which might seriously lead MDD patients to the intention of suicide. However, the effectiveness of ECT on MDD is still controversial because of its threats to life. Therefore, a comprehensive review of the effectiveness of ECT on MDD is important to the decision-making of MDD patients and the future research on the potential benefits and side-effects of ECT. This study reviewed the mechanisms of ECT on MDD, its benefits and potential risks. In ECT, ECS is used to alter the neurochemical levels and structures of brain. ECT is determined to be more cost-effective than rTMS and efficient in treating special populations with MDD. Nevertheless, memory loss after ECT is most concerned in the decision-making of MDD patients but permanent memory loss has not yet been confirmed. Relaspse after ECT could be prevented with continuation therapy. Short-term complications might also reduce the willingness to receive ECT by MDD patients. Future research on the benefits and potential risks of ECT should be done to increase social acceptance to ECT.

Keywords: electroconvulsive therapy, major depressive disorder, effectiveness, benefits, side-effects, decision-making, memory loss, relapse, complications

Introduction

ECT has appeared since 1930s. ECT is the most effective treatment on severe treatment-resistant depression while other therapeutics failed (NICE, 2003). Clinical factors related to treatment resistance in MDD include suicidal ideation, personality disorder and nonresponse to the first antidepressant intake (Souery et al., 2007). The underlying mechanisms of ECT on MDD are still unclear. However, ECT is hypothesized to be associated with the alterations of neurochemical levels, structural and functional changes of brain in MDD patients. Before ECT, MDD patients are prescribed an anesthetic and a muscle relaxant. Either unilateral ECT or bilateral ECT is then employed to achieve seizure threshold in ECT recipients. The changes of electroencephalogram record the initial spike, slow-waves and flattened electroencephalogram during and after ECT. Generally, MDD patients receive 6 to 8 sessions of ECT which is used as a maintenance therapy.

A meta-analysis revealed that ECT benefited MDD patients in the short-term (Lancet et al., 2003). Furthermore, many comparative studies proved that ECT is more effective than rTMS and pharmacotherapy. It is interesting that ECT gives different degrees of effectiveness on diverse populations such as elderly and pregnant. However, the memory loss after ECT is the biggest concern among all the side-effects of ECT. Moreover, relapse after ECT and different immediate complications might also affect the decision-making of MDD patients to accept ECT. Nowadays, the long-term effectiveness of ECT on MDD patients and the preference for adopting unilateral ECT or bilateral ECT are still controversial.

In this article, the underlying mechanisms of ECT on MDD are reviewed. The benefits and potential risks of ECT are also discussed for providing more information to the decision-making of MDD patients.

Mechanisms of ECT

Alterations in neurochemical levels

In the therapeutic mechanism of ECT, it is believed that the brain monoaminergic systems including 5-HT receptors are the most importantly involved among all neurotransmitter systems (Ishihara and Sasa, 1999). Glx, NAA and Cre are also found to be the vital neurochemicals which might affect the neurotrophic process and limbic circuitry in MDD patients. They could be used as key biomarkers and predictors to produce desired therapeutic effects on MDD patients (Njau et al., 2017).

Serotonin

Alterations in the serotonergic system are associated with the interactions between different receptors, ion channels and neurons from Table.1 (Ishihara and Sasa, 1999). $G_{i/o}$ protein is firstly required to activate 5-HT_{1A} receptors to reduce cAMP formation in neurons so that hyperpolarization could then occur by opening K^+ channels. Furthermore, 5-HT_{1A} receptor is also found to work as an auto-receptor in the inhibition of neuronal activity. Moreover, turnover of PI is also carried out by the other 5-HT receptor subtypes activation. cAMP is stimulated by the activation of 5-HT_2 receptors coupled with $G_{q/11}$ proteins and 5-HT_4 receptors coupled with G_s proteins. Therefore, increase in the excitability of neurons is led by closing K^+

Pre-synaptic (serotonin)	
turnover	0
release basal	0
evoked	↓
Receptors	
presynatpic	
behavioral	↓ (hypothermia, 5-HT_{1A})
electrophysiological	0
binding	—
release	0
postsynaptic	
behavioral	↑ (head-twitch behavior, 5-HT_2)
electrophysiological	↑ (5-HT_{1A}, 5-HT_3)
binding	↑ (5-HT_{1A}, cortex or hippocampus) ↑ (5-HT_{2A}, cortex)
transporter	↑
Production of 2nd messengers	
cAMP	↓ (forskolin-induced, 5-HT_{1A})
IP_3	0 or ↑

↑ : increase, ↓ : decrease, 0: no change, —: not determined.

Table.1 Changes of serotonergic system by

channels. Nevertheless, PI turnover caused by the activation of 5-HT receptors remains unchanged in the hippocampus but it is enhanced in the cerebral cortex by repetitive ECS. In contrast, the binding of inositol triphosphate is reduced after 5-HT_2 receptor activation in the hippocampus with the down-regulation of 5-HT_{2A} receptor functions by the activation of 5-HT_{1A} receptors. Hence, it is suggested that the increased 5-HT_{1A} receptor functions might be resulted from the decline in 5-HT_{2A} receptor functions. To conclude, it is found that different 5-HT receptor subtypes are activated to form cAMP and induce PI turnover to affect the neuron excitability to bring about the anti-depressive effects in MDD patients.

Glx

In a study conducted at the hospital in University of California, 50 antidepressant patients with MDD and 33 controls were recruited patients (Njau et al., 2017). They were scanned HAMD at 3 time slots including “baseline” (within 24 hours proceeding the first ECT session), “first follow-up” (between the second and the third ECT sessions) and “second follow-up” (within 1 week of finishing whole ECT treatment). Controls were also administered at “baseline” and “follow-up” 2 time points only. This study mainly addressed the cross-sectional differences between baseline of patients and controls and the use of baseline neurochemicals as treatment outcome predictors.

