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ELECTROCONVULSIVE THERAPY FOR YOUNG MINDS: A SOLUTION FOR MENTAL DYSFUNCTION OR A PROBLEM FOR COGNITION? A SYSTEMATIC REVIEW AND META-ANALYSIS

by
NOUR FOUAD DABBOUSSI

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ABSTRACT
OF THE THESIS OF

Nour Fouad Dabboussi for Master of Science
Major: Neuroscience

Title: Electroconvulsive Therapy For Young Minds: A Solution For Mental Dysfunction Or A Problem For Cognition? A Systematic Review And Meta-Analysis

Introduction

Electroconvulsive therapy (ECT) is a medical treatment that involves brief electrical stimulation of the brain of patients, suffering from schizophrenia and severe major depression disorder, who otherwise would not respond to conventional treatments. The therapeutic effectiveness of ECT is well evident in current medical practice. However, adverse side effects, that include cognitive impairment, were reported following short and long-term exposure to ECT. The present study aims to address the question of whether ECT causes learning and memory deficits in the pediatric population, as the brain of children and adolescents is still undergoing development.

Methods

A systematic review and a meta-analysis were conducted to investigate the effect of ECT on memory functions, focusing on studies that used verbal learning test as an outcome in pediatric patients. Our search strategy, using Medline, Embase, Cochrane library, Web of science and Google scholar, yielded a total of 11 studies, which include 2 case reports, 2 case series, 7 cohort studies and no clinical trials. Criteria for inclusion were (1) Population of pediatric patients aged below 19 (2) Patients being subjected to ECT (3) Study comparator (before and after ECT (self-control) or patients not receiving ECT) and (4) Cognitive performance of patients being assessed objectively before and after ECT. The data were extracted directly from the selected articles and organized in standardized tables by one investigator and verified by a second. The I Square Test assessed the heterogeneity of the studies, using Revman software.

Results and Conclusion

This is the first meta-analysis investigating the effects of ECT on cognitive outcomes in the pediatric population. Our data analysis revealed that cognitive functions in children and adolescents, assessed with the California Verbal Learning test, were not significantly impacted by ECT. While this procedure could have adverse effects on children on the short term, it is generally considered a safe procedure for pediatric cases, with no deleterious cognitive effects on the long term.

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CHAPTER 1

INTRODUCTION

1.1. A Brief History of Electroconvulsive Therapy:

Electroconvulsive therapy (ECT) was first introduced in the 1930s in Rome as a medical procedure for the treatment of certain psychiatric disorders. It involves a brief electrical stimulation of the brain that elicits an epileptic seizure while the patient is under anesthesia (Rudorfer et al., 2003). Because this intrusive method had caused many serious side effects, it was considered the most controversial interventions in the history of medicine (Gazdag and Ungvari, 2019).

Treatment of severe psychiatric conditions with epileptic seizures was a common practice in the twentieth century. Prior to use of ECT, chemical provocation of seizures was introduced by Meduna (Fink, 2009) to treat schizophrenic patients. In 1937, Cerletti was the first scientist who used an electroshock apparatus to provoke consecutive, reliable epileptic seizures in animals (Fink et al., 1985, Oral et al., 2008). After identifying the parameters of a safe electric stimulus, together with Lucio Bini, he performed the first electric seizure induction in a psychotic patient named Enrico X on April 11, 1938 (Gazdag and Ungvari, 2019).

Other types of physical shock therapy had also been tested, but they were all abandoned in favor of ECT, which remains the only somatic therapy from the 1930s still in widespread use today. (Fink et al., 1985, Oral et al., 2008).

The present-day use of ECT has been shown to be safe and efficacious. The procedure has greatly improved and is performed in combination with EEG, ECG, and EMG to monitor its effect on patients. It's administered with a frequency of waves

varying between 30–70 cycles/sec and pulse width of 0.5, 1.0, or 2.0 msec for a stimulus duration varying between 0.2 and 8.0 sec. The energy delivered is 25–300 mcu, depending partially on the resistance of the related tissues. The location of electrodes is crucial for the treatment outcome. Bilateral electrode placement is standard and is chosen when efficacy and immediate response are required. However, unilateral electrode placement, although less effective, may be preferred when the potential effects on memory and cognition are of primary concern. Delivery on the non-dominant side (unilateral non-dominant ECT) mitigates its effects on memory (Rasmussen et al., 2002, Oral et al., 2008).

1.2. Psychotherapeutic use in adult and pediatric population

Recent literature has focused on ECT as an add-on treatment for patients with treatment-resistant schizophrenia, including clozapine-resistant patients. Due to their adverse side effects, patients are referred to ECT only when they fail to respond to multiple medications and psychotherapy. (Kellner et al., 2020; Li et al., 2020). In addition, ECT is recommended for adolescents with severe psychiatric symptoms (eg, catatonia, psychosis, mania), or severe, recalcitrant depression and suicidality, particularly when hospitalization and psychotherapy prove to be inadequate (Puffer et al., 2016).

1.2.1. Schizophrenia

Schizophrenia is a psychiatric disorder characterized by psychotic symptoms of hallucinations, delusions, and disorganized speech as well as by negative symptoms such as low motivation and reduced expressiveness, and cognitive deficits involving

impaired executive functions, memory, and speed of mental processing. Nearly 1% of the world population is affected by the disorder considered among the top 10 global causes of disability (Marder et al., 2019).

Schizophrenia is one of the most common indication for ECT worldwide. It treats acute exacerbations of psychotic illness and mainly positive symptoms; it is less effective for negative symptoms which include at least two features (diminished expression and anhedonia/asociality) that distinguish them from positive symptoms (Blanchard and Cohen, 2006, Carra et al, 2019).

"Moderate- quality evidence indicates that relative to standard care, ECT has a positive effect on medium term clinical response for people with treatment-resistant schizophrenia." (Sinclair et al., 2019, Kellner et al., 2020; Li et al., 2020). Nevertheless, the totality of evidence has not been convincing enough either for the US FDA or for the Cochrane Database to make ECT a standard treatment.

1.2.2. Depressive disorders

The APA (APA, 2001) guidelines support the use of ECT in a major depressive episode (unipolar, bipolar, and mixed). The benefits of ECT have been shown to exceed those of the standard medications used for treatment-resistant bipolar depression (Li et al., 2020).

In general, the therapy has been shown to be effective in all types of depression, especially when associated with one of the following features (APA, 2001): (a) acute suicidality with a considerable risk of acting out suicidal thoughts; (b) psychotic features; (c) rapidly deteriorating physical state due to complications of depression, such as poor oral intake; (d) history of poor response to medications; (e)

history of good response to ECT; (f) patient preference; (g) risks of standard antidepressant treatment overcoming the risks of ECT and (h) catatonia. Infrequent shifts from depression to mania may also take place during the course of ECT; however, the treatment may continue because ECT also has anti-manic properties (Lamprecht et al., 2005, Oral et al., 2008).

1.2.3. Mania

Mania is a psychological disorder with a multidimensional structure in which hyperactivity, increased speech and thought disorder are key features. A systematic review by Riis and Videbech, showed a marked effect of ECT on mania with response/remission rates between 56 and 100%. The randomized controlled trials, which compared ECT to pharmacotherapy for mania, have highlighted the advantage of ECT over psychotropic drugs (Riis and Videbech, 2015).

When mixed episodes are more resistant to pharmacological treatment, (Shim et al., 2018, Swan, 1995, Elias et al., 2021), ECT has often been considered an effective solution for this subgroup. ECT is also effective in delirious mania, which is now recognized as a life-threatening neuropsychiatric syndrome characterized by manic symptoms, psychosis, and disorientation (Jacobowski et al., 2013, Elias et al., 2021). It accounts for 15% to 35% of acute manic presentations (Elias et al., 2021).

1.2.4. Catatonia

Catatonia is a psychomotor syndrome that accompanies several psychiatric and medical conditions. Psychomotor signs range from stupor to agitation, and include

characteristic features such as continuous repetition of stereotyped phrases (verbigeration) and waxy flexibility.

Irrespective of etiology or psychiatric comorbidity, catatonia typically responds very well to ECT where it may be used as a first line of treatment, or more commonly, after benzodiazepines have been shown to be inadequately helpful (Dhossche and Withane, 2019).

Moreover, even if benzodiazepines have a remission rate of approximately 70% and regardless of the cause or the clinical manifestations, there is no true alternative treatment to ECT as a second-line treatment, especially in severe cases with life-threatening conditions, such as malignant catatonia, with a mortality rate of approximately 50% if not treated (Leory et al., 2018).

1.2.5. Other diseases and disorders

ECT is also effectively used in the treatment of a number of other conditions such as Parkinson's disease, neuroleptic malignant syndrome, status epilepticus and obsessive-compulsive disorder (Boonen et al., 2020; Kellner et al., 2020; Zwil and Pelchat, 1994).

