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Combination of Donepezil and Memantine to Mitigate Electroconvulsive Therapy Induced Cognitive Effects

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COMBINATION OF DONEPEZIL & MEMANTINE TO MITIGATE ELECTROCONVULSIVE THERAPY INDUCED COGNITIVE EFFECTS

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Ryan C. Rogers, PA-SII

ABSTRACT

Electroconvulsive therapy is a procedure whereby patients have electricity delivered to their brain to induce a generalized seizure. Electroconvulsive therapy is highly efficacious in treating conditions such as major depressive disorder, but it can induce temporary cognitive deficits and memory loss. Studies suggest that medications used to slow Alzheimer's disease may diminish these adverse effects, but we aim to determine whether donepezil and memantine combination therapy can prophylactically protect cognitive functioning and memory in patients receiving electroconvulsive therapy. Using a randomized control design, we assess patients with major depressive disorder before and after electroconvulsive therapy using a battery of cognition and memory tests, including the Columbia University Autobiographical Memory Interview – Short Form. Changes in these scores will be compared within and between patients taking combination therapy and placebo. This work will help improve our understanding of the effects of electroconvulsive therapy, and potentially help alleviate its adverse cognitive effects.

TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION

Background:

Introduction to Electroconvulsive Therapy and its state today

Electroconvulsive therapy, or ECT, is a procedure in which an electrical current is passed through the brain to induce a brief generalized seizure for the purpose of treating various psychiatric conditions.[1] It is used most commonly for major depressive disorder.[2,3] It is a low-risk procedure done under general anesthesia, that can be performed inpatient and outpatient.[1]

The concept of using induced convulsions to antagonize the symptoms of schizophrenia was proposed as early as 1934 by Ladislas Joseph von Meduna, but the practice of using electricity to induce these convulsions was founded by Ugo Cerletti and Lucio Bini in 1937. ECT quickly became a major treatment modality for schizophrenia and other psychiatric conditions, even though very little was understood on how and why it worked.[4] In its early years, it was associated with some significant complications, such as bone fractures, bitten tongues, and memory loss. For these reasons and because of a lack of public understanding, fear revolved around ECT, including worries that ECT would cause brain damage or that it was similar to lobotomy or the electric chair.[5]

With the introduction of pharmacologic antipsychotics, antidepressants, and antimanic agents, ECT with its negative public image was used much less and even restricted for many years.[5] But ECT was not completely lost, and as time went on, more was understood about ECT and in the way of which it could be conducted. Through much research and modification, ECT evolved into a much safer procedure with fewer side effects. Its use had a gradual resurgence when practitioners realized some psychiatric

conditions and symptoms can be resistant to medications. Unfortunately, negative media portrayals, public misinformation, and even state laws still restrict its use to this day.[4,5]

Modern ECT is a very quick procedure. First, the patient will be laying on a bed with an IV established. Next, the ECT team starts monitoring the patient's vital signs, blood oxygen levels, cardiac rhythms, and electrical activity of the brain. Next, electrodes are placed on the patient's scalp on locations specified by the practitioner. The patient is then put to sleep under general anesthesia and a muscle relaxer, after which the patient receives a bite block and an oxygen mask. The practitioner then delivers electricity to the patient from an ECT device, inducing a generalize seizure that typically lasts between 15-70 seconds. Electrode placement and stimulus duration, pulse width, frequency, and amplitude will vary per provider judgment and facility protocols. After the seizure is complete, the patient gradually wakes up and is monitored for no less than 30 minutes before being cleared to leave. The number and frequency of the treatments needed for a patient is determined by the practitioner, but most patients remit from their psychiatric condition within 6-12 treatments, typically with 2-3 treatments being performed per week.[1,4,6,7] This is called an acute series of ECT.

If ECT is stopped abruptly and no other intervention begins, patients can see relapse rates up to 84% following the acute series. To prevent patients from having relapses, continuous ECT is often offered after the acute course. In continuous ECT, the frequency of procedures is tapered off over weeks and months, for up to 6 months, usually to a frequency of once per month. Maintenance ECT is offered after continuous ECT, with the purpose of preventing the recurrence of new psychiatric episodes. In this setting, ECT is given at the minimum frequency needed to prevent relapse.[8]

Presently, it is used as a second-line therapy for various psychiatric conditions after psychotherapeutic and/or pharmacological interventions have proven to be ineffective, as is the case in treatment resistant depression (TRD). It is also used as a first-line option for severe and life-threatening psychiatric emergencies, such as acute suicidal ideation, where rapid response is required. [1,9] It is most commonly used to treat major depressive episodes, both in unipolar and bipolar disorders; in fact, major depressive disorder (MDD) patients represent 94% of all ECT patients in the united states (U.S.).[2] It is the most effective treatment for MDD, with 70-90% of ECT patients having a response to treatment, and remission rates being 50-80% .[1,10-12] When MDD qualifies as TRD, broadly defined as when at least two adequate trials of different oral antidepressants fail to properly treat MDD, ECT becomes the gold-standard therapy with trials showing 50-60% remission rates as opposed to 13-14% remission rates with another trial of oral antidepressants.[13-16] Despite its high efficacy, only about 1 out of 10 hospitals in the U.S. offer ECT[17], and a 2014 statistic showed that only 0.25% of nearly 100,000 Americans with MDD received one or more ECT treatments.[2] A recent 2021 estimate states that 30.9% of people with MDD have TRD,[18] showcasing a gross underutilization of ECT in the U.S. It should be noted that ECT is not the only therapeutic option for TRD. Transcranial magnetic stimulation (TMS) can also be used, but can be less effective and more expensive than ECT.[19] Another option available is ketamine; although studies demonstrate it is effective in the rapid reversal of depressive symptoms, it is much newer and has yet to be compared thoroughly to ECT.[16] ECT is also very effective in treating treatment resistant schizophrenia and neuroleptic malignant syndrome (NMS), meaning the difficulty in accessing ECT is not just detrimental to the MDD and TRD population,

especially when it is also the first line treatment for patients with malignant catatonia or benzodiazepine resistant catatonia.[9,20,21]

The adverse effects of modern ECT are minimal compared to what it once was thanks to its advancement over 80 years. For example, muscle relaxers are used to prevent broken bones by diminishing the severity of the convulsions; bite blocks prevent tongues from being bitten; and anesthesia puts the patient to sleep so they do not remember undergoing a seizure.[22,23] Even in modern ECT though, depending on how it is administered, about 26-60% of patients still report having subjective memory loss from treatment.[24-26] Patients today may specifically experience acute postictal confusion, post-acute non-memory cognitive impairment, anterograde amnesia, and retrograde amnesia.[1,26] All patients will experience some degree of disorientation and confusion after their seizure when waking up from anesthesia, but this postictal confusion typically subsides within 10-20 minutes and is resolved within an hour.[1] Non-memory cognitive functioning includes other aspects of one's mental ability to process information, perform tasks, and problem solve. Objective tests demonstrate a deficit in these abilities 0 to 3 days post-ECT, but they return to or improve from baseline on day 4 to 14 post-ECT.[26,27]

Anterograde amnesia is a form of memory loss in which there is an impaired ability to record new memories, such as trouble remembering events on the days following ECT. Objectively, the severity of this condition is strongest immediately after treatment within day 0 and day 3 post-ECT, but will subside and resolve within 4 to 14 days post-ECT.[1,26,27] Retrograde amnesia is a form of memory loss in which there is an impaired ability to recall old memories; in this case, memories that predate the start of ECT. This memory loss is usually limited to events occurring within the first few weeks

or months before staring ECT, with memories more proximal to the start of ECT being more susceptible than memories further before the start of ECT.[1] These memories include both autobiographic and semantic memories, which are memories of your personal life events and memories of facts respectively.[26] Memories lost from retrograde amnesia via ECT take longer for patients to recover than anterograde amnesia. Objective tests show pre-ECT memories can return within 2 months,[28] but they have also demonstrated retrograde amnesia persisting over 6 months, after which it is unclear if the memories were ever recovered.[26,29,30]