The recent findings proposed that Glx level varied by region in Fig.1. The mood improvements were related to the increase of Glx in sgACC and its decrease in the left hippocampus after ECT treatment. It was also important that this joint change might demonstrate the dissociations between dorsally mediated hyporeactive top-down and ventrally mediated hyperreactive bottom-up circuitry in MDD patients (Njau et al., 2017). It was addressed that the mood regulation was closely related to prefrontal cortex while the

autonomic response to emotion was tightly associated with the ventral network (Clark et al., 2006). Since sgACC connected both subcortical and cortical limbic circuitry, it played an important role in holding dACC through the cingulum and the hippocampus formation. Hence, changes in Glx with ECT in different regions in brain might affect the prefrontal mood regulation and subcortical emotional responses in MDD.

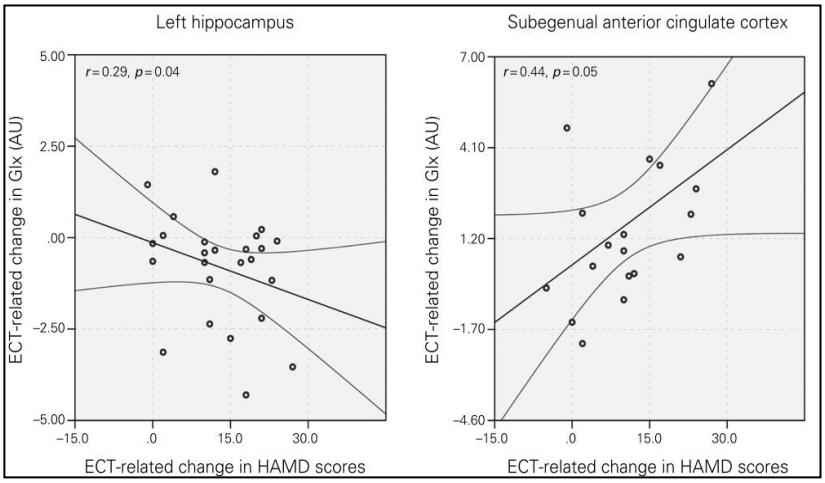

Figure.1 Joint longitudinal changes in HAMD scores and Glx concentration.

NAA

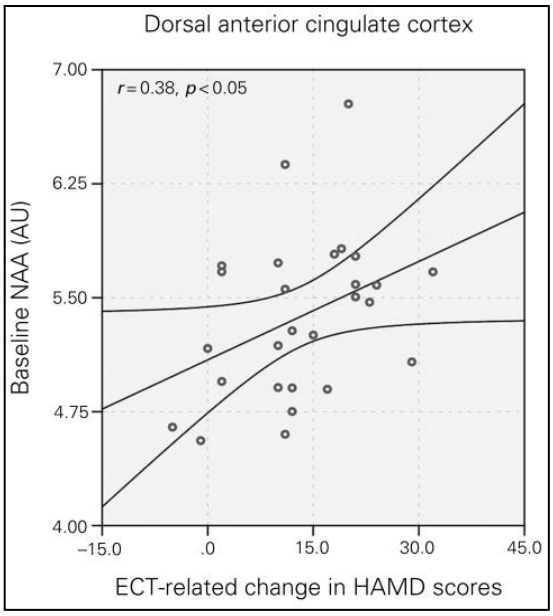

Figure.2 Changes of NAA concentration and HAMD scores in dACC.

NAA reduction was also observed due to the secondary mechanism from the restorative neural process in brain after ECT (Njau et al., 2017). Fig.2 showed that NAA decreased in dACC and right hippocampus with ECT which matched with the research result implying the linkage between NAA decline with neural atrophy (Eisch and Petrik, 2012). However, NAA decline might be due to the adult neurogenesis after giving ECS (Chen et al., 2009) and the formation of

pre-existing limbic circuitry into mature neurons by ECS, so this might indicate that the consecutive neurotrophic incidents might require the prerequisite neural changes led by the decrease in NAA levels with ECT in MDD patients (Njau et al., 2017).

Cre

Besides the alterations of Glx and NAA levels with ECT in MDD patients, the increase in Cre levels in dACC and sgACC with ECT was also detected (Njau et al., 2017). Since Cre is a key biomarker of energy metabolism (Yildiz-Yesiloglu et al., 2006), its increase might be due to the restorative process in dorsal corticolimbic network. However, no observation in the relationship between Cre increase and mood ratings was found in the study (Njau et al., 2017). This might suggest that further study on the effects of higher Cre observed in MDD patients is needed.

Structural and Functional Changes of Brain

Variation in brain activity of MDD patients after ECT might be due to the structural and functional changes in the brain of MDD patients (Qiu et al., 2016). The changes in grey matter volume of amygdala might further connect to the fusiform area of brain after ECT (Wang et al., 2017). Moreover, the reduction of frontal cortical connectivity after ECT was also observed (Perrin et al., 2012).