In children, ECT is currently used infrequently but remains an option to consider for patients who are resistant to first and second-line of pharmacologic regimens, as well as for those with urgent need for a rapid remission (Benson and Seiner, 2019; Morales et al., 2005).

In adults, ECT has been shown to be effective in the treatment of severe mood disorders, particularly unipolar depression and bipolar disorder, catatonia and, to a

lesser degree in schizophrenia. It has also been used in autism and Tourette's syndrome with onset in childhood or adolescence (Shoirah and Hamoda, 2011).

1.3. Mechanism of action of ECT

Several studies have been conducted to elucidate the mechanisms of ECT action on the brain. Major pre-clinical studies have shown that electroconvulsive stimulation (ECS), induces neurogenesis, to compensate for the loss of neurons and glial cells resulting from stress-induced damage and depression. (Theilmann et al., 2014; Li et al., 2020). On the other hand, pre-clinical studies have provided evidence about the modulatory effect of ECT on brain metabolism and related neural signaling, particularly dopamine. Tsen et al., have shown that repeated ECS enhances dopamine activity in the substantia nigra pars compacta, and improves dopamine-induced synaptic potentiation, an effect linked to the antidepressant action of ECT (Tsen et al., 2013, Kobayashi et al., 2017, Biedermann et al., 2021).

Moreover, ECT has proved to improve depressive behaviors through modulation of glutamate signaling. This was evident in the study by Dong et al., in which ECT was shown to decrease glutamate and up-regulate NMDA-NR2B expression in depressed rats. (Dong et al., 2010).

There are several other cellular mechanisms by which ECT can exert its therapeutic effect; most important among these are the decrease of α2-adrenoceptors and neuroplastic changes in the somatostatin system (Olesen et al., 2018, Lillethorup et al., 2014), reduction of muscarinic cholinergic number in the cerebral cortex (Lerer, 1985), enhancement of serotonergic neurotransmission, activation of the mesocorticolimbic dopamine system (Baldinger et al., 2014), attenuation of

microgliosis and astrogliosis in the hippocampus (Limoa et al., 2016), and an increase in ATP-directed microglial process motility (Sepulveda-Rodriguez et al., 2019).

Electroconvulsive stimulation can also increase the concentrations of NGF in the frontal cortex and concentrations of BDNF in the hippocampus, and striatum while decreasing GDNF, indicating that neurotrophic factors play a role in the mechanism of action of ECS (Angelucci et al., 2002). Interestingly, on a macroscopic level, electroconvulsive shock restores the lowered coverage of brain blood vessels by astrocytic endfeet and ameliorates depressive-like behavior in rats (A. Azis et al., 2019).

In addition to this direct effect, ECS has also been shown to influence gene expression as a mechanism underlying some of its therapeutic and adverse side effects. Ndrg2 expression in the frontal cortex, may be decreased after antidepressant treatment and ECT suggesting that it may be associated with treatment-induced adaptive neural plasticity in the brain, a chronic target of antidepressant action (Takahashi et al., 2005). VEGF, VEGFR2, components from mTORC1 pathway and Brd1 gene mRNA were all upregulated by repeated ECS, indicating their involvement (Elfving et al., 2002, Fryland et al., 2012).

Like animal studies, investigations with human subjects has been also performed. A study by Wang and colleagues showed that in major depressive disorder patients who received previous medications, ECT enhances the feedforward cortical-subcortical connectivity from the fusiform face area to amygdala. (Wang et al., 2017).

A subsequent study by the author has indicated that ECT may induce brain plasticity reflected by grey matter volume increase in patients with schizophrenia receiving antipsychotic medications in limbic areas like the parahippocampal gyrus/hippocampus by different mechanics from those induced by antipsychotic

medications and this may ameliorate the positive psychotic symptoms of patients suffering from schizophrenia (Wang et al., 2019).

Takamia and colleagues have similarly showed that a volume increase in dentate gyrus CA4 region is induced by ECT and correlated with clinical remission for patients with major depressive disorder and concluded that neuroplastic change in the CA4/DG might be at the origin of some of the short-term antidepressant effects of ECT (Takmiya et al., 2019).

1.4. ECT adverse effects

Common ECT adverse effects are commonly multifactorial, mostly occurring during or shortly after the ECT session when patients may suffer from dry mouth, nausea, headache, and myalgia.

1.4.1. Cognitive effects of ECT

The cognitive effects of ECT include an immediate post-procedure confusional state mainly related to the seizure, mostly subacute attention and executive problems, anterograde amnesia, and retrograde amnesia (Andrade et al., 2016).

ECT also is shown to provoke anterograde amnesia, a temporary functional memory deficit, which may become progressively more pronounced over a course of ECT. It resolves within one or two weeks following completion of the acute course of ECT and is the reason for restricting cognitively demanding work in patients.

It also causes retrograde amnesia manifested by mostly forgetting recent events, which occurred during the time of the ECT. Spotty memory loss from past months or years can occur (Weiner, 2017).

Several reviews and/or meta-analyses on cognitive effects of ECT concluded that the most cognitive deficits are transient and accounts for severe, permanent memory loss that are difficult to confirm objectively (Kellner et al., 2020).

In this regard, a systematic review and meta-analysis on the objective performances associated with ECT, Semkovka and colleagues have showed that cognitive problems associated with ECT mainly resolve after the first 3 days post-treatment and that processing speed, working memory, anterograde memory, and some aspects of executive function were enhanced beyond baseline levels when tested 15 days following ECT (Semkovska and McLoughlin, 2010).

Similarly, Lima and colleagues in their systematic review about ECT use in adolescents have concluded that it achieves high remission rates, and presents few and relatively non-problematic adverse effects (Lima, 2013).

A more recent study by Laundry and colleagues has asserted that while the cognitive side effects are the main concern for patients and ECT clinicians, most patients will not experience long-term cognitive deficits (Laundry et al., 2020).

Interestingly, Schat and colleagues conducted a study about the age of patients and its relation to cognitive side effects of ECT and demonstrated that during ECT follow-up, the improvement in semantic memory after its alteration was greater in older patients (Schat et al., 2007).

Therefore, even though ECT is a fast, safe, and life-saving treatment modality, it is rarely recommended for children and adolescents given the long-term adverse effects of ECT (Bilginer and Karadeniz, 2019). Until this day, there is no systematic or prospective studies discussing the risks and benefits of the use of ECT in adolescents. Most of the publications in this field remain in the form of case reports or case series.

More importantly, it is imperative that clinicians exercise special caution when prescribing therapies with potential cognitive side effects, particularly for children and adolescents, whose brain is still under development. A new and safer method is needed to alleviate the psychiatric symptoms exhibited in the pediatric population at this critical age period.

1.4.2. Seizures

Adverse effects related to seizure include prolonged seizures (>180 seconds) that occur in 1% to 2% of ECT-treated patients (Whittaker et al., 2007); such seizures favor the post-ECT confusion and memory impairment.

Less commonly, patients experience nonconvulsive and focal tardive seizures in the post-ECT recovery period. These prolonged or tardive seizures can, in rare cases, persist as convulsive or nonconvulsive status epilepticus reflected as unexplained abnormalities in mental state and behavior post-ECT (Cristancho et al., 2008).

Prolonged seizures and status epilepticus are more likely in patients with medical conditions or who are on medications that lower the seizure threshold. However, when ECT was resumed after removal of the suspected predisposing agent (eg, antibiotics), there were no further complications. ECT, by itself, raises the seizure threshold and so is not epileptogenic (Andrade et al., 2016).

1.4.3. Cardiovascular and respiratory problems

Cardiovascular problems, the most common cause of morbidity and mortality with

ECT, decreased in numbers after following continuous patient monitoring, and improving anesthesiological technique (Rabheru, 2001).

In fact, stimulation of vagal nuclei after the electric stimulation may result in transient asystole. ECT may cause transient ECG change as well, which are more serious in patients with cardiac illness (Rabheru, 2001).

Regarding ECT respiratory complication, they may manifest in pneumonitis, neurogenic pulmonary edema, and pulmonary embolism caused by aspiration (Andrade et al., 2016).

1.5. Objective

The first objective of this study is to systematically review the literature and provide evidence pertaining to the adverse effect of ECT on cognitive functions in the pediatric population.

A second objective is to perform a meta-analysis of the effect of ECT on verbal learning in our population of interest. Verbal learning is defined, following the dictionary of the American Psychological Association (APA), as “The process of learning about verbal stimuli and responses, such as letters, digits, nonsense syllables, or words.” (APA dictionary of psychology).

CHAPTER 2

METHODS

2.1. Protocol Registration

We prospectively submitted the systematic review protocol for registration on PROSPERO (CRD42020218692) which is an international database of systematic reviews registered prospectively with a health related outcome aiming to provide a comprehensive listing of systematic reviews registered at start point to help avoid duplication and reduce opportunity for reporting bias (Page et al., 2018).