Much has been done to minimize the occurrence and severity of these cognitive adverse effects. Modifications such as switching from a bilateral to unilateral electrode placement, switching from sine wave to brief pulse square wave (and further to ultra-brief pulse square wave) stimuli, switching from an age-based energy dosing estimate to performing stimulus titration past the seizure threshold to prevent using excessive energy, and limiting the ECT course so that the frequency and amount of treatments is not greater than those required to produce the therapeutic effect, have all significantly reduced the prevalence and severity of these cognitive side effects.[1,4,31] Yet these adverse effects still occur, and remain a deterrent to patients that could potentially benefit from ECT. A systematic review estimates that ECT-related anxiety occurs in 14% to 75% of patients, mostly over fears of memory impairment and brain damage.[32] ECT professionals have acknowledged this fear and stigma as a major barrier to care and to ECT's expansion.[33]

Although a large factor, patient stigma is not the only barrier that prevents patients from receiving ECT. The same ECT professionals also acknowledged provider stigma, lack of ECT trained professionals, lack of space, and legal barriers as additional

impediments.[33] All of these barriers can be thought to stem from a lack of awareness and understanding of ECT from patients, providers, hospitals, law makers, and insurance companies alike. With a greater public understanding of ECT, the superficial fear around this treatment can be eased, and its utilization can be optimized. Reducing the memory and cognitive side effects of ECT can help bring about this acceptance, and can perhaps lead to treatment truly being offered when it should, and help those that truly need it.

Neurobiological mechanisms of ECT and the role medication could play

There are many theories about the mechanisms of action surrounding ECT, its effects on the brain, and its role in treating psychiatric issues, but the exact mechanisms remain unknown. The theories on how ECT treats depression and psychiatric symptoms can be broadly put into one of three categories: the neurophysiological hypothesis, the neuroplastic hypothesis, and the neurobiochemical hypothesis.[1,34] The neurophysiological hypothesis suggests that ECT alters the structural abnormalities of the brain typically seen in mood disorders. These alterations include changing the brain's regional cerebral blood flow and glucose metabolism, changing the brain's seizure threshold, changing the brain's microenvironment due to transient breaches in the blood brain barrier (BBB), and changing the brain's electrical activity and waveform in different areas. The neuroplastic hypothesis suggests that ECT re-regulates the abnormal neural network connectivity and regional brain volumes seen in psychiatric disorders. ECT induces an increase in neurotropic factors, like brain-derived neurotrophic factor (BDNF), which leads to neurogenesis and neuroplastic changes, including increased neuronal connectivity, functional capacity, and volume in the hippocampus, amygdala, and other areas.

The neurobiochemical hypothesis suggests that the ECT changes modulate the

neurotransmitter and hormonal systems of the brain, of which people with psychiatric conditions may have deficiencies. ECT has shown to have an effect on the neurotransmission of almost all major neurotransmitters, such as serotonin, dopamine, acetylcholine, glutamate, GABA, epinephrine, and norepinephrine, which all have varying effects on a person's mood and cognitive functioning. Likewise, ECT enhances the secretion of adrenocorticotrophic hormone, cortisol, prolactin, and other hormones from the hypothalamus while reducing cortisol induced inhibition of neuroplasticity, though how it is related to ECT's therapeutic effects have yet to be isolated.[1,34]

These are just some of the potential changes ECT can bring about in the brain. Many other changes are theorized to explain ECT's effect on cognition and memory. Structurally, ECT may have these effects because: it induces subtle neuronal or glial damage; it impacts blood pressure and the BBB to induce mild cerebral edema; it changes the volumes and connectivity of different areas in the brain.[35-38] The changes ECT has on neural dynamics can also be at play, like influencing neural oscillation changes, inducing pathological hyperstimulation of neurons, and disrupting long term potentiation.[35,36]

Many neurobiochemical theories also exist. ECT creates high serum cortisol levels, which can impair memory and cognition.[35,37-39] Proinflammatory processes, such as ECT shocks up-regulating COX-2 enzyme activity in the amygdala and dentrate gyrus, may also play a role as they do in Alzheimer's disease (AD).[35,39] Glutamatergic signaling is pathologically upregulated during the ECT seizure, which can result in excessive NMDA-mediated calcium entry into neurons. This excitotoxicity results in oxidative stress and osmotic influx, which can lead to cell death, neurotransmission impediment, and an oversaturation effect exhausting hippocampal long term potentiation induction;

ultimately causing permanent memory loss, disruption of memory creation, and impaired learning capability.[35,39] Cholinergic neurotransmission impairment, a mechanism for the amnesic properties of AD, can also be influencing ECT's effects. Electroconvulsive shocks induce a surge of acetylcholine (ACh) followed by a drop in ACh levels in the postictal period. The lower ACh levels are accompanied by an increase of acetylcholinesterase levels, which would keep ACh levels lower than normal. This along with repeated electroconvulsive shocks down-regulating muscarinic cholinergic receptors can be associated with amnesic properties.[37,39]

Without knowing the exact mechanisms for ECT's cognitive effects, it is extremely difficult to develop a definitive pharmacological approach to mitigate them. Many pharmacological interventions have been attempted for the cognitive protection of ECT patients, but none have yet to be established in practice within the U.S. or internationally.[40,41] Currently there are no FDA-approved treatments for ECT-induced adverse cognitive effects, nor for cognitive impairments in neurologic and psychiatric disorders except Alzheimer's disease.[42] Because of this, studies have investigated using AD medications alongside ECT treatment to mitigate the adverse cognitive effects. The medications researchers have been investigating include acetylcholinesterase inhibitors (AChEIs) and NMDA receptor antagonists (NMDAr antagonists); these are the only FDA approved drugs for cognitive enhancement.[43] Responses with this treatment augmentation could answer some of the questions about the neurobiochemical theories of ECT, and help protect the memory and cognitive abilities of this patient population.

Similar to ECT, hypotheses are still being made for explaining AD's pathophysiology and symptomatology. AD's cholinergic hypothesis theorizes AD's

cognitive decline is due to changed acetylcholinesterase activity and reduced brain acetylcholine levels from atrophying cholinergic neurons in the nucleus basalis and other areas. This is because cholinergic neurotransmitter activity plays an import role in our memory, leaning, attention, and behavior. Therefore AChEIs, like donepezil, prevent acetylcholinesterase from breaking down acetylcholine and preserves acetylcholine levels towards a more normal concentration. This in turn theoretically preserves the cognitive function of AD patients.[44] This could possibly apply to ECT since the induced seizures are shown to cause an acute rise in acetylcholine levels in the brain quickly followed by a drop in acetylcholine levels during the postictal period, with an associated increase in acetylcholinesterase levels. Repeated treatments of ECT have also shown to down-regulate muscarinic cholinergic receptors, making acetylcholine less effective at performing its role for memory and cognition.[39,45,46] Henceforth, an AChEI could theoretically normalize and protect the acetylcholine levels and activity in the brains of ECT patients. This hypothesis is possible given some of the positive cognitive outcomes reported when comparing this adjunctive treatment to placebos in this setting, but the data reported is limited and mixed so it requires further investigation.[40,47,48]

The glutamatergic hypothesis for AD discusses how the disease is linked to excessive glutamate release, and that in turn leads to excessive NMDA receptor activation. Over activation of this receptor leads to a pathological level of calcium influx within the neuron, which causes gradual synaptic dysfunction and ultimately neuronal cell death.[49,50] NMDAr antagonists, like memantine, help diminish the degradation of neurons facing calcium toxicity by blocking the excessive amount of glutamate trying to bind to them, but while still allowing normal levels of glutamate activation to occur. The

protection of neurons in this way is what theoretically preserves cognitive function in AD patients.[39,51] This also can be applied to ECT, as it has been shown to cause changes in glutamate levels within different parts of the brain,[52] and because of a theory that post-ECT memory dysfunction stems from the seizure increasing the effect of glutamate on NMDA receptors through hyper co-activation of reverberating pathways which ultimately irreversibly damages neurons and impedes neurotransmission.[42,53,54] Study evidence of NMDAr antagonists aiding cognitive retention in ECT patients makes this theory plausible, but like AChEIs their data is limited.[39,40,48]

Through utilizing this theoretical link between AD's and ECT's mechanisms of action regarding memory and cognitive deficits, AD's treatment protocols offer potential solutions to ECT's adverse effects. In moderate to-severe AD, utilizing combination therapy with both donepezil and memantine has shown to have greater treatment efficacy than either drug alone.[55,56] Although both AChEIs and NMDAr antagonists are being researched separately for cognitive prophylaxis in ECT patients, no study has yet tested them together in combination therapy.