Amygdala

Amygdala is a significant target organ of ECT which is related to emotional response and memory processing in order to achieve the

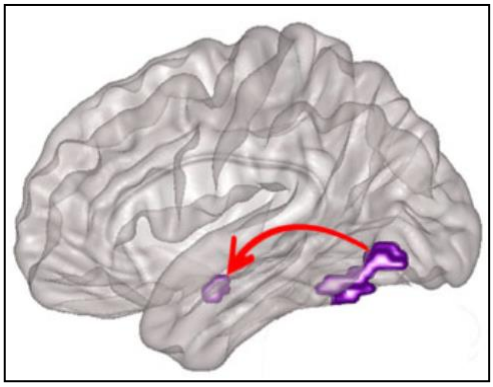

Figure.3 Feedforward activity from cortical fusiform area to subcortical area.

effective performance in MDD patients (Qiu et al., 2016). Increase in the grey matter voxel of bilateral amygdala in the brain of MDD patients was identified after ECT (Tendolkar et al., 2013). Furthermore, the increase in amygdala volume led to the feedforward activity from cortical fusiform area to the subcortical area in Fig.3 (Wang et al., 2017). The feedforward activity might enhance the neurogenesis of amygdala to result in better emotional and memory processing in ECT recipient. Moreover, ECT might also improve the social memory processing and negative emotional control since both of the amygdala and fusiform area involves in cognitive memory (Rock et al., 2014). Therefore, the feedforward activity from amygdala to fusiform area might explain the significant effect of ECT on MDD patients.

Cingulate Gyrus

Besides the changes of amygdala volume, reduction of grey matter volume in the right cingulate gyrus of MDD patients was revealed after ECT (Qiu et al., 2016). This result was compatible with a study showing the smaller right rostral-anterior cingulate volume observed in MDD patients (Hoogenboom et al., 2013). However, the brain activity of left anterior cerebellum lobe decreased while that in another side of lobes was in normal changes. This might hypothesize that ECT could bring partial improvement in the cerebellum which might lead to the partial remission of depressive symptoms after ECT (Qiu et al., 2016). Hence, ECT might involve the changes of brain activity and thereby displaying its effectiveness to reduce depressive symptoms on MDD patients.

Frontal Cortex

The decrease in global functional connectivity in left DLPFC offered great reduction in depressive symptoms in Fig.4 (Perrin et al., 2012). Such reduction also associated with other brain areas such as angular gyrus and somatosensory association cortex in Fig.5. After ECT, decrease in functional activity in these areas might be effective in restoring emotional function on MDD patients. Therefore, the reduction in the function connectivity in left DLPFC after ECT offered a certain degree of alleviating the MDD burden.

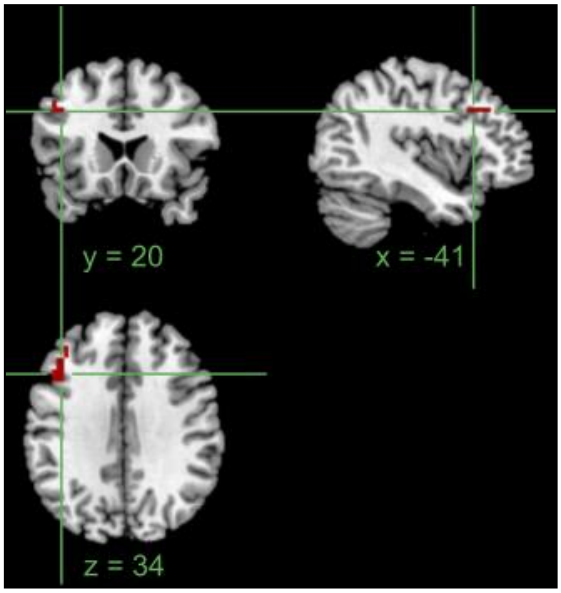

Figure.4 3D orthogonal indication of left DLPFC cluster of voxels (red).

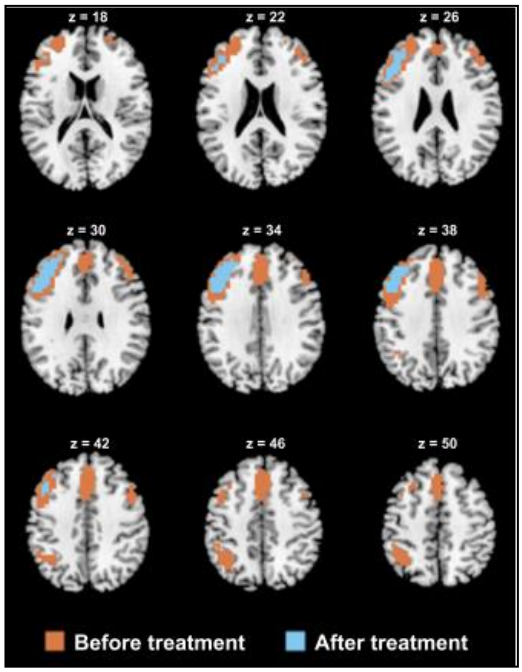

Figure.5 Functional connectivity in MDD patients before ECT (orange) and persisting connectivity after ECT (blue).

Benefits of ECT

High Cost-effectiveness

ECT is proposed to provide higher cost-effectiveness than rTMS due to its lower cost per health outcome. rTMS is a non-invasive treatment making use of magnet to stimulate targeted brain region of MDD patients while ECT generates direct current to the whole brain of MDD patients (Mishra et al., 2011). However, some studies show that the cost-effectiveness of ECT is lower than that of rTMS, which is assumed to depend on the current prevalence of MDD in the corresponding region.

ECT deserved higher cost-effectiveness than rTMS as a result of its lower cost per QALY in United States (Aziz et al., 2005). QALY is a measure of health-related quality of life relating to the life expectancy under different resource allocation through numerous health conditions (NICE., 2013). The analysis showed that ECT is more cost-effective than rTMS because ECT offered lower cost per QALY ($24,616) than that of rTMS ($57,762). It also revealed thathigh cost of rTMS might be due to the higher usage of informal care such as personal care and care outside the home by family (Aziz et al., 2005).
Moreover, we could result that ECT alone was on average more effective and less expensive than rTMS alone on MDD patients from Table.2 (Vallejo-Torres et al., 2015). These results are also in line with another result that the mean cost of rTMS (£1444) was remarkably higher than that of ECT (£1314) due to the differences of session numbers received between ECT and rTMS recipients in United Kingdom (Knapp et al., 2008).