2.2. Search Strategy

MedLine,Embase and Google Scholar were searched on 9 February 2020 and Cochrane CENTRAL and Web of Science on 26 January 2020. A thorough search strategy was built for each of the mentioned databases with the supervision of a specialized librarian. The strategy includes Mesh and keywords of concepts related to ECT, cognition and age groups of children and adolescents.

- **Medline search strategy was:**

1 psychiatric somatic therapies/ or convulsive therapy/ or electroconvulsive therapy/ or electric stimulation/ or electroshock/ or shock treatment/

2 (((Therap* or treatment) adj2 ((psychiatric adj2 somatic) or electroshock or (electr* adj2 shock) or (electr* adj2 convuls*) or electroconvuls* or shock? or convuls* or (convuls* adj2 shock?))) or elelctrotherapy or (electric* adj2 stimulation*) or electroplexy).ti,ab.

3 1 or 2

4 cognition/ or comprehension/ or executive function/ or learning/ or imprinting, psychological/ or memory/ or exp memory, long-term/ or mental recall/ or recognition, psychology/ or retention, psychology/ or spatial memory/ or overlearning/ or problem-based learning/ or problem solving/ or spatial learning/

5 ((cognitive adj2 (function? or task? or thinking)) or understand* or comprehen* or train* or (association * adj2 concept*) or (memor* adj2 (episodic or (long adj2 term) or spatial or anterograde or remote or event)) or (mental adj2 recall) or recogni* or (learning adj2 ((problem adj based) or spatial or verbal)) or (knowledge adj2 aquisition) or overlearn* or (over adj2 learn*) or (problem* adj1 solving)).ti,ab.

6 4 or 5

7 adolescent/ or exp child/ or infant/ or infant, newborn/

8 (child* or infan* or newborn? or adolescen* or toddler? or juvenil?e? or junior? or young? or youth? or teen* or bab* or youngster? or nenonate? or (little adj2 (m?n or wom?n or boy* or girl*))).ti,ab.

9 7 or 8

10 3 and 6 and 9

- **Embase search strategy was:**

1 'convulsive therapy'/de OR 'electroconvulsive therapy'/de OR 'electrotherapy'/de

2 electroplexy:ti,ab,kw OR ((treatment$ NEAR/2 convuls* NEAR/2 shock$):ti,ab,kw) OR ((therap* NEAR/2 convuls* NEAR/2 shock$):ti,ab,kw) OR ((treament$ NEAR/2 convul*):ti,ab,kw) OR ((therap* NEAR/2 convul*):ti,ab,kw) OR ((treament$ NEAR/2 shock$):ti,ab,kw) OR ((therap* NEAR/2 shock$):ti,ab,kw) OR ((treatment$ NEAR/2 electro NEAR/2 convuls*):ti,ab,kw) OR ((therap* NEAR/2 electro NEAR/2 convuls*):ti,ab,kw) OR ((treatment$ NEAR/2 electric NEAR/2

convuls*):ti,ab,kw) OR ((therap* NEAR/2 electric NEAR/2 convuls*):ti,ab,kw) OR ((treatment$ NEAR/2 electric NEAR/2 shock$):ti,ab,kw) OR ((therap* NEAR/2 electric NEAR/2 shock$):ti,ab,kw) OR ((treatment* NEAR/2 electroshock$):ti,ab,kw) OR ((therap* NEAR/2 electroshock$):ti,ab,kw) OR ((treatment* NEAR/2 psychiatric NEAR/2 somatic):ti,ab,kw) OR ((therap* NEAR/2 psychiatric NEAR/2 somatic):ti,ab,kw)

3 #1 OR #2

4 'cognition'/de OR 'comprehension'/de OR 'executive function'/de OR 'imprinting (psychology)'/de OR 'memory'/de OR 'long term memory'/exp OR 'learning'/de OR 'recognition'/de OR 'spatial memory'/de OR 'overlearning'/de OR 'problem based learning'/de OR 'problem solving'/de OR 'spatial learning'/de

5 (understading*:ti,ab,kw OR comprehen*or:ti,ab,kw) AND training*:ti,ab,kw OR recognit*:ti,ab,kw OR retention:ti,ab,kw OR ((problem NEAR/2 solving):ti,ab,kw) OR ((over NEAR/2 learning):ti,ab,kw) OR ((knowledge NEAR/2 acquisition):ti,ab,kw) OR ((learning NEAR/2 verbal):ti,ab,kw) OR ((learning NEAR/2 spatial):ti,ab,kw) OR ((recall NEAR/2 phenomenon):ti,ab,kw) OR ((mental NEAR/2 recall):ti,ab,kw) OR ((event NEAR/2 memory):ti,ab,kw) OR ((remote NEAR/2 memory):ti,ab,kw) OR ((anterograde NEAR/2 memory):ti,ab,kw) OR ((spatial NEAR/2 memory):ti,ab,kw) OR ((episodic NEAR/2 memory):ti,ab,kw) OR ((long NEAR/1 term NEAR/2 memory):ti,ab,kw) OR ((association$ NEAR/2 concept$):ti,ab,kw) OR ((cognitive NEAR/2 thinking):ti,ab,kw) OR ((cognitive NEAR/2 task$):ti,ab,kw) OR ((cognitive NEAR/2 function$):ti,ab,kw)

6 #4 OR #5

7 'adolescent'/de OR 'juvenile'/de OR 'child'/exp OR 'infant'/de

8 ((little NEAR/2 (m$n OR wom$n OR boy* OR girl*)):ti,ab,kw) OR child*:ti,ab,kw OR infan*:ti,ab,kw OR newborn$:ti,ab,kw OR adolescen*:ti,ab,kw OR toddler$:ti,ab,kw OR juvenil$e$:ti,ab,kw OR junior$:ti,ab,kw OR young$:ti,ab,kw OR youth$:ti,ab,kw OR teen*:ti,ab,kw OR bab*:ti,ab,kw OR youngster$:ti,ab,kw OR nenonate$:ti,ab,kw

9 #7 OR #8

10 #3 AND #6 AND #9

Some grey literature sources were searched electronically on 28 January.

Additional articles were included from references of previous systematic reviews on electroconvulsive therapy and cognition as well other relevant studies. We did not limit our search by language.

- **Cochrane Library search strategy was:**

#1 MeSH descriptor: [Convulsive Therapy] this term only

#2 MeSH descriptor: [Electroconvulsive Therapy] this term only

#3 MeSH descriptor: [Psychiatric Somatic Therapies] this term only

#4 MeSH descriptor: [Electric Stimulation] this term only

#5 MeSH descriptor: [Electroshock] this term only

#6 {OR #1-#5}

#7 (Electroplexy OR (treatment? NEAR/2 convul*) OR (therap* NEAR/2 convul*) OR (treatment? NEAR/2 shock?) OR (therap* NEAR/2 shock?) OR (treatment? NEAR/2 electric NEAR/2 convuls*) OR (therap* NEAR/2 electric NEAR/2 convuls*) OR (treatment? NEAR/2 electric NEAR/2 shock?) OR (therap* NEAR/2 electric NEAR/2 shock?) OR (treatment? NEAR/2 electroshock?) OR (therap* NEAR/2

electroshock?) OR (treatment? NEAR/2 psychiatric NEAR/2 somatic) OR (therap* NEAR/2 psychiatric NEAR/2 somatic)): ti,ab,kw

#8 {OR #6-#7}

#9 MeSH descriptor: [Comprehension] this term only

#10 MeSH descriptor: [Executive Function] this term only

#11 MeSH descriptor: [Learning] this term only

#12 MeSH descriptor: [Imprinting, Psychological] this term only

#13 MeSH descriptor: [Memory] this term only

#14 MeSH descriptor: [Memory, Long-Term] explode all trees

#15 MeSH descriptor: [Recognition, Psychology] this term only

#16 MeSH descriptor: [Retention, Psychology] this term only

#17 MeSH descriptor: [Spatial Memory] this term only

#18 MeSH descriptor: [Overlearning] this term only

#19 MeSH descriptor: [Problem-Based Learning] this term only

#20 MeSH descriptor: [Problem Solving] this term only

#21 MeSH descriptor: [Spatial Learning] explode all trees

#22 {OR #9-#21}

#23 (understading* OR comprehen* OR training* OR recognit* OR retention OR (problem NEAR/2 solving) OR (over NEAR/2 learning) OR (knowledge NEAR/2 acquisition) OR (learning NEAR/2 verbal) OR (learning NEAR/2 spatial) OR (recall NEAR/2 phenomenon) OR (mental NEAR/2 recall) OR (event NEAR/2 memory) OR (remote NEAR/2 memory) OR (anterograde NEAR/2 memory) OR (spatial NEAR/2 memory) OR (episodic NEAR/2 memory) OR (long NEAR/1 term NEAR/2 memory)