Statement of Problem

ECT is an underutilized and stigmatized tool used to treat various psychiatric disorders. This makes ECT difficult to access and difficult to accept for the people that would benefit from it. It is historically known that ECT can cause temporary cognitive deficits, including memory loss. Many advancements have been made to reduce its occurrence and severity, but unfortunately these adverse effects are still present today, continuing the call for more interventions and modifications to ECT's induction.

Secondarily, much is still not known about ECT's true mechanisms of action.

Many theories speculate as to why ECT causes these cognitive side effects, but more info is needed in order create new methods of cognitive protection. Currently no FDA-approved pharmacologic treatments exist for the cognitive preservation of ECT patients. Researchers have been investigating the use of AD medication for this purpose, specifically AChEIs and NMDAr antagonists, but the literature is limited.

Currently, AChEIs and NMDAr antagonists have only been researched separately for the cognitive protection of ECT patients. In treating moderate-to-severe forms of AD, donepezil and memantine are used in combination to help preserve the cognitive functioning of AD patients. This combination has not yet been investigated for the purpose of preserving memories and cognition in ECT patients. Filling this gap in the literature has the potential to better protect patients from ECT's side effects, destigmatize ECT, and provide insight into ECT's mechanisms of action.

Goals & Objectives:

We are proposing a double-blind randomized controlled trial (RCT) comparing the effects of donepezil/memantine combination prophylaxis to a placebo group in adults undergoing ECT. The goal is to determine the efficacy of donepezil/memantine combination therapy in providing cognitive protection for patients undergoing ECT. The objective is to compare changes in the cognitive assessment scores of ECT patients being given donepezil/memantine combination therapy to ECT patients undergoing no prophylactic pharmacotherapy.

Hypothesis:

We hypothesize that patients given donepezil/memantine combination therapy will have a significantly greater mean CUAMI-SF score 24 hours after finishing the ECT

series when compared to patients with no prophylactic pharmacotherapy intervention to protect cognition and memories.

Secondarily, we hypothesize that patients given donepezil/memantine combination therapy will have significantly greater mean MOCA, Digit Span Forwards, and Digit Span Backwards scores 24 hours after finishing the ECT series when compared to patients with no prophylactic pharmacotherapy intervention to protect cognition and memories.

References:

1. McCall WV. Handbook of ECT: A Guide to Electroconvulsive Therapy for Practitioners: Charles H. Kellner. Cambridge University Press, New York. 2019. ISBN 978-1-108-40328-3. *The Journal of ECT.* 2019;35(2):144.
2. Wilkinson ST, Agbese E, Leslie DL, Rosenheck RA. Identifying Recipients of Electroconvulsive Therapy: Data From Privately Insured Americans. *Psychiatr Serv.* 2018;69(5):542-548.
3. David L. Perez EDM, Brent P. Forester, Bruce H. Price. Depression and Psychosis in Neurological Practice. *Bradley and Daroff's Neurology in Clinical Practice*. Eighth ed: Elsevier Inc; 2022:97-119.
4. Mankad MV, Beyer JL, Weiner RD, Krystal AD. *Clinical manual of electroconvulsive therapy.* Arlington, VA: American Psychiatric Publishing, Inc ; US; 2010.
5. Fink M. Convulsive therapy: a review of the first 55 years. *J Affect Disord.* 2001;63(1-3):1-15.
6. Lisanby SH. Electroconvulsive therapy for depression. *N Engl J Med.* 2007;357(19):1939-1945.
7. Peterchev AV, Rosa MA, Deng ZD, Prudic J, Lisanby SH. Electroconvulsive therapy stimulus parameters: rethinking dosage. *J ECT.* 2010;26(3):159-174.
8. Petrides G, Tobias KG, Kellner CH, Rudorfer MV. Continuation and maintenance electroconvulsive therapy for mood disorders: review of the literature. *Neuropsychobiology.* 2011;64(3):129-140.
9. Kellner CH, Obbels J, Sienaert P. When to consider electroconvulsive therapy (ECT). *Acta Psychiatr Scand.* 2020;141(4):304-315.
10. van Diermen L, van den Ameele S, Kamperman AM, et al. Prediction of electroconvulsive therapy response and remission in major depression: meta-analysis. *Br J Psychiatry.* 2018;212(2):71-80.
11. Park MJ, Kim H, Kim EJ, et al. Recent Updates on Electro-Convulsive Therapy in Patients with Depression. *Psychiatry Investig.* 2021;18(1):1-10.
12. Fink M. What was learned: studies by the consortium for research in ECT (CORE) 1997-2011. *Acta Psychiatr Scand.* 2014;129(6):417-426.
13. Greenberg RM, Kellner CH. Electroconvulsive therapy: a selected review. *Am J Geriatr Psychiatry.* 2005;13(4):268-281.

14. Zisook S, Ganadjian K, Moutier C, Prather R, Rao S. Sequenced Treatment Alternatives to Relieve Depression (STAR*D): lessons learned. *J Clin Psychiatry.* 2008;69(7):1184-1185.
15. McIntyre RS, Filteau MJ, Martin L, et al. Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. *J Affect Disord.* 2014;156:1-7.
16. Mathew SJ, Wilkinson ST, Altinay M, et al. ELEctroconvulsive therapy (ECT) vs. Ketamine in patients with Treatment-resistant Depression: The ELEKT-D study protocol. *Contemp Clin Trials.* 2019;77:19-26.
17. Sackeim HA. Modern Electroconvulsive Therapy: Vastly Improved yet Greatly Underused. *JAMA Psychiatry.* 2017;74(8):779-780.
18. Zhdanava M, Pilon D, Ghelerter I, et al. The Prevalence and National Burden of Treatment-Resistant Depression and Major Depressive Disorder in the United States. *J Clin Psychiatry.* 2021;82(2).
19. Magnezi R, Aminov E, Shmuel D, Dreifuss M, Dannon P. Comparison between neurostimulation techniques repetitive transcranial magnetic stimulation vs electroconvulsive therapy for the treatment of resistant depression: patient preference and cost-effectiveness. *Patient Prefer Adherence.* 2016;10:1481-1487.
20. Petrides G, Malur C, Braga RJ, et al. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. *Am J Psychiatry.* 2015;172(1):52-58.
21. Luchini F, Medda P, Mariani MG, Mauri M, Toni C, Perugi G. Electroconvulsive therapy in catatonic patients: Efficacy and predictors of response. *World J Psychiatry.* 2015;5(2):182-192.
22. Woo SW, Do SH. Tongue laceration during electroconvulsive therapy. *Korean J Anesthesiol.* 2012;62(1):101-102.
23. Kadiyala PK, Kadiyala LD. Anaesthesia for electroconvulsive therapy: An overview with an update on its role in potentiating electroconvulsive therapy. *Indian J Anaesth.* 2017;61(5):373-380.
24. Chakrabarti S, Grover S, Rajagopal R. Electroconvulsive therapy: a review of knowledge, experience and attitudes of patients concerning the treatment. *World J Biol Psychiatry.* 2010;11(3):525-537.
25. Brus O, Nordanskog P, Båve U, et al. Subjective Memory Immediately Following Electroconvulsive Therapy. *J ECT.* 2017;33(2):96-103.
26. Porter RJ, Baune BT, Morris G, et al. Cognitive side-effects of electroconvulsive therapy: what are they, how to monitor them and what to tell patients. *BJPsych Open.* 2020;6(3):e40.
27. Semkovska M, McLoughlin DM. Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. *Biol Psychiatry.* 2010;68(6):568-577.
28. Lisanby SH, Maddox JH, Prudic J, Devanand DP, Sackeim HA. The effects of electroconvulsive therapy on memory of autobiographical and public events. *Arch Gen Psychiatry.* 2000;57(6):581-590.
29. Sackeim HA. Autobiographical memory and ECT: Don't throw out the baby. *The journal of ECT.* 2014;30(3):177.
30. Sackeim HA, Prudic J, Fuller R, Keilp J, Lavori PW, Olfson M. The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology.* 2007;32(1):244-254.
31. Prudic J. Strategies to minimize cognitive side effects with ECT: aspects of ECT technique. *J ECT.* 2008;24(1):46-51.