	Cost (95% CI)	QALY (95% CI)using McSad
ECT	€16 690	0.2137
rTMS	€16 858	0.1783
rTMS followed by ECT	€20 279	0.2631
Incremental		
ECT *v.* rTMS	€−168 (€−4065 to 4294)	0.0354 (−0.0319 to 0.0912)
rTMS + ECT *v.* ECT	€3589 (€577 to 6664)	0.0494 (0.0183 to 0.1148)
ICER		
ECT *v.* rTMS		ECT alone dominates
rTMS + ECT *v.* ECT		€72 668

Table.2 Expected cost and QALY of ECT and rTMS.

However, the results above are in contrast to the statement insisting ECT had less cost-effectiveness than rTMS. It calculated that the total cost for rTMS was $57,845,347 while that was $186,359,571 for ECT (Kozel et al., 2004). It might be because of the lack of informal care costs included and the consideration of cost-utility in terms of the long-term effectiveness from ECT (Ghiasvand et al., 2015). Furthermore, Israeli citizens take further advantage of receiving ECT under the insurance coverage by Health Maintenance Organizations who are responsible of their hospitalization costs (Magnezi et al., 2016). Therefore, ECT is more cost-effective than rTMS because of its lower mean cost and more health outcomes.

Fast Remission

After ECT, higher remission and response rate are observed in MDD patients. The definition for remission is different in those studies because the recovery of MDD is hard to be quantified. Treatment-resistance in MDD is divided into 11 clinical factors including anxiety comorbidity, personality disorder, suicide ideation and social phobia (Souert et al., 2007). Hence, we could only determine the remission of ECT by using self-rating scales of MDD patients. Nevertheless, the calculation of ECT response rate might vary in different research due to its selection preference to MDD patients.

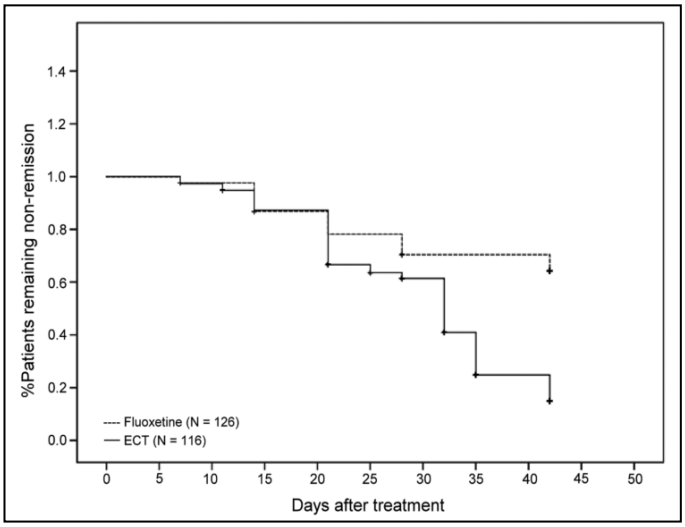

Figure.6 Time to remission to ECT and fluoxetine.

Comparing to the use of fluoxetine, which is an antidepressant to reduce depressive symptoms by blocking the reuptake channel of serotonin, ECT offered faster remission and response rate in MDD patients (Lin et al., 2017). Remission in this study was assessed by HAMD-17 and MWSAS. HAMD-17 includes 17 items with Likert scale and results in severe depression if scores over 17 (Hamilton, 1980) while MWSAS is used to assess the total function status associated with the degree of depressive disorder (Mundt et al., 2002). From Fig.6, MDD patients had significantly decreased HAMD-17 and MESAS after ECT compared with the patients with fluoxetine (Lin et al., 2017). This indicated that ECT had higher efficacy than pharmacotherapy in MDD patients due to the remarkable reduction of depressive symptoms after ECT. Furthermore, the ECT recipients (71.2%) also showed higher remission rate than the patients with fluoxetine (27.7%) from Fig.7. Response rate was defined as at least 50% reduction of the baseline HAMD-17 score which is resulted in faster response to ECT (mean time = 29.9 days) than fluoxetine uptake (mean time = 35.2 days). Pharmacotherapy with other antidepressants including lithium and selective serotonin reuptake inhibitors also revealed its 4 times slower response than ECT. ECT offered about 6 times greater likelihood of a positive response when compared to the monoamine oxidase inhibitors which inhibit the activity of monoamine oxidase to significantly reduce depressive symptoms (Pagnin et al., 2004).

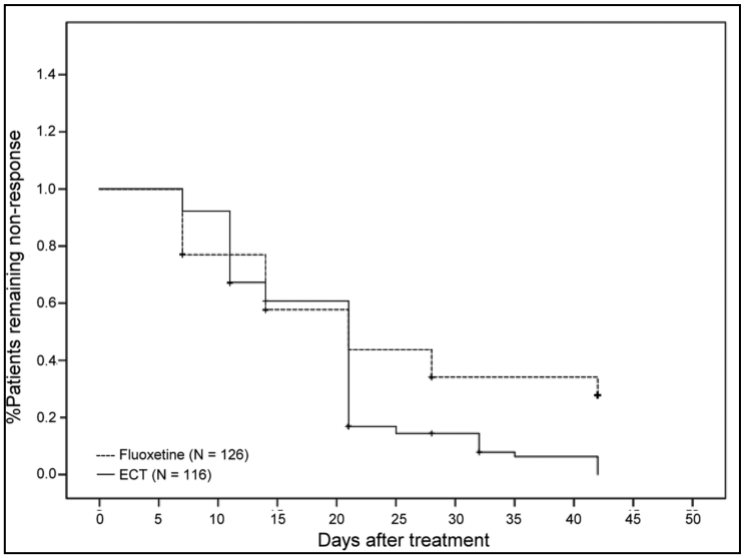

Figure.7 Time to response to ECT and fluoxetine.