OR (association? NEAR/2 concept?) OR (cognitive NEAR/2 thinking) OR (cognitive NEAR/2 task?) OR (cognitive NEAR/2 function?)): ti,ab,kw

#24 {OR #22-#23}

#25 MeSH descriptor: [Adolescent] this term only

#26 MeSH descriptor: [Child] explode all trees

#27 MeSH descriptor: [Infant] this term only

#28 MeSH descriptor: [Infant, Newborn] this term only

#29 {OR #26-#29}

#30 (child* or infan* or newborn? or adolescen* or toddler? or juvenil?e? or junior? or young? or youth? or teen* or bab* or youngster? or nenonate? or (little NEAR/2 (m?n or wom?n or boy* or girl*))):ti,ab,kw

#31 {OR #30-#31}

#32 (#8 AND #25 AND #31)

- **Web of Science search strategy was:**

#1 TS= ((psychological NEAR/1 technique) OR electroplexy OR (treatment? NEAR/2 convuls* NEAR/2 shock?) OR (therap* NEAR/2 convuls* NEAR/2 shock?) OR (treatment? NEAR/2 convul*) OR (therap* NEAR/2 convul*) OR (treatment? NEAR/2 shock?) OR (therap* NEAR/2 shock?) OR (treatment? NEAR/2 electro NEAR/2 convuls*) OR (therap* NEAR/2 electro NEAR/2 convuls*) OR (treatment? NEAR/2 electric NEAR/2 convuls*) OR (therap* NEAR/2 electric NEAR/2 convuls*) OR (treatment? NEAR/2 electric NEAR/2 shock?) OR (therap* NEAR/2 electric NEAR/2 shock?) OR (treatment? NEAR/2 electroshock?) OR (therap* NEAR/2

electroshock?) OR (treatment? NEAR/2 psychiatric NEAR/2 somatic) OR (therap* NEAR/2 psychiatric NEAR/2 somatic))

#2

TS=(understading* OR comprehen* OR training* OR recognit* OR retention OR (prob lem NEAR/2 solving) OR (over NEAR/2 learning) OR (knowledge NEAR/2 acquisition) OR (learning NEAR/2 verbal) OR (learning NEAR/2 spatial) OR (recall NEAR/2 phenomenon) OR (mental NEAR/2 recall) OR (event NEAR/2 memory) OR (remote NEAR/2 memory) OR (anterograde NEAR/2 memory) OR (spatial NEAR/2 memory) OR (episodic NEAR/2 memory) OR (long NEAR/1 term NEAR/2 memory) OR (association? NEAR/2 concept?) OR (cognitive NEAR/2 thinking) OR (cognitive NEAR/2 task?) OR (cognitive NEAR/2 function?))

#3 TS= (child* or infan* or newborn? or adolescen* or toddler? or juvenil?e? or junior? or young? or youth? or teen* or bab* or youngster? or nenonate? or (little NEAR/2 (m?n or wom?n or boy* or girl*)))

#4 #3 AND #2 AND #1

2.3. Inclusion exclusion criteria

To be included in this review studies had to meet the criteria of our PICO question (P for population, I for intervention, C for comparator, O for outcome).

The inclusion criteria thus were: (1) Population of pediatric patients aged below 19 (2) Patients being subjected to ECT (3) Study comparator being either the patients themselves before and after ECT (self-control) or a second arm of patients not receiving ECT (4) Cognitive performance of patients being assessed objectively before and after ECT.

Study designs eligible for inclusion were case report, case series, retrospective or prospective cohort studies, RCT.

Studies not meeting the above mentioned requirements were excluded, as well as those with no objective measurement for the outcome of interest or where the outcome was not measured at the adequate time points before or after.

We have also excluded reviews, editorials, study protocols, hypothesis abstracts.

2.3.1. Intervention

Eligible studies were supposed to have considered ECT as a therapeutic intervention. We did not limit our review to particular ECT modes such as unilateral or bilateral ECT or number of therapy sessions.

2.3.2. Outcome

Outcomes of interest were cognitive functioning measured in patients following treatment by ECT measured at short-term as well as at a follow up points after ECT. Any assessment of the cognitive functions at more than 5 months after the last session of ECT was considered a long term follow- up point.

Any aspect of cognitive functioning was considered relevant for analysis, such as anterograde and retrograde memory, attention, orientation, working memory, verbal learning, language and visual-spatial task and IQ.

We have classified the studies in the narrative part of the results section according the specific dimension of cognitive and intellectual ability they evoke: Verbal

learning, IQ and Orientation, attention, memory, language, visual-spatial skills altogether.

2.4. Study selection process

Screening was performed over 2 phase: (1) Phase 1 title and abstract as a preliminary screening and (2) full text screening of the included studies.

Studies titles and abstracts as well as full text were screened by two reviewers separately.

Studies which title and abstract were not revelatory about the elements we were checking for inclusion where referred for full text screening.

In both phases, disagreements were resolved by consensus or by referring to a third reviewer.

We recorded reasons for exclusion and reported the results of the selection process using a PRISMA flow diagram (Moher et al., 2009). There were no restrictions placed on the length of the study, schedule of treatment, geographic location of study, publication status or publication date.

2.5. Data extraction process

We extracted data from the studies concerning their designs and settings including country, year, duration, health care facility, limitations. Data specific to patients like their number, gender, sociodemographic details and diagnosis were extracted as well as information ECT settings (electrode placement, pulse width, frequency, duration, current, number of sessions), control groups, used cognitive tests and the outcome they measure.

2.6. Data analysis process

We used the Newcastle-Ottawa quality assessment scale to assess three criteria of nonrandomized studies: (1) selection, including representativeness of the exposed subjects, selection of the non-exposed subjects, ascertainment of exposure, and prove that the outcome of interest was absent at the beginning of the study; (2) comparability, evaluating whether the study adjusted for confounders; and (3) outcome, assessing the acceptability of the follow-up period, subjects retention and the ascertainment of outcome follow-up data from all (Wells et al., 2000). We evaluated the quality of the studies by adding stars in each domain: 3 or 4 stars for selection, 1 or 2 stars for comparability, and 2 or 3 stars for the outcome domain indicate 'good 'quality; 2 stars for selection, 1 or 2 stars for comparability, and 2 or 3 stars for outcomes indicate 'fair' quality; and 0 or 1 star for selection, or 0 stars for comparability, or 0 or 1 stars for the outcome domain indicate 'poor' quality (Wells et al., 2000).

We synthesized data in both narrative and tabular formats.

We have included using the GRADEpro software a 'Summary of findings' table for comparison of the therapeutic intervention of ECT to no ECT (Guyatt et al., 2008). It provides key information concerning the magnitudes of relative and absolute effects of ECT, the amount of available evidence and the certainty of the evidence.

For the statistical part, we did a meta-analysis of association by pooling risk ratios (RRs) using Revman software (Revman 5.4)**.** Depending on availability of these data from observational studies, the availability of a second arm control group and the presence of a common measured aspect of cognitive functioning, we were able to pool only 2 studies which commonly studied the effect of ECT on verbal learning. We have adopted a fixed-effects models and standardized mean difference as our outcome was

measured by 2 different scales. We have calculated 95% confidence intervals and two sided P values for each outcome.

Heterogeneity was assessed using the I^2 calculation which is a tool to quantify inconsistency (heterogeneity) provided by the Revman software as well. It assesses the proportion of variation that is not due to chance. It varies from 0%-100%. Substantial heterogeneity when the I^2 value is greater than 50% (The Cochrane Collaboration, 2020).

It should be also noted that the studies were suitable to be pooled together despite the variability in ECT settings (frequency applied, number of sessions) as our interest was the application of ECT as an intervention regardless of other details. Similarly, regarding the variability in time point collection of the cognitive test results at follow up, variability was tolerated given that both studies collected the test results at an interval longer than 6 months.

Publication bias was planned to be visually assessed with a funnel plot, as asymmetry in a funnel plot may be indicative for publication bias or other reporting biases.

CHAPTER 3

RESULTS

3.1. Study selection and characteristics

Our search of the electronic databases yielded a total of 2407 unique citations. Additional searches identified 3 additional references. We excluded 2376 studies at the title abstract stage. At the full text stage, 11 were excluded for the following reasons: not adequate publication type (n = 4), outcome of interest was not measured (n = 5), subjective measurement of outcome (n = 2), different intervention (n = 1), different population (n = 7), inadequate time point for outcome measurement (n = 1).

The specific reasons for exclusion for each of the initially retrieved article are reported in table 1.

Table 1 Reasons for exclusions of the initially retrieved article.