32. Obbels J, Verwijk E, Bouckaert F, Sienaert P. ECT-Related Anxiety: A Systematic Review. *J ECT.* 2017;33(4):229-236.
33. Wilkinson ST, Kitay BM, Harper A, et al. Barriers to the Implementation of Electroconvulsive Therapy (ECT): Results From a Nationwide Survey of ECT Practitioners. *Psychiatr Serv.* 2021;72(7):752-757.
34. Singh A, Kar SK. How Electroconvulsive Therapy Works?: Understanding the Neurobiological Mechanisms. *Clin Psychopharmacol Neurosci.* 2017;15(3):210-221.
35. McClintock SM, Choi J, Deng ZD, Appelbaum LG, Krystal AD, Lisanby SH. Multifactorial determinants of the neurocognitive effects of electroconvulsive therapy. *J ECT.* 2014;30(2):165-176.
36. Andrade C. Molecular mechanisms underlying electroconvulsive therapy-induced amnestic deficits: A decade of research. *Indian J Psychiatry.* 2008;50(4):244-252.
37. Matthews JD, Blais M, Park L, et al. The impact of galantamine on cognition and mood during electroconvulsive therapy: a pilot study. *J Psychiatr Res.* 2008;42(7):526-531.
38. Bassa A, Sagués T, Porta-Casteràs D, et al. The Neurobiological Basis of Cognitive Side Effects of Electroconvulsive Therapy: A Systematic Review. *Brain Sci.* 2021;11(10).
39. Pigot M, Andrade C, Loo C. Pharmacological attenuation of electroconvulsive therapy--induced cognitive deficits: theoretical background and clinical findings. *J ECT.* 2008;24(1):57-67.
40. Verdijk J, van Kessel MA, Oud M, et al. Pharmacological interventions to diminish cognitive side effects of electroconvulsive therapy: A systematic review and meta-analysis. *Acta Psychiatr Scand.* 2022.
41. Kellner CH, Adams DA, Benferhat A. Further improving the cognitive effect profile of electroconvulsive therapy (ECT): the case for studying carbamylated erythropoietin. *Med Hypotheses.* 2015;84(3):258-261.
42. Koola MM. Galantamine-Memantine Combination for Cognitive Impairments Due to Electroconvulsive Therapy, Traumatic Brain Injury, and Neurologic and Psychiatric Disorders: Kynurenic Acid and Mismatch Negativity Target Engagement. *Prim Care Companion CNS Disord.* 2018;20(2).
43. Mehlman MJ. Cognition-enhancing drugs. *Milbank Q.* 2004;82(3):483-506, table of contents.
44. Haake A, Nguyen K, Friedman L, Chakkamparambil B, Grossberg GT. An update on the utility and safety of cholinesterase inhibitors for the treatment of Alzheimer's disease. *Expert Opin Drug Saf.* 2020;19(2):147-157.
45. Lerer B. Studies on the role of brain cholinergic systems in the therapeutic mechanisms and adverse effects of ECT and lithium. *Biol Psychiatry.* 1985;20(1):20-40.
46. Lerer B, Stanley M, McIntyre I, Altman H. Electroconvulsive shock and brain muscarinic receptors: relationship to anterograde amnesia. *Life Sci.* 1984;35(26):2659-2664.
47. Henstra MJ, Jansma EP, van der Velde N, Swart EL, Stek ML, Rhebergen D. Acetylcholinesterase inhibitors for electroconvulsive therapy-induced cognitive side effects: a systematic review. *Int J Geriatr Psychiatry.* 2017;32(5):522-531.
48. Niu Y, Ye D, You Y, Wu J. Prophylactic cognitive enhancers for improvement of cognitive function in patients undergoing electroconvulsive therapy: A systematic review and meta-analysis. *Medicine (Baltimore).* 2020;99(11):e19527.
49. Folch J, Busquets O, Ettcheto M, et al. Memantine for the Treatment of Dementia: A Review on its Current and Future Applications. *J Alzheimers Dis.* 2018;62(3):1223-1240.
50. Liu J, Chang L, Song Y, Li H, Wu Y. The Role of NMDA Receptors in Alzheimer's Disease. *Front Neurosci.* 2019;13:43.

51. Kuns B, Rosani A, Varghese D. Memantine. *StatPearls*. Treasure Island FL: © 2021, StatPearls Publishing LLC.; 2021.
52. Njau S, Joshi SH, Espinoza R, et al. Neurochemical correlates of rapid treatment response to electroconvulsive therapy in patients with major depression. *J Psychiatry Neurosci.* 2017;42(1):6-16.
53. Abbasinazari M, Adib-Eshgh L, Rostami A, Beyraghi N, Dabir S, Jafari R. Memantine in the prevention or alleviation of electroconvulsive therapy induces cognitive disorders: A placebo controlled trial. *Asian J Psychiatr.* 2015;15:5-9.
54. Alizadeh NS, Maroufi A, Jamshidi M, Hassanzadeh K, Gharibi F, Ghaderi E. Effect of Memantine on Cognitive Performance in Patients Under Electroconvulsive Therapy: A Double-Blind Randomized Clinical Trial. *Clin Neuropharmacol.* 2015;38(6):236-240.
55. Guo J, Wang Z, Liu R, Huang Y, Zhang N, Zhang R. Memantine, Donepezil, or Combination Therapy—What is the best therapy for Alzheimer's Disease? A Network Meta-Analysis. *Brain and Behavior.* 2020;10(11):e01831.
56. Chen R, Chan PT, Chu H, et al. Treatment effects between monotherapy of donepezil versus combination with memantine for Alzheimer disease: A meta-analysis. *PLoS One.* 2017;12(8):e0183586.

CHAPTER 2: REVIEW OF THE LITERATURE

Introduction:

Currently, there are no studies published evaluating the use of an AChEI with a NMDAr antagonist as a prophylactic treatment to preserve the cognitive functions of patients undergoing ECT. This review of the current literature serves to summarize and critically evaluate relevant research leading to the proposed study. The review was conducted from August 2021 to March 2022 using PubMed, Ovid (Medline(R) ALL, Embase, APA PsychInfo, APA PsycExtra, APA PsycArticles Full Text), Scopus, DynaMed, and Google Scholar. The search terms used within these databases can be found in Appendix I. The review was limited to articles written in English.