Hence, ECT is suggested to show higher efficacy and faster remission than pharmacotherapy in MDD patients.

However, the response rate of ECT is suggested to be highly calculated which might lead to the wrong estimation of its fast response rate (Lin et al., 2017). Since the MDD patients usually receives 6 to 12 treatments (APA, 2001) and they would have less favorable response after 12 treatments (Waite and Easton, 2013) The calculation of ECT response rate included those MDD patients might result in the excessive high response rate. It is suggested that the variables such as sex and age which likely affect the effectiveness of ECT on different MDD patients selected should have minimized in the further research.

Effective to Special Population

It is interesting that ECT is remarkably effective to special population consisting of the elderly, pregnant and MDD patients with medical conditions due to its high efficacy and safety despite the existence of side-effects. Although ECT is specific to certain population with MDD, ECT still poses unavoidable threats to those populations.

Elderly

	Total (n = 402)	**18–45 years Young (n = 137)**	**46–64 years Middle age (n = 173)**	**65–85 years Old (n = 92)**
HAM-D-17				
	N (%)	**N (%)**	**N (%)**	**N (%)**
Responders (relative decrease ≥ 50%)	247 (61.4)	87 (63.5)	96 (55.5)	64 (69.6)
Remitters (final score ≤ 7)	118 (29.4)	43 (31.4)	48 (27.7)	27 (29.3)
	Mean (sd)	**Mean (sd)**	**Mean (sd)**	**Mean (sd)**
Baseline score	24.2 (4.3)	23.3 (4.1)	23.9 (4.3)	25.8 (4.2)
Final score	10.9 (5.3)	10.2 (4.9)	11.1 (5.2)	11.6 (6.1)
Mean change score	13.1 (6.7)	12.9 (5.9)	12.7 (6.4)	14 (8.1)

Table.3 Compasions of scores on HAMD-17 among different age groups.

ECT offers more favorable benefits due to their high medication resistance and coexisting medical conditions (Prudic et al., 1994). Medication resistance is associated with the age which means higher age results in larger medication resistance (Alexopoulos et al., 1996). Therefore, the use of antidepressants is usually not effective to the elderly with MDD (Rabheru, 2001). Moreover, although the older MDD patients also receive ECT with cardiovascular disease (Zielinski, 1993) or stroke (Murray, 1987) which increases the risks of participating in ECT, the research showed that the oldest MDD patients were still be able to safely complete the whole ECT (James, 1999). In Table.3, the older ECT recipients (8.1) scored higher mean HAMD-17 change comparing with the adolescents (5.9) and the adults (6.4) with MDD (Socci et al., 2017). It proved that ECT is more effective to the elderly with MDD due to the significant reduction of depressive symptoms. Therefore, ECT is effective to the elderly with MDD in terms of its higher efficacy and response rate.

Nevertheless, ECT posts great threats to the older MDD patients because of the induced confusion and memory impairment (Tomac et al., 1997). They are likely to have long-term retrograde amnesia and anterograde after ECT which troubled their normal daily life. For the sake of higher life expectancy of older MDD patients, they are suggested to be handled with special medical care and preliminary process including the additional monitoring and echocardiography which is a sonogram of the heart to monitor its normal functioning (Antosik-Wójcińska and Święcicki, 2016). However, a study insisted that the global cognitive function (Guy, 1976) which was measured by the score gained from the mini-mental state examination could be improved even though the retrograde amnesia and anterograde after ECT (Socci et al., 2017).

Pregnant

American Psychiatric Association proposed that ECT is a primary therapy for pregnant with MDD (APA, 1993) because ECT showed its remarkable efficacy and low risks to the third trimesters of pregnancy (Walker, 1994). Compared with medication on MDD patients, it might pose threats to both the mother and fetus. Lithium is a key chemical leading to premature labour and toxicity (Altshuler et al., 1996). The study also indicated the use of tricyclic antidepressants could induce withdrawal symptoms in neonates. Hence, it is relatively safe to apply ECY on pregnant with MDD (Miller, 1994).

However, there are still potential risks of ECT during pregnancy. the use of anticholinergic agents could lead to fetal tachycardia and gastric reflux during ECT (Diaz, 1991). It is suggested to select a better anesthetic and muscle relaxant such as succinylcholine with normal doses would not cross placenta to affect the fetal development (Moya and Kvisselgaard, 1961). Therefore, it is essential to carefully apply ECT for the pregnant with MDD.

Medical Conditions

Some MDD patients with medical conditions require cautious management of ECT to prevent the development of severe complications and mortality during or after ECT. ECT was successfully applied to the MDD patients with a brain tumor and elevated intracranial pressure (Patkar et al., 2000). Moreover, a 79-year-old MDD patient with cerebellar ischemic stroke also safely benefited through ECT (Weintraub and Lippmann, 2000). For MDD patients with intracranial vascular masses also succeeded to undergo the whole ECT without serious side-effects (Hunt and Caplen, 1998). Hence, ECT is effective to MDD patients even though they have medical conditions which significantly increase the potentials risk of ECT.