Author and year	Title	Reason for exclusion
Chess (1969)	An interactive concept of childhood schizophrenia	Editorial
Dhosee (2019)	Electroconvulsive Therapy for Catatonia in Children and Adolescents	Different outcome measured
Fink (1993)	Electroconvulsive therapy in children and adolescents	Editorial
Loiseau (2017)	Electroconvulsive Therapy Use in Youth in the Province of Quebec	Subjective (Survey)
Moise (1996)	Case Study: Electroconvulsive therapy in adolescents	Subjective (Survey)
Nelson (1965)	Effect of electric shock as a reinforce of the behavior of children	Different intervention
Oltedal (2015)	Effects of ECT in treatment of depression: study protocol for a prospective neuroradiological study of acute and longitudinal effects on brain structure and function	Study protocol
Rey (1997)	Half a Century of ECT Use in Young People	Outcome couldn't be measured
Seow (2019)	A Retrospective Study of Cognitive Improvement Following Electroconvulsive Therapy in Schizophrenia Inpatients	Not pediatric population
Skneekloth (1993)	Electroconvulsive therapy in adolescents	Different outcome measured
Squire (1976)	Anterograde Amnesia Following Electroconvulsive Therapy: No Evidence for State-Dependent Learning	Not pediatric population
Tor (2017)	Effectiveness of Electroconvulsive Therapy and Associated Cognitive Change in Schizophrenia	Not pediatric population
Vila (2019)	ECS-induced neurogenesis and congitive side effects	Abstract
Weeks (1980)	Antidepressant and Neurocognitive Effects of Isoflurane Anesthesia versus Electroconvulsive Therapy in Refractory Depression	Not pediatric population
Wong (2019)	Effectiveness and Cognitive Changes with Ultrabrief Right Unilateral and Other Forms of Electroconvulsive Therapy in the Treatment of Mania	Not pediatric population
Zhand (2015)	Use of Electroconvulsive Therapy in Adolescents With Treatment-Resistant Depressive Disorders, A Case Series	Different outcome measured
Gonzalez (2002)	selective alteration of the declarative memory systems in patients treated with a high number of electroconvulsive therapy sessions	Not pediatric population
Meter (2011)	Retrograde amnesia after electroconvulsive therapy: A temporary effect?	Not pediatric population
Mohapatra (2015)	Electroconvulsive Therapy in a Child Suffering from Acute and Transient Psychotic Disorder with Catatonic Features	Inadequate time point collection of cognitive test at baseline
Bertagnolli (1990)	A Review of ECT for Children and Adolescents	Outcome was not measured at end
Kaliora (2014)	Electroconvulsive Therapy in Youth in a Tertiary Academic Center An 11-Year Experience	Time point of collection not specified

The Figure 1 illustrates the study selection process reported in the form of the PRISMA flow chart diagram.

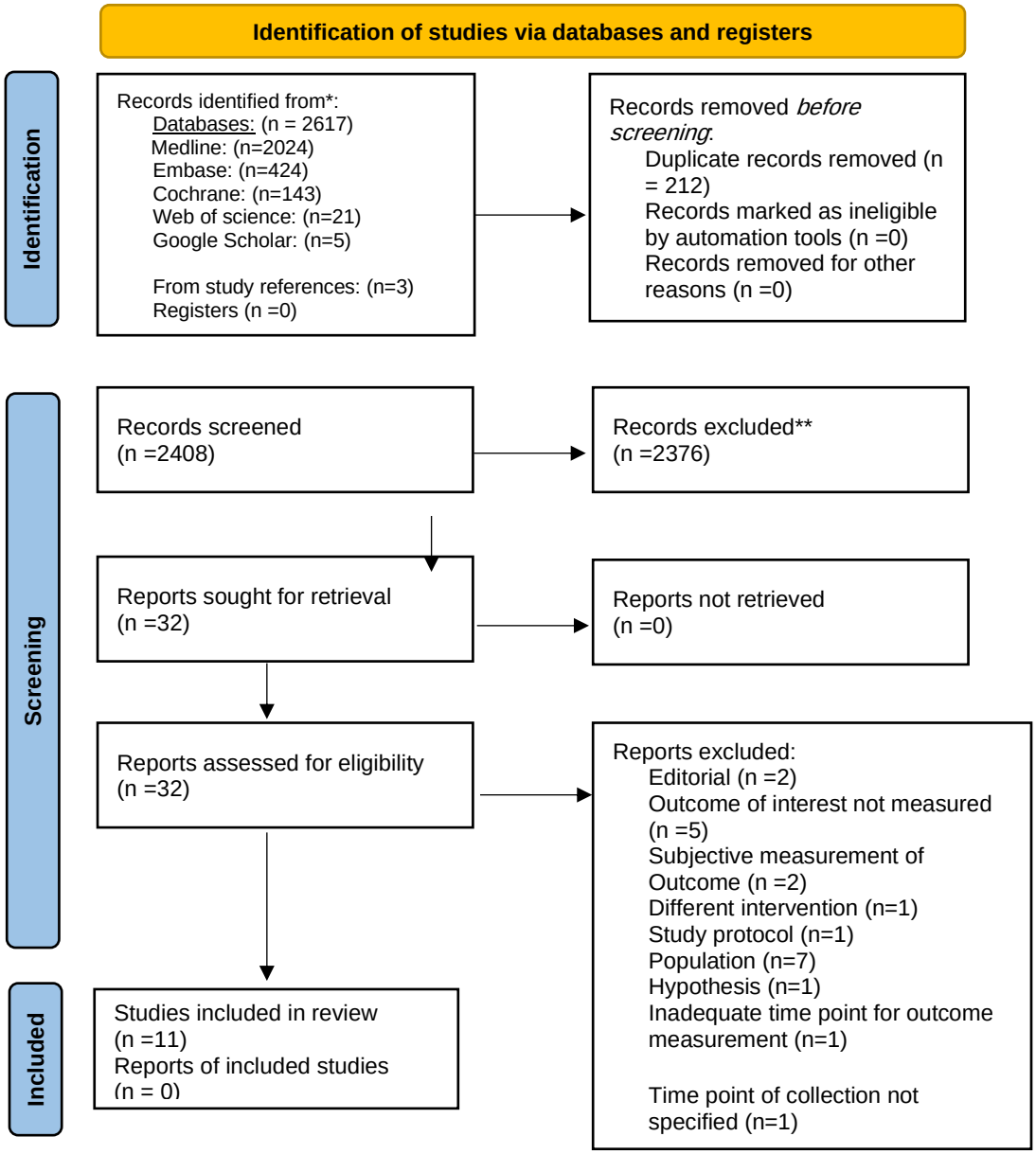

Fig. 1 PRISMA flow chart diagram

Tables 2, 3, 4 and 5 show a summary of the general characteristics of these studies. All of them have looked at the influence of ECT administered as a treatment for the disorder/disease of the involved subjects on their cognitive functioning measured with specialized mental tests.

Table 2 Settings of the included studies including study method, year, duration, number participants, country and health care facility.

Authors	Method	Study duration	Nb of participants	Country	Health care facility	Year
Cohen et al.	Retrospective cohort	NA* (retrospective study)	10	France	Department of Neuropsychology, Groupe Hospitalier Pitié-Salpétrière	2000
De la Serna et al.	Retrospective cohort	NA (retrospective study)	9	Spain	Psychology Department of Hospital Clinic of Barcelona	2011
Etain et al.	case serie	NA	6	France	Service de psychopathologie de l'enfant et de l'adolescent, Hôpital Robert Debré, Paris, France	2001
Ghaziuddin et al. (1996)	Prospective cohort	3 year period	11	USA	Department of Psychiatry, University of Michigan, Michigan.	1996
Ghaziuddin et al. (1999)	Case report	NA	1	USA	Department of Psychiatry, University of Michigan, Michigan.	1999
Ghaziuddin et al. (2000)	retrospective cohort	NA (retrospective study)	16	USA	Department of Psychiatry, University of Michigan	2000
Ghaziuddin et al. (2011)	Case serie	NA	6	USA	Department of Psychiatry, University of Michigan	2011
Ghaziuddin et al. (2020)	Prospective cohort	1996–2010. Response to treatment was examined after the initial treatment and during a 1-year follow-up	54	USA	Department of Psychiatry, University of Michigan	2020
Wachtel et al.	case report	NA	1	USA	Department of Psychiatry; Kennedy Krieger Institute; Johns Hopkins School of Medicine	2012
Bender et al.	Prospective cohort	1942-1947	98	New York	Children's Ward of Psychiatric Bellevue Hospital	1947
Gurevitz et al.	Prospective cohort	The year 1947	16	USA	Children psychiatric service at Bellevue hospital	1954

***no information concerning the corresponding characteristic could be retrieved from the studies.**

Table 3 Characteristics of the patients included in each study including socio-demographic details, diagnosis, age and sex.