Review and Critical Evaluation of Empirical Studies:

Empirical studies regarding the amnesic and cognitive effects of ECT

Reviewing the past literature regarding ECT and its associated cognitive effects is essential to understand the issue at hand. Identifying what domains of cognition are affected by ECT allows one to select proper tools to objectively track its change. A list of all the tests mentioned in this section with their acronyms can be found in Appendix II.

One extremely comprehensive overview regarding the cognitive effects of ECT is a meta-analysis done by Semkovska et al. (2010),[1,2] which aimed to determine the pattern, extent, and post-treatment resolution of ECT-associated cognitive dysfunctions. The studies collected only contained MDD patients without other psychiatric co-morbidities, and studies using bitemporal, unilateral, and/or mixed electrode placements. They pooled and analyzed the tests used to objectively measure different aspects of cognition and categorized them into different cognitive domains, as well as marked their

outcome progressions within three different time intervals. The cognitive domains were: global cognition, processing speed, attention/working memory, verbal episodic memory, visual episodic memory, spatial problem solving, executive functioning, and intellectual ability. The time intervals gauging the presence of deficits in these domains post-ECT were: subacute (0-3 days post-ECT), short-term (4-15 days), and long-term (>15 days). A total of 84 studies, consisting of 2981 participants and 22 standardized objective neuropsychological tests, were collected and meta-analyzed.

They reported their statistics within each individual test and not their assigned cognitive domain, making it difficult to summarize their results plainly. Overall, this paper showed that ECT for depression can cause significant cognitive impairment, and this impairment can be expected 0-3 days post-ECT. These subacute deficits are medium-large in effect for episodic memory, executive functioning, and some aspects of verbal memory, but small for processing speed, spatial problem solving, and global cognition. After two weeks have past, the majority of cognitive functions improved relative to baseline. This paper synthesized a lot of data to get a clear picture on the nature of ECT's cognitive disruptions, but one major flaw with this meta-analysis is that it excluded a well-documented and concerning cognitive side effect, which is retrograde amnesia.[1,3]

Very recently, a new meta-analysis by Landry et al. (2021)[4] was published with the same purpose as the one done by Semkovska et al. (2010),[2] except the new meta-analysis also included all mental disorders indicated for ECT, more long-term results, and autobiographical memory. They used 91 studies involving 29 different cognitive tests with an aggregated sample of 3762 individuals for data extraction to meta-analyze and calculate effect size estimates of the differences in cognitive scores pre- and post-ECT.

The cognitive tests were again categorized into cognitive domains, which were: global cognition, attention/working memory, autobiographical memory, executive functions, processing speed, verbal fluency, verbal learning, verbal memory, visual learning, visual memory, and visuospatial abilities. The post-ECT results of these tests were also separated into one of three time points: Immediate (within 24 hours of the last ECT treatment), short-term (1-28 days post-ECT), and long-term (more than 1-month post-ECT). For the highlights of their results: 1) Immediately after ECT there was no significant impact on global cognition (95% CI −0.162 to 0.421; p = 0.383), with the remainder of the domains providing insignificant data. 2) For the short-term period, cognitive scores post-ECT were significantly worse relative to pre-ECT scores for autobiographical memory (95% CI 0.145 to 0.595, p=0.001), verbal fluency (95% CI 0.197 to 0.418, p=0.0001), and verbal memory (95% CI 0.098 to 0.477, p=0.003), with no significant impact on the rest of the domains besides a small improvement in executive functioning and the presence of significant publication bias (t=2.2; P=0.03). 3) For the long-term period, test scores significantly improved in executive functions, processing speed, verbal fluency and verbal learning, verbal memory, visual learning, visual memory, and global cognition, with no significant effect on attention/working memory and autobiographical memory.

What this paper added to the previous meta-analysis was that autobiographical memories and some aspects of verbal usage were significantly impaired during the short-term period post-ECT, while the remaining aspects of cognition were unaffected or improved after ECT. Despite this updated information providing autobiographical memory and longer-term data, this study had significant confounders with the use of all

psychiatric diagnosis being included, likely impacting test results in various ways. Also, their choice of timespan for their immediate (less than 24 hours) and short-term (1-28 days post-ECT) period groups was odd when considering the findings and timespans used by Semkovska et al. (2010).[2] By using 1-28 days as their "short-term" period, they over-generalized the cognitive changes within this time frame since previous literature suggests most cognitive deficits last till about 14 days maximum,[1,2,5] ultimately mixing together early negative cognitive effect scores with later recovered or improved scores. Also, by using scores recorded 0-24 hours post-ECT, they would be including post-ictal and post-anesthesia cognitive states, likely influencing the patient's cognition.

Both of these meta-analyses showed that cognitive functioning can worsen or improve after ECT on various domains. A likely reason why there were improved cognitive scores post-ECT from baseline is because ECT effectively treats depression.[2] Depression itself can cause cognitive deficits, with greater depression severity at baseline being associated with worse performance on cognitive tests.[4,6,7] Hence, the remission of this condition can improve cognitive functioning.

Although it is easy to automatically resort to objective tests to monitor for post-ECT changes, it is important to consider subjective memory changes in patients to optimize patient-centered care. This is because, more often than not, clinicians underestimate treatment harms and overestimate treatment benefits.[8] Therefore accounting for the additional risk of subjective memory loss in ECT can help improve treatment outcomes and patient willingness to be retreated,[9] since there is a wide variation of 36%-98% of ECT patients who would consider having a second course of ECT.[10] Often it is the case that objective measures of memory do not correlate with

subjective accounts of memory loss. Patients typically present with more subjective than objective memory complaints, and that these subjective reports haven been shown to be heavily influenced by their mood state.[11,12] Despite this, patient satisfaction is important to maintain continuity of care, and there remains the possibility that subjective assessments of memory can represent uninvestigated components of cognitive functioning not shown in objective batteries.[11]

Empirical studies regarding the pharmacological treatment of Alzheimer's disease

In regards to the proposed study's pharmacological intervention, efficacy within its current scope of use should be reviewed to help ensure an effect can take place if one is to be had. AChEIs and NMDAr antagonists are the main treatments for AD, with donepezil being the most commonly used AChEI and memantine being the most prevalent NMDAr antagonist.[13] Donepezil and memantine are both shown to effective in the symptomatic treatment of AD, improving aspects such as memory, awareness, and activities of daily living (ADLs) in this population.[14] The combination of these two medications under the brand name Namzaric was approved by the FDA in 2014 to treat patients with moderate-to-severe symptoms of dementia.[14,15] In a recent meta-analysis done by Guo et al. (2020),[14] the efficacy and risks of memantine and donepezil as a combination for AD was compared to both to memantine and donepezil individually and to placebo. A total of 54 RCTs were meta-analyzed, with their outcomes demonstrating the intervention's efficacy (sub-divided into cognition, global assessment, daily activities, and neuropsychiatric symptoms), acceptability, cost, and adverse effects in AD patients.

Guo et al. (2020)[14] found combination therapy to be the most effective treatment in improving cognition (ADAS-cog 95% Crl -0.86 to 10.73, SIB 95% Crl 2.29 to 16.97),

global assessment (CGI 95% Crl -6.07 to 1.09 when compared to 2nd place donepezil), activities of daily living (ADL 95% Crl -8.06 to 40.52), and neuropsychiatric symptoms (NPI 95% Crl -8.06 to -0.15). They also found that combination treatment was better accepted by patients than donepezil but lower than memantine, was more cost-effective than donepezil alone when accounting for efficacy, and was no different than monotherapies in reported adverse events. This paper hence demonstrated the superiority of donepezil/memantine combination therapy over monotherapies for the treatment of AD, along with demonstrating its practicality within the clinical setting. This meat-analysis was consistent with previous reviews,[13,16] but its inclusion of memantine monotherapy made this paper unique in the literature and relevant to the proposed study.