Potential risks of ECT

Memory Loss

The most concern of MDD patients is the memory loss after ECT. Anterograde amnesia and retrograde amnesia are suggested to be induced after ECT. Memory loss seriously impacts the daily life of MDD patients. However, the cognitive impairments related to ECT are limited to be short-term rather than long-term and even could be recovered afterwards.

	Pts <70 years (n = 40)		Pt ≥70 years (n = 41)		All patients	
	Pre-ECT (%) (n = 34)	Post-ECT (%) (n = 36)	Pre-ECT (%) (n = 31)	Post-ECT (%) (n = 34)	Pre-ECT (%) (n = 65)	Post-ECT (%) (n = 70)
Muscle aches/pain	17.6	30.6	35.5	17.6	26.2	24.3
Constipation	38.2	36.1	67.7	50.0	52.3	42.9
Headache	26.5	27.8	16.1	29.4	21.5	28.6
Confusion	45.5*	27.8	41.9	54.5*	43.8*	40.6*
Clumsiness	33.3*	11.1	32.3	26.5	32.8*	18.6
Blurred vision	14.7	19.4	32.3	32.4	23.1	25.7
Dry mouth	64.7	38.9	61.3	52.9	63.1	45.7
Anterograde memory impaired	44.1	61.1	54.8	47.1	49.2	54.3
Retrograde memory impaired	29.4	22.2	25.8	23.5	27.7	22.9
Palpitations	23.5	13.9	29.0	8.8	26.2	11.4
Dizziness	28.1#	27.8	45.2	20.6	36.5#	24.3
Drowsiness	50.0	33.3	29.0	32.4	40.0	32.9
Nausea/vomiting	6.1*	13.9	12.9	5.9	9.4*	10.0
Neck stiffness	20.6	13.9	9.7	11.8	15.4	12.9
Urinary retention	14.7	19.4	19.4	8.8	16.9	14.3
Urinary incontinence	5.9	2.8	9.7	0	7.7	1.4
Faecal incontinence	0	0	9.7	0	4.6	0
Bruising	23.5	19.4	16.1	29.4	20.0	24.3
Neurological dysfunction	2.9	8.3	12.9	26.5	6.2	17.1
Medical complications	5.9	5.6	9.7	5.9	7.7	5.7
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)
Total burden score	9.9 (8.6)	8.3 (6.2)	12.0 (9.7)	9.4 (7.2)	10.9 (9.2)	8.8 (6.7)

Table.4 Side-effects of ECT.

Short-term memory loss is observed in MDD patients due to the immediate anterograde amnesia and retrograde amnesia after ECT. Short-term confusion after ECT led to the immediate retrograde amnesia due to the worse post-ECT memory performance compared with pre-ECT (Meeter et al., 2011). This might be because of the sudden inability to access memory after ECT. Such results were also matched with the immediate memory loss due to the failure of word recall and recognition (Sackeim et al., 1993). From Table.4, more anterograde memory impairments were found in the post-ECT patients (54%) than the pre-ECT patients (49.2%) (Brodaty et al., 2001). Moreover, remarkable

decrease in memory recall after ECT was revealed which proved that ECT recipients had to face the immediate memory loss after ECT (Loo et al., 2008). Furthermore, MDD patients also gave rise to the deteriorated functions on immediate recall and delayed recall from Table.5 (Boere et al., 2016). Hence, ECT is concluded to have short-term memory loss on MDD patients who are failed in immediately accessing the memory.

	ECT	Control	
Immediate recall (n = 11; n = 9)			
T0	31.55 (11.0)	33.78 (8.5)	T(18) = -0.50; p = 0.62
T1	30.00 (9.3)	37.56 (11.0)	T(18) = -1.67; p = 0.11
T2	27.91 (7.7)	35.00 (13.7)	T(18) = -1.46; p = 0.16
T3	34.00 (5.4)	40.29 (6.0)	T(18) = -2.48; **p = 0.02**
Delayed recall (n = 11; n = 9)			
T0	6.5 (3.2)	6.3 (2.8)	T(18) = 0.16; p = 0.88
T1	5.3 (2.6)	7.9 (3.4)	T(18) = -1.98; p = 0.06
T2	3.5 (2.4)	7.8 (3.8)	T(18) = -3.16; **p = 0.01**
T3	6.5 (2.2)	7.7 (2.5)	T(18) = -1.15; p = 0.27

Table 5. Mean values (SD) of immediate and delayed recall.

However, ECT is opposed due to its long-term memory loss which seriously deteriorated the social acceptance of ECT (Stoudemire et al., 1995). In fact, there is still lack of evidence proving the persistent memory impairment after ECT. ECT recipients showed recovery of the original memory functioning including episodic memory, processing speed and executive functioning after 2 weeks of ECT (Semkovska and McLoughlin, 2010). Moreover, retrograde amnesia on MDD patients cannot be found after 3 months of ECT (Meeter et al., 2011). This is also supported by a study showing that memory loss of MDD patients was only limited to the first 3 days after ECT (Berg, 2011). Furthermore, higher scores from Rey auditory verbal learning test 2 months after ECT (91.0) showed better memory functioning than that before ECT (88.3) (Porter et al., 2008). Hence, long-term memory loss after ECT is not solid because it is limited within a short period of time after ECT and gradual recovery of memory loss is also observed after a certain time of ECT.

Relapse

Relapse means the subsequent return of depressive symptoms after ECT (Jelovac et al., 2013). Relapse is always a key side-effect after ECT (Sackeim, 1994). Prolonged remission of MDD is required after discontinuation of ECT (Kellner, 2013). It is important to prevent relapse after ECT to increase the social acceptance of ECT. However, a widely effective therapy to prevent relapse after ECT has not yet been determined.