Author	Socio-demographic characteristics	Diagnosis	Age	Sex	Control
Cohen et al.	11.2 y of education	severe mood disorder	mean of 17.6	4 M, 6 F	10 patients not treated with ECT
De la Serna et al.	2.22 on scale	schizophrenia spectrum disorders	13-18	2 M, 7 F	9 patients not treated with ECT
Etain et al.	NA	3 depression; 2 neuroleptic malignant syndrome 1 schizophrenia	14-16	3 M, 3 F	comparison of pre-ECT and post-ECT
Ghaziuddin et al. (1996)	NA	Pharmacotherapy-Refractory Depression	mean OF 16.3	1 M, 10 F	comparison of pre-ECT and post-ECT
Ghaziuddin et al. (1999)	NA	Bipolar Mania	16	F	comparison of pre-ECT and post-ECT
Ghaziuddin et al. (2000)	Mean education in grades was 10.2; mean IQ was 103.7	14 unipolar depression, 2 bipolar depression.	mean of 15.9	3 M, 13 F	comparison of pre-ECT and post-ECT
Ghaziuddin et al. (2011)	NA	severe treatment resistant major depression	14-17	4 M, 2 F	comparison of pre-ECT and post-ECT
Ghaziuddin et al. (2020)	NA	unipolar or bipolar disorder	mean age 15.8	24 M, 30 F	comparison of pre-ECT and post-ECT
Wachtel et al.	NA	malignant catatonia	16	M	comparison of pre-ECT and post-ECT
Bender et al.	NA	Schizophrenia	Below 12	70 M 98 F	comparison of pre-ECT and post-ECT
Gurevitz et al.	NA	Schizophrenia	mean of 9.11	15 M 1 F	Comparision of pre-ECT and post-ECT

Table 4 ECT settings in each study including electrode placement, pulse width, frequency, duration, current and number of sessions.

Author	Electrode placement	Pulse width	Frequency	Duration	Current	Number of sessions
Cohen et al.	Bilateral	NA	NA	NA	NA	mean of 9.8
De la Serna et al.	Bifrontotemporal electrode	1	65hz	0.89 s	0.63	13 (thrice per week)
Etain et al.	Bilateral	NA	NA	0.4 to 0.8 s	30 to 80 mA	9 (thrice per week)
Ghaziuddin et al. (1996)	Bilateral	1.0 msec	60 hz	2 s	0.8 A	11.2. (thrice per week)
Ghaziuddin et al. (1999)	Bilateral	NA	NA	Clinical seizure duration: 45.75 ; EEG seizure duration: 71.1.	NA	12 sessions
Ghaziuddin et al. (2000)	bilateral (3), unilateral (3), or a combination of the two modes (10)	NA	NA	NA	NA	Mean of 10.8 sessions.
Ghaziuddin et al. (2011)	NA	NA	NA	NA	NA	Mean of 37 sessions
Ghaziuddin et al. (2020)	Bilateral placement	0.78	NA	NA	155.5 mC	Mean of 13.7 sessions.
Wachtel et al.	Bilateral	1ms	90 Hz	4 s	800 mA	61 session
Bender et al.	NA	NA	NA	1/10 s or 2/10 s	NA	below 40 sessions
Gurevitz et al.	Bilateral	NA	NA	0.2-0.2 s	NA	Series of 20 shocks

Table 5 Characteristics related to the study outcome including study results, cognitive outcome studied, used test, time point of collection.

Author	Outcome measured	Used test	Time point collected	Results
Cohen et al.	1. Orientation, attention, memory, language, visual-spatial skills and calculation; 2. Attention; 3. Verbal learning	1. Mini-Mental State 2. The attention section of the Wechsler Memory Scale—Revised 3. The California Verbal Learning Test.	At baseline and at 3.5 years follow-up after last ECT session.	Not suffer measurable cognitive impairment at long-term follow-up
De la Serna et al.	1. IQ; 2. Working memory; 3. Attention; 4. Verbal learning; 5. Executive functions.	1. Block Design and Vocabulary subtests of the Wechsler Adult Intelligence Scale-III Revised (WAIS III) (Wechsler 2001) or the Wechsler Intelligence Scale for Children-Revised (Wechsler 1974); 2. Scores obtained on Digits backward and Letter-Number Sequencing of the WAIS III (Wechsler 2001); 3. Trail Making Test part A (TMT-A) (Reitan and Wolfson 1985) and digits forward of the WAIS III (Wechsler 2001); 4. Verbal Learning Test-Complutense Spain, the Spanish adaptation of the California Verbal Learning Test; 5. The Wisconsin Card Sorting Test (WCST), the interference part of the Stroop test (Golden 1978), the TMT part B (TMT-B), and the verbal fluency task.	At baseline and at 2 yrs. follow-up after last ECT session.	No significant differences in any changes in clinical or neuropsychological variables between the groups during follow-up or after 2 yrs.
Etain et al.	IQ	Test de Wechsler. WAIS III	Follow-up points ranged from 15 days to 2 yrs. depending on each case.	ECT does not seem to have caused alterations to long-term cognitive functions
Ghaziuddin et al. (1996)	1- Cognitive functioning in the areas of memory, orientation, concentration, language, and calculation. 2- Visual attention and working memory. 3- General memory assessment. 4- The fluency of speech, considered a measure of efficiency of search in long-term memory.	1- Mini-Mental State Examination. 2- Wechsler Memory Scale-Russell. 3- General memory assessment. 4- Verbal Fluency Test.	Both 1-5 days before and 1-5 days after the last ECT.	The Mini-Mental State Examination showed no significant decline in cognitive functioning. Neuropsychological testing completed in 5 subjects both before ECT and 1-5 days after the last treatment, indicated a significant decline in attention, concentration, and long-term memory search.
Ghaziuddin et al. (1999)	IQ	Wechsler Intelligence Scale for Children	20 month pre-ECT, 2 weeks pre-ECT, 3 month post ECT	Comparison of 2-week pre-ECT and 3-month post-ECT cognitive testing revealed no change in IQ.
Ghaziuddin et al. (2000)	1. Digit span; 2. Immediate and delayed verbal memory; 3. Immediate and delayed visual memory; 4. Verbal fluency phenomics; 5. Verbal memory	1. Digit span task; 2. For subjects ages 15 and younger, the Story Memory subtest of the Wide Range Assessment of Memory and Learning, for subjects ages 16 and older, the Logical Memory subtest of the	At baseline, 7.0 ± 10.3 days and 8.5 ± 4.9 months follow-up after the last ECT.	Comparison of pre-ECT and the first post-ECT testing administered during the first 10 days of the treatment yielded significant impairments of concentration and attention,

	semantics; 6. executive functions.	Wechsler Memory Scale (WMS; Wechsler 1945) was used; 3. For subjects ages 15 and younger, the Design Memory subtest of the WRAML was used. For subjects ages 16 and older, the Visual Reproduction subtest of the WMS was used. 4. Naming as many words as subjects could think of (Benton and Hamsher 1989); 5. Naming as many animals as subjects could think of within a 1-min time limit (Morris et al. 1989); 6. Halstead Category Test or Boll Category Test.		verbal- and visual-delayed recall, and verbal fluency. A complete recovery of these functions was noted at the second post-ECT testing. There was no deficit in the ability to problem solve during the initial or the subsequent testing.
Ghaziuddin et al. (2011)	1. Intellectual functioning; 2. Academic achievement-reading; 3. Verbal Memory; 4. Visual attention and working memory..	1. The Wechsler Abbreviated Scale of Intelligence (WASI); 2. The Wide Range Achievement TestVThird Edition (WRAT-3); 3. (a.The Wechsler Memory ScaleVThird Edition (WMSIII). b. California Verbal Learning TestVSecond Edition(CVLT-II)); 4. Trail making test.	Follow-up points ranged from 5 days to 5.5 month depending on each case.	comparison of pre-ECT and post-ECT neuropsychological functioning revealed a trend toward improved auditory and verbal memory on most of the results
Ghaziuddin et al. (2020)	Orientation, attention, memory, language and visual-spatial skills.	Mini-Mental State Examination	At baseline, at initial treatment and during a 1-year follow-up (at 3, 6 and 12 months).	The only side effect noted at the 1-year follow-up was self-reported memory loss involving events during and around the index treatment course. Subjective memory loss after ECT 66%; Confusion after ECT 40%.
Wachtel et al.	Evaluation of intellectual functioning independent of spoken language	Comprehensive Test of Nonverbal Intelligence. visual memory: Developmental Neuropsychological Assessment Test 2005 and the updated Neuropsychological Assessment Test, Second Edition, 2010 version	Before, onset and after 61 ECT	No evidence of decline in intellectual functioning and acute or delayed memory
Bender et al.	IQ	IQ test	Before shock, immediately following shock, and at intervals thereafter whenever possible	The psychological tests are further characterized by lack of any evidence for a lasting effect on the intellectual functioning and development of the child as a result of the electric shock, although 5 children showed some interference in function immediately after treatment.
Gurevitz et al.	1. Fluid reasoning, knowledge, quantitative reasoning, visual-spatial processing and working memory; 2. Non Verbal intelligence; 3- IQ	1. The revisited Standford-Binet; 2. The Non Language Multi-Mental Test; 3. The Goodenough Draw-A-Man test; 4. The Bender Gestalt structural aspects; 5. The good enough structural aspect test; 6. The tree fence road test.	Just before, 24-48 hours after ECT, 5-27 months after ECT.	Intellectual efficiency was significantly reduced immediately after shock but recovered by the time of follow-up. Some evidence of the non-language test that logical reasoning processes where differently organized at time of follow-up than before shock. 5-27 months later there was

				significance enhancement in performance in tasks of non- verbal intelligence and IQ measurement.