Empirical studies exploring AChEIs to reduce ECT's cognitive changes

The possible relationship between ECT's cognitive effects and AD's cognitive effects through cholinergic inhibition was mentioned earlier in Chapter 1. This led to some researchers exploring the use of AChEIs, like donepezil, to mitigate ECT's cognitive effects, with mixed results. Overall, 6 RCT studies involving donepezil and 3 additional studies involving other AChEIs used in AD were found. Of the 6 donepezil studies, 4 demonstrated significant cognitive benefit or recovery in ECT patients.[17-22] Of the 3 additional studies which investigated rivastigmine and galantamine, only the 1 study investigating rivastigmine definitively demonstrated a significant improvement in post-ECT cognition scores.[23-25]

The first RCT investigating donepezil as a possible cognition-preserving agent in human ECT patients was done by Prakash, Kotwal, & Prabhu (2006).[22] This triple-blind placebo controlled trial focused on the patient's recovery from their post-ictal state within

90 minutes of finishing their final ECT, in contrast to all the other studies later measuring the patient's level of cognitive functioning at later time-points. After 6 to 10 ECT sessions, the patient after their final session was immediately administered the Mini-Mental State Exam (MMSE) every 5 minutes for 90 minutes. Their study results suggested that patients taking 5mg/day donepezil had a significantly faster recovery of cognitive deficits post-ECT, but the applicability of this study is only limited to the state of the patient up to 90 minutes after their final ECT. Although they reasoned time-to-recovery following ECT may predict later cognitive outcomes, this study did not investigate far enough to display if such effects occurred. Additionally, the practice effect from doing the same test every 5 minutes would significantly confound results.

The latest and the largest RCT done so far investigating this topic has been performed by Zarean, Sedehi, & Heshmati (2021).[19] They performed a double-blind placebo-controlled RCT to examine the effects of donepezil on the cognitive performance of patients with mood disorders undergoing ECT. A total of 94 patients, aged 15-65, having MDD or bipolar disorder were either given 5mg/day donepezil or placebo while being administered bitemporal ECT three times per week up to a total of 6 – 10 ECT sessions. They cognitively assessed via the MMSE and ACE-R 24 hours before beginning ECT, 2 hours after their fourth ECT session, and one month after the last ECT session. They found that the mean MMSE score ($p = 0.026$). and mean ACE-R score ($p = 0.019$) across all three measurements were significantly higher in the donepezil group than the placebo group. Mean scores for four of the five cognitive subscales of the ACE-R were also noted to have significantly improved compared to placebo. These results suggest ECT patients receiving donepezil will have higher cognition scores shortly and

long after treatment than patients not taking donepezil. This study did a good job controlling for potential confounders, taking into account the 15 days donepezil needs to achieve a steady-state,[26] and providing beneficial long-term data for the literature. They were unable to account for different side-medications, disease durations, nor quantities of mood disorder episodes between groups, but randomization would have helped control for any confounding effects they would have had.

The remaining tests are no less relevant to the literature, but will be explained in brief. Nazarinasab, Behrouzian, & Hajatzadeh et al. (2019)[20] tested 5mg/day donepezil against 3mg/day rivastigmine and against placebo in 60 total patients undergoing ECT with various disorders using the MMSE to measure cognition at unspecified times before, half-way through, and after their acute series of ECT. Their results found that, for the middle and post-ECT assessments, placebo scores significantly decreased while the AChEI groups were not statistically changed from baseline. Shams-Alizadeh et al. (2019)[17] tested the effects of 5mg/day donepezil against placebo in 70 total patients undergoing ECT with various disorders using the MMSE and WMS-III one day before and 2 days after an acute series of ECT. Their results did not show donepezil having significantly improved cognitive scores compared to placebo. Prakash et al. (2019)[21] tested the effects of 10mg/day donepezil against placebo in 90 patients undergoing ECT with depression or psychosis using the WMS-III Indian adaptation to evaluate memory two days before, an unspecified time after, and 4 weeks after an acute series of ECT. Their results found that the placebo group had significant "immediate memory" worsening over the course of ECT till 4 weeks have past, while donepezil had no such worsening. Dutta, Sarkar, and Andrade (2020)[18] tested the effects of 10mg/day donepezil

against placebo in 30 patients undergoing ECT with either depression or schizophrenia using the PGI-MS to measure cognition 2 days before and 2, 7, and 30 days after an acute series of ECT. Their results found no significant difference between donepezil and placebo in short-term worsening nor in the long-term improvement of cognitive scores.

Empirical studies exploring NMDAr antagonists to reduce ECT's cognitive changes

The possible relationship between ECT's cognitive effects and AD's cognitive effects through excessive glutamate release, NMDA receptor activation, and calcium toxicity were mentioned earlier in Chapter 1. This led to some researchers exploring the use of NMDAr antagonists, like memantine, to mitigate ECT's cognitive effects, with more promising results compared to AChEIs. Overall, 3 RCTs involving memantine were found, all originating from Iran and Iraq. All 3 of these studies showed memantine significantly protecting the cognitive abilities of ECT patients, but the data from these studies only encompass effects 24 hours after the final ECT in an acute series.[27-29] Over 20 additional studies involving ketamine, a NMDAr antagonist, on humans and rats were also found. However, their studies will not be discussed here since ketamine is not used to treat AD. Also of note, three recent meta-analyses showed there is a lack of any favorable effect by ketamine for the cognitive outcomes of ECT patients.[30-32]

The first clinical trial studying the effect of memantine on ECT-induced cognitive dysfunction was performed by Abbasinazari et al. (2015).[29] They performed a double-blind placebo-controlled RCT involving 40 patients with MDD to explore memantine's efficacy, safety, and tolerability in this setting. Twenty-four hours before starting their first ECT, patients were given 5mg/day memantine or placebo, and then assessed with the MMSE. Right unilateral ECT was administered every other day until 4 sessions were

complete. They were again administered the MMSE 24 hours after the last ECT treatment. Total MMSE scores and MMSE Item 3 scores (a task to measure related to recent memory) were compared to their baseline scores from before starting ECT.

They found that the memantine group had significantly higher post-ECT scores in both the total MMSE ($p = 0.02$) and in Item 3 of the MMSE ($p < 0.001$) when compared to placebo. They also found no statistical difference between the before and after ECT scores for the memantine group ($p = 0.13$), as well as found a significant decrease in total MMSE scores for the placebo group ($p = 0.003$). What this is demonstrating is that 5mg/day memantine can protect patients from some of the cognitive effects ECT can illicit. Although this simple study was novel for using memantine in this way, their study had a small sample size, a very short course of ECT, and only used the MMSE with one of its subset items to measure cognition. Although effective as a first step, this study only contributed a small amount data towards what they sought to investigate.

Alizadeh et al. (2015)[28] shortly followed Abbasinazari et al. (2015)[29] with their own double-blind placebo-controlled RCT, except they used included more ECT-indicated diagnoses, higher doses of memantine, and more cognitive tests. They tested 38 participants with the MMSE and the direct digit span and backward memory span tests of the Wechsler Adult Intelligence Scale both 24 hours before and after their first and final ECT treatments respectively. If not placed in the placebo group, participants were given 10mg/day of memantine to start, later followed by an increase to 20mg/day till the end of their ECT course. The participants received 4 to 12 total bilateral ECT sessions, with 3 sessions being performed per week. After comparing post-ECT scores to baseline, they found that the intervention group had greater mean MMSE scores ($p < 0.001$), greater

mean backward digit span scores ($p = 0.001$), and insignificant changes in mean forward digit span scores following ECT, all while the control group had a significant decrease in all mean scores following ECT. This again suggests memantine can help protect cognitive functioning in ECT patients. Despite adding much needed data to the literature and using a more generalizable scenario, this study had a few issues. First, the inclusion of various psychiatric diagnoses within the study promoted confounding. Second, the use of a 10mg/day memantine followed by a 20mg/day dosage of memantine a week later may not be clinically applicable, as that titration rate is not recommended by the FDA.[33] They also did not seem to include all of their data within the paper, sometimes making statements about the significance of results without showing their respective p-values.