Although high remission rate and fast response after ECT are reported in the part of "Benefits of ECT ", early relapse after ECT still poses threats to MDD patients (Sackeim et al., 2001). According to a meta-analysis in 2013, continuous increase in the relapse rates after ECT was observed over time from Fig.8 (Jelovac et al., 2013). It also resulted in the higher relapse rate within the first 6 months after ECT. Moreover, serious relapse after ECT also led to the drop out of ECT by MDD patients (Kellner et al., 2006). This showed that relapse after ECT deteriorated the willingness to continuous ECT by MDD patients. Furthermore, a case study also showed that a 96-year-old female MDD patient with severe aortic stenosis experienced the relapse after ECT which gave rise to the rearrangement of ECT sessions (Cristancho et al., 2008). Therefore, it is important to investigate the optimal therapy to prevent relapse after ECT.

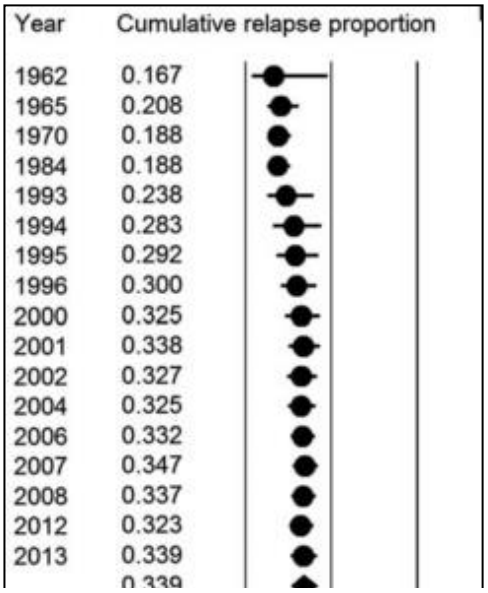

Figure.8 A cumulative analysis of relapse rates after 6 months of ECT.

To prevent the relapse after ECT, many research suggested that it could be prevented by continuation pharmacotherapy. The early findings showed that one-third of ECT recipients had maintained improvement with continuation antidepressants at least 4

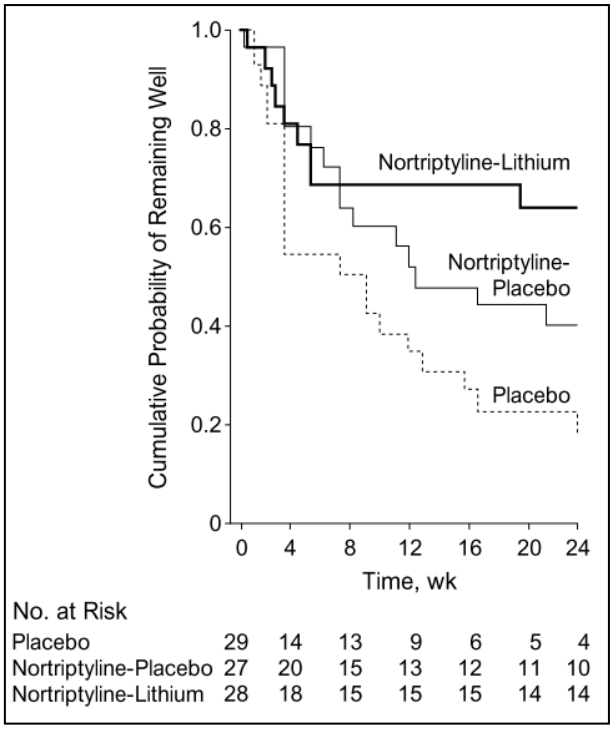

Figure.9 Kaplan-Meier Esitmates of patients with nortriptyline-lithium, nortriptyline-placebo and placebo alone.

months after ECT (Riddle and Scott, 1995). Moreover, nortriptyline-lithium combination treatment is significantly effective to relapse after ECT comparing with the placebo and nortriptyline alone (Sackeim et al., 2001). From Fig.9, it illustrated that higher proportion of MDD patients remained well under continuation nortriptyline-lithium combination treatment than the nortriptyline-placebo treatment and the placebo alone. Furthermore, this result is also in line with another research showing that lithium treatment offered lower risk of relapse after ECT (Itagaki et al., 2017). However, no solid evidence could prove which antidepressant would offer the highest effectiveness in preventing relapse after ECT (Jelovas et al., 2013). Hence, optimal pharmacotherapy has to be further confirmed to prevent the relapse after ECT.

Complications

ECT could induce many complications such as physical, cardiovascular and pulmonary complications (Lippmann et al., 1993; Cristancho et al., 2008). Complications after ECT might be due to the anesthesia and muscle relaxant applied to MDD patients before ECT (Trakada, 2017). It is uncommon to show cardiovascular problems and mortality after ECT (Cristancho, 2008).

Physical Complications

From Table.6, Physical complications after ECT include scalp burn and post-ECT urinary stasis. Post-ECT urinary stasis might be due to the anticholinergic medication which is a frequent anesthetic to ECT recipients. However, it is suggested to be solved by the usage of bethanechol reversing cholinergic blockade (Lippmann et al., 1993).

	Instances	*Number of Patients*
Side Effects		
Agitation	7	4
Hypertension	8	5
Muscular discomfort	4	4
Cutaneous eruption	2	1
Tongue pain	1	1
Profound confusion	3	3
Nausea while gaining IV access	2	2
Physical Complications		
Posttreatment urinary stasis	1	1
Scalp burn	1	1
Deviations From Protocol		
Bite block not inserted	5	4
Succinylcholine given before anesthesia	2	2
Mechanical Difficulties		
Trouble gaining IV access	3	3
Headband loosened	2	2
Medicinal Problems		
Low potency of methohexital	1	1
Inappropriate dose of methohexital	1	1
Inappropriate dose of succinylcholine	2	2
Imprecise Seizure Determinations		
Seizure time undetermined clinically	54	23
Seizure time undetermined electroencephalographically	18	13

Table.6 Technical difficulties during ECT.