3.2. Forest plot and meta-analysis

We have constructed a forest plot and conducted a meta-analysis based on 2 studies only (Cohen et al. (2000) and De la Serna et al. (2011)). As for the remaining 9 studies, the absence of control group caused the risk of bias to be significantly high and their inclusion in the meta-analysis statistically inadequate.

Cohen et al. (2000) and De la Serna et al. (2011) examined the effect of ECT on verbal learning by comparing the results obtained from ECT-exposed patients with those of normal subjects.

Pooling the results of the 2 studies together in one meta-analysis has yielded a pooled estimate with a positive value of 0.12 indicating that ECT can improve verbal learning. Similarly, the results of the forest plot have revealed the likelihood of a more favourable outcome for the ECT group compared with controls. However, the value of the pooled estimate is considered small, the confidence interval is large crossing 0 and ranging from negative to positive values (CI: 0.51; 0.74), and the P value of the overall effect test was insignificant ($p = 0.71$). The favourability for ECT over no ECT for the improvement of verbal learning test scores used by the 2 studies implies that the use of ECT is considered a safe and effective intervention for patients suffering from severe psychiatric disorders (Figure 2).

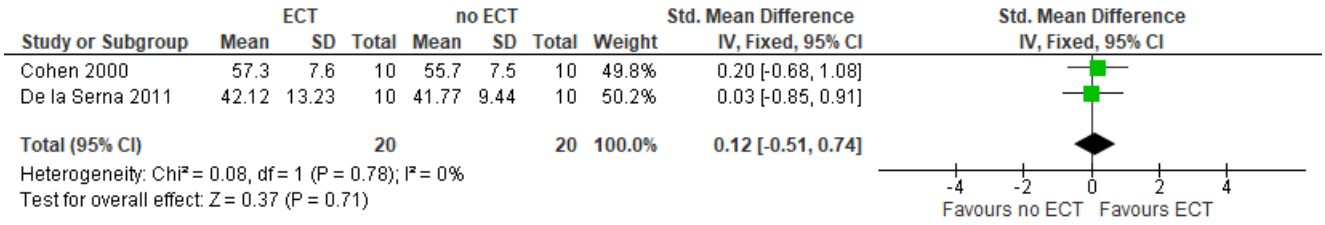

Figure 2 Forest plots of verbal learning for ECT versus no ECT application.

3.3. Risk of bias

For the 2 studies included in the meta-analysis, the risk of bias was generally good after considering the observational designs. For the remaining studies, the risk of bias was high and the quality of studies was judged as poor given the absence of control group. Table 5 shows the components of evaluation of the risk of bias of the included studies.

Table 6: Risk of bias of the studies based on the New Castle Ottawa- Quality Assessment Scale.

	Selection			**Comparability**		**Outcome**			**Quality score**
	Representative-ness of exposed cohort	Selection of the non-exposed cohort from same source as exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Comparability of cohorts.	Assessment of outcome	Follow-up long enough for outcome to occur	Adequacy of follow-up	
Cohen	Truly representative of the population as patients were selected consecutively from chart review and all adolescents were treated with ECT for mood disorder before 19 years of age in five psychiatry departments in Paris. *	Yes *	Medical records *	Yes all	10 psychiatric comparison subjects were choosed who had never been given ECT but were individually matched with the ECT subjects for sex, age, date and place of hospitalization, and DSM-IIIR, except for 1 patient who couldn't be matched for the same subtype of mood disorder or clinical severity. In addition, global assessment of functioning score was not matched for both groups. For this reason, we will assign only 1 star for this section *	Medical records *	Yes *	Yes, all subjects participated in the follow-up. *	Good
De la Serna	Truly representative of the population as patients were selected consecutively and subjects admitted in the study were selected from a pool of patients with schizophrenia admitted to the inpatient ward of the Child and Adolescent Psychiatry and Psychology Department of Hospital Clinic of Barcelona. *	Yes *	Medical records *	Not stated	Subjects treated with ECT were compared with 9 subjects selected from the same schizophrenia or diagnosed patients treated during the same period. Schizophrenia (n = 7) or schizoaffective disorder (n = 2) was diagnosed in these controls, and they were treated with psychiatric drugs but without ECT. They were matched for age, socioeconomic status, and PANSS at baseline. Socioeconomic status of the sample was estimated with the Hollingshead Redlich scale. **	Medical records *	Yes *	Yes, all subjects participated in the follow-up. *	Good
Etain	Truly representative of the population as patients were selected consecutively from files of patients aged between 14 and 16 years, hospitalized between the	No control	Medical records *	Not stated *	No control	Medical records *	Yes *	Yes, all subjects participated in the	Poor

	year 1980 and 2000 at the service of psychology, Hospital of Robert Debré, Paris, France. *							follow-up. *	
Ghaziuddin 1996	Truly representative of the population as patients were selected consecutively from hospitalized adolescents from 1993 to 1996 at Department of Psychiatry, University of Michigan, Ann Arbor, Michigan with inclusion criteria being diagnosis with severe depression score equal or above 55 on the Children Depression Rating Scale and prior failure of 3 or more antidepressant trials. *	No control	Medical records *	Not stated *	No control	Medical records *	Yes *	No, not all subjects participated in the follow-up. *	Poor
Ghaziuddin 2000	Not sure	No control	Medical records *	Not stated	No control *	Medical records *	Yes	No, not all subjects participated in the follow-up.	Poor
Ghaziuddin 2011	Not sure	No control	Medical records *	Not stated	No control *	Medical records *	Yes *	Yes, all subjects participated in the follow-up.	Poor
Ghaziuddin 2020	Truly representative of the population as patients were selected consecutively from medical records and all available information from patients younger than 18 years of age, with a diagnosis of severe mood disorder, and who had received their first course of ECT at an academic medical center from 1996 to 2010. *	No control	Medical records *	Not stated	No control	Medical records *	Yes *	No, not all subjects participated in the follow-up.	
Ghaziuddin 1999	Not representative of the population as it's a case.	No control	Medical records *	Not stated	No control	Medical records *	Yes *	Yes *	Poor

Wachtel	Not representative of the population as it's a case. *	No control	Medical records *	Intellectual disability at baseline	No control	Medical records *	Yes *	Yes *	Poor
Bender	Truly representative of the population as patients were selected consecutively from patients admitted to the Children Ward of the Psychiatric Division of Bellevue Hospital between the year 1942-1947.	No control	Medical records *	Not sure	No control	Medical records *	Yes *	No, not all subjects participated in the follow-up.	Poor
Gurevitz	Not evident *	No control	Medical records *	Not sure	No control	Medical records *	Yes *	No, few missed the Goodenough or the Bender-Gestalt test on 1 occasion. *	Poor

3.4. Heterogeneity

The statistical test of heterogeneity measured by the I^2 test was 0.00% indicating that the two selected studies are homogenous and that there are no significant differences underlying their findings.

3.5. Publication bias

Given that only two studies were included in our meta-analysis, publication bias could not be assessed. Funnel plots used to reveal publication bias[2], can only be applied when there are at least 10 studies in the meta-analysis, otherwise the power of the tests is too poor to distinguish chance from real asymmetry (Cochrane Collaboration, 2020).

3.6. Grading of the certainty of the evidence

The certainty of evidence of the effect of ECT on verbal learning, as a cognitive outcome in the two studies included in our meta-analysis, was measured using Gradepro. A summary of our findings is presented in table 7 and has shown that the certainty of evidence was very low.

Table 7: Summary of findings table grading the certainty of the evidence following the GRADEpro method.

ECT vs no ECT effect on verbal learning
Patient or population: Cognitive functioning deterioration
Setting: Children and adolescents
Intervention: ECT
Comparison: no ECT

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no ECT	**Risk with ECT**				
Verbal Learning	-	SMD **0.12 SD higher** (0.51 lower to 0.74 higher)	-	40 (2 observational studies)	⨁◯◯◯ VERY LOW [a]	ECT may increase/have little to no effect on verbal Learning but the evidence is very uncertain.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **SMD:** Standardized mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. The total number of participants is small (n=40). Also, the confidence interval of the absolute effect includes values reflecting both benefit and harm.