The third and final RCT involved with memantine by Sarraf et al. (2020)[27] almost exactly mimicked the protocol of Abbasinazari et al. (2015),[29] but used 6 ECT sessions instead of 4, and they compared memantine to melatonin and not a placebo. They found that MMSE ($p = 0.04$) and item 3 MMSE scores ($p = 0.03$) at the end of ECT were significantly increased compared to baseline, but there was no placebo to compare the results to.

Meta-analyses of the effect of AChEIs and NMDAr antagonists in ECT patients

Two recent meta-analyses were performed investigating the use of pharmacologic interventions to diminish ECT-induced cognitive side effects. The meta-analysis done by Niu et al. (2020)[34] included 5 RCT studies comparing a cognitive enhancer to a placebo, using a total of 202 patients of various psychiatric diagnoses. These studies involved either memantine, galantamine, donepezil, or rivastigmine, as well as included the MMSE, 3MS, or RBANS as measures of cognitive performance. Using standard mean

differences (SMD) with 95% CI on a fixed-effect model, they reported that the overall cognitive functioning score in the cognitive enhancer group was significantly higher than the placebo group (SMD = 0.47, 95% CI=0.18 to 0.75, p = 0.001), and that only two trials of the five reported a statistically significant protective effect (Alizadeh memantine SMD = 0.88, 95% CI = 0.21 to 1.55; rivastigmine SMD = 0.93, 95% CI = 0.08 to 1.78). This means that overall, the use of medications to diminish ECT-induced cognitive side effects is possibly viable. It also suggests that the use of memantine and rivastigmine may be more efficacious than the other medications included in the study. However, these results should only be considered "broadly representative," since it was derived from a small quantity of relevant but heterogenous studies. But, through evaluating the reliability of the studies done thus far and outlining what direction results are ultimately pointing towards, this meta-analysis is an asset towards ECT literature.

The meta-analysis done by Verdjik et al. (2022)[32] was much broader than the one listed prior, performing a quantitative synthesis of 26 studies using 12 different pharmacologic interventions and totaling 1387 patients with various diagnoses. They used studies where cognition was assessed within a short-time following the end of an acute series of ECT. The data collected was from tests measuring global cognition, immediate recall, delayed recall, and executive functioning, in studies investigating ketamine, memantine, acetylcholinesterase inhibitors, thyroid medications, calcium antagonists, and more. With this compilation of studies, they were able to quantify the size of effect for each intervention and qualify the evidence behind it. In relevance of the proposed study, this meta-analysis determined that there is low-quality evidence demonstrating memantine having a large effect, very low-quality evidence demonstrating

AChEIs having no effect to a large effect, and very low-quality evidence demonstrating ketamine having no effect on the diminishment of ECT-induced cognitive side effects. It is therefore implying that AChEIs and NMDAr antagonists may help diminish the negative cognitive effects seen in ECT patients shortly following the end of their treatment. It further implies through low-quality evidence that memantine is more likely to have a stronger effect than an AChEI, and ketamine is not likely to have any effect. The same problems of the previous meta-analysis are also applicable here, with the addition of even more heterogeneity in cognitive tests and medications used.

Overall, the limited literature surrounding AChEIs and NMDAr antagonists for the cognitive protection and recovery of ECT patients suggests that these medications may indeed provide some benefit. With the promising results shown and discussed, this topic warrants further investigation, and so the proposed study was created.

Review of Studies Regarding Possible Confounding Variables:

With over 80 years of research behind ECT, many variables have been identified to alter the likelihood and severity of ECT-cognitive effects.[1] Identifying and controlling these possible confounding variables is crucial to the study, as their influence can skew results into a misrepresentation of drug efficacy in this setting.

Demographic factors

Cognition and memory are multifactorial processes, influenced on various fronts. In regards to ECT, various individual patient factors have shown to influence post-ECT cognitive outcomes. The reviews done by Porter et al. (2020)[1] and McClintock et al. (2015)[35] are useful summaries and references on this topic, but both highlighted its limited investigation. Both mentioned advanced age as a possible but unconfirmed risk

factor, referencing only one outdated article from 1975[36] using memory tests in ECT patients six to nine months after treatment. The most recent meta-analysis regarding age and other factors is from a previously mentioned study by Landry et al. (2021).[4] The secondary objective of their review was to identify baseline clinical characteristics that may mark a greater risk of cognitive deficits from ECT. They found age had a negative association with verbal fluency ($p = 0.003$), but not on 10 other cognitive domains.

In regards to gender, only one study found that females are more vulnerable to autobiographical memory deficits post-ECT.[37] Intellectual ability, like age, was cited to be a possible risk factor according to the outdated 1975 article in the reviews,[1,35,36] but the meta-analysis from the before mentioned Semkovska et al. (2010)[2] displayed a non-significant relationship. Limited research has also shown that the presence of psychotic symptoms can worsen pre-ECT cognition scores,[38] and the presence of pre-existing cognitive difficulties can exacerbate negative post-ECT cognitive outcomes.[1,35,39] The severity of depression at the time of testing can also adversely affect cognition test scores.[7] Lastly, lithium has been associated with an increased risk of ECT cognitive side effects.[1,40] Other possible risk factors listed by McClintock et al. (2015)[35] included: the presence of comorbidities, the quantity of distinct neuropsychiatric episodes experienced, and how long one has had their psychiatric condition.

ECT induction factors

More concrete information is known about how ECT parameters can affect treatment efficacy and side-effects. The summaries by Porter et al. (2020)[1] and McClintock et al. (2015)[35] again provide together a good general overview of this topic. Additional details can be obtained through a focused review by Peterchev et al. (2011).[41]

One of the most notable factors affecting cognition is electrode placement. Electrode placement determines the degree of stimulation within different brain regions; the distance between the electrodes determines the focality or generalizability of the stimulus. Therefore, electrode placement allows one to target specific structures that may provide more therapeutic benefit, while avoiding areas that could cause cognitive side effects.[41] The two most commonly used electrode placements are right unilateral (RUL) and bitemporal aka bilateral (BL) placement. It is traditionally thought that BL placement is more efficacious at treating psychiatric disorders than RUL, but at the cost of greater cognitive impairment.[1,35,41] This was derived by various RCTs,[42-45] but some studies did suggest there is no such correlation.[46] Interestingly, different meta-analyses on the subject provided inconsistent results. Another meta-analysis by Semkovska et al. (2011)[47] comparing unilateral to bilateral electrode placements suggested that patients 0-3 days after RUL ECT have significantly less impairments in global cognitive status, delayed verbal memory retrieval, and autobiographical memory than patients who received BL ECT. A specific RUL vs. BL meta-analysis done by Kolshus et al. (2016)[48] corroborated these results finding significantly greater autobiographical memory deficits in BL placement over RUL placement through CUAMI & CUAMI-SF (Columbia University Autobiographical Memory Interview – Short Form) scores. Recently though, the meta-analysis by Landry et al. (2021)[4] suggested that there is a small significant difference in verbal memory between the two placements, but no significant differences in global cognitive screening, autobiographical memory, and verbal fluency.

Followed by electrode placement, stimulus waveform and pulse width have also been found to be significant influencers. Sine wave stimulus was the first form used in

ECT, but it is now obsolete to rectangular wave forms. This was following clinical evidence that there is no difference in efficacy between the two waveforms, but sine waveforms significantly decreased cognitive functioning across various domains when compared to rectangular waveforms.[35,37,41] Current clinical practice uses bidirectional rectangular brief pulse width (between 0.5–2 ms) or ultra-brief pulse width (less than 0.5 ms) stimulus.[35] Between the two widths, the reviews[35,41] along with a meta-analysis by Tor et al. (2015)[49] comparing the two widths in RUL electrode placements suggested brief pulse width has an efficacy advantage over ultra-brief, but this comes with significantly more cognitive side effects in memory and global cognition.