Confusion

Mild confusion after ECT is a common complication among those side-effects (Cristancho et al., 2008). This might be due to the insufficient separation of the time intervals between ECT sessions and prolonged seizure (Lippmann et al., 1993). It is notable that increased chance of confusion after ECT could be observed in the older MDD patients (Cristancho et al., 2008). However, the acute confusional states after ECT are difficult to bring about severe threats to MDD patients (Pogarell et al., 2005).

Cardiovascular Complications

Cardiovascular events after ECT could lead to mortality in MDD patients (Stoudemire et al., 1990). In a case of a 45-year-old female with negative family history for cardiac disease and smoking habit, acute myocardial infarction was caused by increasing releases of cardiac enzymes after 15 minutes of ECT (Cristancho et al., 2008). Generally, mortality is estimated to be 1 in 10000 patients or 3 to 4 in 100000 ECT sessions (Abrams, 1992)). Such mortality usually associates with the cardiac complications induced by the use of anethersitc and muscle relaxant (Rabheru, 2001).

Pulmonary Complications

A case reported the pulmonary edema after ECT in MDD patients with epileptic seizures (Stoudemire et al., 1990). This study also suggested that the increase in pulmonary blood flow could induce the neurogenic pulmonary edema after ECT. Pulmonary hypertension after ECT is also common in the MDD patients with high cardiovascular morbidity (Cristancho et al., 2008).

Other complications

Common complications such as headache, muscle pain and discomfort after ECT could be due to the use of anesthetic, muscle relaxant and prolonged seizure (Lippmann et al., 1993). A case of a 50-year-old man also experienced transient hemiparesis which led to difficulty in focal weakness in either body side (Liff et al., 2013). Rare complications of galactopoiesis and hyperprolactinemia after ECT are also firstly reported in a case of 48-year-old man with MDD (Tokutsu, 2012).

Summary points

ECT is the most effective treatment on the treatment-resistant patients under the changes of structures and functions in brain. The underlying mechanisms of ECT are still unclear. ECT brings many benefits to MDD patients. However, ECT also leads to various side-effects on MDD patients.

The underlying mechanisms of ECT involve the alternations in neurochemical levels, structural and functional changes of brain. ECT involves sensitizing different serotonin receptors to reduce depressive symptoms. The variations in Glx and NAA levels are also important to regulate emotional control and memory processing. Cre is a key chemical for energy metabolism which might need further study on its function on treatment MDD.

ECT benefits MDD patients due to it high cost-effectiveness, efficacy and safety. ECT is more cost-effective than rTMS and pharmacotherapy because of its lower mean cost and higher QALY. Fast remission and response rate to ECT also benefit MDD patients in alleviating depressive symptoms. Interestingly, ECT effectively works to special population including the elderly, pregnant and MDD patients with medical conditions.

However, ECT might lead to adverse effects including memory loss, relapse and complications on MDD patients. They show difficulties in immediate recall and delayed recall due to the short-term memory loss after ECT. Nevertheless, no permanent memory loss has been confirmed after ECT. Relapse after ECT is also observed but it could be rehabilitated with the continuation therapies after ECT. Short-term complications could also be recovered afterwards. Complications related to cardiovascular system might lead to mortality after ECT. It is hoped that MDD patients should depend on their physical conditions and financial affordability for the decision-making to ECT acceptance.

Future issues

Future research on the underlying mechanisms of ECT on MDD is important to explore its higher effectiveness and efficacy on MDD patients. Moreover, further analysis on the potential risks after ECT especially the memory loss and the prevention of complications is needed to increase social recognition of ECT. Furthermore, future research on the optimal seizure threshold of ECT is required to maximize the power of ECT to offer higher effectiveness on MDD patients.

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Tables with titles and Figures with legends

Table.1	Different subtypes of 5-HT receptors are involved in the alterations in the serotonergic systems including cAMP production and G-protein binding.
Table.2	Less cost and higher QALY are resulted in ECT alone than rTMS alone.
Table.3	Comparison of scores on HAMD-17 among different age groups show that ECT is more effective to the elderly MDD patients in terms of reducing depressive symptoms.
Table.4	Side-effects of ECT lead to the burden of MDD patients.
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Table.6	Technical difficulties during ECT and side-effects of ECT.
Figure.1	Longitudinal changes in HAMD scores and Glx concentration in left hippocampus and sgACC.
Figure.2	Changes of baseline NAA concentration and HAMD scores in dACC.
Figure.3	Feedforward activity from cortical fusiform area to subcortical area which is colored in purple.
Figure.4	3D orthogonal indication of left DLPFC cluster of voxels colored in red showing its reduction of function.

Figure.5	Functional connectivity in MDD patients before ECT which is colored in orange while the persisting connectivity after ECT is in blue. Changes of brain activity could be observed.
Figure.6	Larger portion of MDD patients remaining non-remission in fluoxetine group than that of ECT group which shows faster remission.
Figure.7	Larger portion of MDD patients remaining non-response in fluoxetine group than that of ECT group which shows higher response rate.
Figure.8	A cumulative analysis of relapse rates after 6 months of ECT illustrates the higher risk in the first 6 months after of ECT.
Figure.9	Kaplan-Meier Esitmates of patients with nortriptyline-lithium, nortriptyline-placebo and placebo alone indicate the most effective nortriptyline-lithium combination on MDD remission.