3.7. Studies general settings

A total of 11 studies were included. All of them were observational, with 3 retrospective studies, 4 prospective studies, 2 case reports and 2 case series. Two studies (18%) addressed long-term effects of ECT on cognition, while 3 (27%) addressed short-term and 6 (55%) addressed both. Out of these 11, only 2 had a control group of patients. Other studies compared the scores of the cognitive performance measuring tests for the patients before and after being subjected to bilateral ECT for which the number and frequency varied according to each study. Additionally, the number of

participants ranged from 1 to 98 each, with a total of 228, including Asian, European and American populations. All studies have been carried out in the pediatric population. Our search did not identify any eligible randomized trials.

3.8. Outcomes, tests and time point of data collection reported by the studies

With regard to our outcome of interest, some studies included IQ scores as a reflection of the cognitive influence of ECT, while different studies assessed orientation, attention, memory, language, visual-spatial skills, calculation, verbal learning as well as other aspects. The included studies provided an extensive overview of cognitive aspects potentially influenced by ECT. However, data collection was done at different time points.

In addition, the different cognitive tests used in each study were discussed with reference to the measured outcome and the specific age group tested. The Mini-Mental State Examination, the Wechsler memory and intelligence scale, the IQ test and others were the tools reported by the studies. All studies reported absence of cognitive impairments resulting from ECT at long term. At short-term, some observed significant cognitive deterioration in fields; however, the studies that had a follow-up on their affected subjects, reported no long-term cognitive deficits in these patients. Given the heterogeneity between studies regarding the reported cognitive tests and outcomes, it was only possible to partially group them in categories in the following narrative parts.

3.9. Studies details and findings

Four studies were concerned about the effect of ECT on verbal learning as a cognitive outcome. Cohen et al. (2000), De La Serna et al. (2011), Ghaziuddin[1]* et al. (2000) and Ghaziuddin et al. (2011) have reported the results of verbal learning tests in adolescents diagnosed with severe mood disorders, schizophrenia spectrum disorders and depression, to whom ECT was administered with different methods according to the specific medical condition. Cohen et al. (2000) and De La Serna et al. (2011) came up with results showing that the participating group of patients, constituting 10 subjects for Cohen et al. (2000) and 9 for De La Serna et al. (2011), did not differ on any objective measure of verbal learning and attention, as well as of orientation, memory, visual-spatial skills, calculation, working memory, executive functions and IQ or their changes at the planned long-term follow-up periods.

In the other 2 studies, Ghaziuddin et al. (2000 & 2011) have examined the results of cognitive tests of adolescent patients diagnosed with various subtypes of depression and have compared their scores before and after being subjected to ECT as prescribed to them at the Department of Psychiatry, University of Michigan.
By comparing pre-ECT and the first post-ECT testing administered less than 1 month after treatment, Ghaziuddin et al. (2000) has shown that ECT has resulted in significant impairments in verbal delayed recall, and verbal fluency with complete recovery at long term treatment, which is also the case for attention, concentration and visual- delayed recall for the 16 included patients. They have, however, found no change in the ability to problem solve during the initial or the subsequent testing.

*We note that the 5 studies by Ghaziuddin et al., included in our review may have common patients between them. However, it was not possible to identify the overlap in their included population.

Interestingly, Ghaziuddin et al. (2011) have even revealed a trend toward improved verbal memory on most of the results of comparison of pre-ECT and post-ECT testing measured mostly at short-term intervals following treatment of 6 depressed adolescent patients.

Similar to Cohen et al. (2000), other studies have also focused on the functions of attention, orientation, memory, language, visual-spatial skills, calculation and verbal learning evaluated by the Mini-mental state examination test. Of these studies, Ghaziuddin et al. (1996 & 2020) reported that the Mini-mental State Examination showed no significant decline in cognitive functioning in 11 patients with pharmacotherapy refractory depression, and 54 unipolar or bipolar disorder patients prior to and post ECT application. In addition, Ghaziuddin et al. (1996) have clarified that a significant decline in attention, orientaion, concentration, and long-term memory occurred in 5 subjects both before ECT and 1-5 days after the last treatment as demonstrated by neuropsychological testing.

IQ was another aspect that was the focus of 4 studies as an indicator of cognitive functioning in response to ECT. Bender et al. (1947), have prospectively evaluated the effect of ECT as a treatment for 98 schizophrenic children at Children's Ward of Psychiatric Bellevue Hospital. Children were followed before shock, immediately following shock, and at intervals thereafter whenever possible to show lack of any evidence for a lasting effect on the intellectual functioning and development of the child. For this same outcome, Ghaziuddin et al. (1999) have identically reported a case of a 13-year-old girl with bipolar mania subjected to 12 bilateral ECT sessions. Comparison of 2-week pre-ECT and 3-month post-ECT cognitive testing showed no change in IQ. Another case report as well by Wachtel et al. (2012) of an adolescent with

malignant catatonia who received 61 sessions of ECT confirmed no evidence of decline in intellectual functioning and memory after the therapy, and at the end of all the prescribed sessions. The study by Etain et al. (2001), which also reported IQ testing before and following ECT for 3 adolescents with depression, showed that ECT does not cause alterations to short- term cognitive functions at different times of follow- up as compared to baseline, even though no statistical analysis has been performed to accurately rate the significance of difference in IQ scores before and after the treatment.

In the prospective study by Gurevitz et al. (1954), 16 pediatric patients diagnosed with schizophrenia and subjected to series of 20 shocks, had their IQ scores measured. Similar to previously reported studies, they have compared the subjects performance on non-verbal intelligence test, fluid reasoning, knowledge, quantitative reasoning, visual-spatial processing and working memory tests. They showed that intellectual efficiency and logical reasoning was significantly altered immediately after shock but recovered by the time of follow-up (5-27 months), and even reported significant enhancement in non- verbal intelligence and IQ measurement (measured by the Non-Language Multi-Mental test and the Goodenough Draw-A-Man test).

CHAPTER 4

DISCUSSION

This is the first meta-analysis investigating the effect of ECT on behavioral cognitive outcomes in children and adolescents. Given the vast range of cognitive tests used in patients with psychiatric disorders, we focused on the effects of ECT, one of the most controversial medical therapy, on verbal learning. The findings of our included prospective and retrospective cohort studies and case reports, that assessed cognitive performance in the short and long term following ECT, indicate that ECT does not cause any significant long-term harmful effect on cognitive functions in the pediatric population. Our findings, however, appear inconsistent with that of Gurevitz et al. (1945) and Ghaziuddin et al. (2000) who have reported significant impairment in concentration, attention, visual-delayed recall, verbal fluency, verbal intelligence and delayed-recall, reasoning, knowledge, visual-spatial processing and working memory, at 24-48 hours and 10 days post treatment.

Not only that, Ghaziuddin et al. (2011) have even reported improvement in delayed story memory performance for most of the subjects including 3 subjects whose performance was collected at short term and 1 at long term follow-up. This discrepancy is likely due to the small sample size in each study, the non-randomly assigned experimental and control group (when present), bias in cognitive assessment, the variable testing time points in the retrospective cohort studies (Ghaziuddin et al., (2000)) and lastly, the different types of selected studies. Moreover, the risk of bias assessment using the New Castle Ottawa scale has signified a poor overall quality of the vast majority of our included studies, particularly due to the lack of a control group. In

addition, the resulting values of the pooled estimate, the confidence interval and the P value of the overall effect cannot, with certainty, confirm whether ECT has any short-term or long-term detrimental effect on cognitive functions in children and adolescents. The certainty of evidence assessed in our study was also found to be very low, an indication of low confidence in the estimated effect, possibly due to the inconsistency in the observational design of the 2 included studies and the high risk of bias. This suggests that ECT may have the ability to enhance verbal learning though the evidence is very uncertain.

This uncertainty is likely attributable to the small number of participants in the studies included in this meta-analysis (n=40). Also, it is interpreted by the confidence interval of the absolute effect that includes values reflecting both benefit and harm. However, despite the small number of studies included in our meta-analysis and the limitations of the studies included in our systematic review, it's important to note that a rigorous search of the literature has been done in regard to our question of interest. The results provided an access to the totality of cohort studies, case reports and case series and contributed to the evidence on which physicians may recommend or discourage the application of ECT for a given pediatric case. More importantly, our established body of narrative and quantitative results fill a gap in the medical literature and prompt the need for a controlled clinical trial or a randomized controlled clinical trial to be performed, in order to confirm with complete certainty the effect of ECT on cognitive functions.

CHAPTER 5

CONCLUSION

Our findings indicate that it is reasonable to recommend and prescribe ECT for a pediatric case that showed resistance to other therapeutic strategies, with no concern about lasting cognitive deterioration resulting from the procedure. Data also indicated that ECT has no deleterious effect on verbal learning in these patients. However, due to the uncertainty of the findings of the meta-analysis and the primary limitations of the systematic review, represented by the small sample size of the included studies and their design lacking random assignments of the groups or control groups, the decision to recommend ECT should take into consideration the emergency of the case, the existence of an alternative therapeutic solution, and the potential side effects on cognition.

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