More factors to consider are ECT stimulus pulse amplitude, train frequency, and duration. These factors along with pulse width make up the total charge delivered by an ECT device. Adequate charges are essential to induce a proper seizure, and practitioners will personalize these parameters in accordance to the patient's seizure threshold. Overshooting the seizure threshold with large amplitudes, frequencies, or train durations is associated with greater cognitive impairment, and thus titration protocols are used to dose adjust down to the lowest charge necessary to produce an adequate seizure.[35,41]

Lastly, details surrounding the ECT course schedule should be noted, but data is limited. The number of ECT sessions has not shown to be associated with any change in cognitive functioning.[2,7,36] Despite this though, 12 treatments is often near the upper limit of treatments performed in an acute series, as most patients who respond to ECT do so within this number of treatments.[1] The frequency of ECT sessions per week in an acute series is usually 2 or 3 sessions a week, with 3 sessions per week believed to provide quicker psychiatric symptom relief but greater cognitive side-effects.[1,2]

Review of Relevant Methodology:

So far, the strengths and weakness of similar previous studies were reviewed, and confounding variables were identified. In order to justify the proposed study's methodology, this section reiterates what has already been discussed, and presents additional information to validate the choices made in the study's design.

Study design

The proposed study will be a randomized double-blind placebo-control trial, a design used to determine causality in the clinical setting and limit both selection and information bias.[50] This RCT will compare the objective and subjective cognitive test scores of 2 different groups of patients being treated with ECT for MDD. The intervention group will be given a potential cognition protecting medication combo, and the control group will be given a placebo. The study will compare the cognitive scores of patients before their first ever ECT session and after their final ECT session in an acute course. It will also compare the mean post-ECT cognitive test scores between the two groups. To objectively measure cognition, the CUAMI-SF, MOCA, Digit span forward, and digit span backward tests will be used. The objective tests will be preceded by a subjective measure of cognition through the Squire Subjective Memory Questionnaire (SSMQ). The CUAMI-SF scores will the primary outcome of the study, since autobiographical memory loss is one of the principal side effects of concern to patients.[51] The remaining test scores are secondary outcomes.

A combination of donepezil and memantine has been chosen to be this study's novel pharmacological intervention. This combination was chosen for various reasons: 1) This FDA-approved combo is commonly used in moderate-to-severe AD, and has

demonstrated superior efficacy over both donepezil and memantine monotherapies.[14,15] 2) Donepezil is the most commonly used AChEI in AD,[13] and is shown to be more effective than galantamine and more tolerable than rivastigmine in treating AD symptoms.[52] 3) Memantine is the only FDA-approved medication of its class to treat AD.[53]

ECT induction parameters will be standardized to limit potential confounders. A minimum of 6 and maximum of 12 ECT sessions will be used to measure cognition. This aligns with the recommended number of treatments to include in an acute series, as outlined by the American Psychological Association taskforce's report on ECT.[1,54] Rules, regulations, and considerations from Yale's Institutional Review Board (IRB) will structure this study and provide security for the participants.

Sample population

The target population is adult MDD patients, both males and females, aged 18-65 years old, with moderate-to-severe depression, residing in the United States. Only unipolar MDD is being targeted due to its prevalence in clinical practice,[55] and to prevent other mood disorders and psychiatric conditions from becoming confounders to the results. The age range is put in place to control for age as a possible confounder.[4]

Inclusion criteria

The inclusion criteria of this study imitates previous studies. Inclusion criteria will include: the primary diagnosis of MDD in accordance to the DSM-V, planned ECT treatment for a current major depressive episode, ages 18-65, English as their primary language, moderate-to-severe depression as defined by baseline Hamilton Depression Rating Scale (HAMD-17) scores of 17 or greater, and the informed written consent of the patient.[23,29,56,57] The HAMD-17 is a widely used clinical rating scale for depression

severity, and will serve to validate their MDD diagnosis, screen patients for moderate-to-severe depression, and help eliminate depression severity as a confounder.[7]

Exclusion criteria

The exclusion criteria of the study is based off of previous studies investigating the effects of AChEIs and NMDAr antagonists, along with additional potential confounders mentioned in the earlier section of this chapter.

Patients using any of the following medications during or within 3 months of starting the study will be excluded.[17] Due to also being investigated for mitigating ECT-induced side effects: another AChEI or cholinergic agent, another NMDAr antagonist (like ketamine anesthesia), melatonin, dexamethasone, vasopressin, naloxone, piracetam, nitroprusside, thyroid medications, calcium channel blocker, COX-2 inhibitors, and opioids.[19,32,58] Despite being a potential confounder to results, patients on lithium will not excluded as the randomization of this trial should account for it.[1,40]

Patients having any of the following conditions within their past medical history will be excluded. Due to their influence on the brain and cognition, as well as their possibility to confound results: neurological disorders, strokes, seizures, cognitive disorders, learning disabilities, brain trauma, and brain surgeries.[17,19-21,27-29] Due to their influence on the study medications, being contraindicated for said medications, or for being a safety risk factor in ECT: renal or hepatic impairment, current pregnancy, recent post-partem, breastfeeding, obstructive sleep apnea, other sleeping disorders, cardiac disease, gastrointestinal lesions, and confirmed or suspected allergies to donepezil or memantine.[17,19,20,27-29,33,59] Conditions that qualify for exclusion so long as they are present during or within 3 months of the study, due to their ability to potentially influence

cognition and confound results: catatonia, substance abuse disorder, alcohol abuse, schizophrenia, schizoaffective disorder, bipolar disorder, eating disorders, obsessive compulsive disorder, post-traumatic stress disorder, and psychosis.[17,19,20,27-29,35,38,39] Inability or unwillingness to give written informed consent will result in exclusion.

Memory, cognition tests, and depression tests: primary and secondary outcomes

Currently, there is no "gold standard" cognitive screening tool to measure these induced effects in ECT patients,[60] so the tests chosen to be used in this study are based off of previous literature regarding ECT and mild cognitive impairment (MCI).

The Columbia University Autobiographical Memory Interview – Short Form (CUAMI-SF) scores will be the primary outcome measure of the study. The CUAMI-SF is a shorter version of the CUAMI. They are both objective standardized tests used to monitor the loss of autobiographical memory in ECT patients through eliciting and recording a large number of memories before the initial treatment, followed with prompting patients to retrieve said memories later in or at the end of the treatment course to create an overall percentage of memory consistency.[1,61] These measures are the most commonly used methods in contemporary literature to track retrograde autobiographical memory deficits after ECT.[1] Although prevalent in research, it is not used clinically, has limited data available in the literature, has not been thoroughly peer-reviewed, and is plagued with harsh controversy surrounding its validity.[51,62] In defense of this test, it is sensitive to the different approaches of ECT induction, has displayed greater amnesic scores in post-ECT patients than amnesic scores of normal controls over time, and demonstrates covariation with subjective patient reports of post-ECT amnesia.[1,51] The issue with this test is that it is difficult to distinguish a loss of autobiographical memory

due to ECT from a loss of consistency due to time and a loss of specificity due to depression.[63] Also some items asked in the test can be discriminative in certain people or populations with different lifestyles.[1] Because it is currently considered the best attempted scale to measure autobiographical memory loss in ECT patients to date,[1] and because its presence in ECT literature, the CUAMI-SF was chosen to be part of the study. This test has not been used before in AChEI or NMDAr antagonist trials against ECT cognitive side effects, and so the results of this study will produce novel information regarding pharmacotherapy prophylaxis for autobiographical memory in this setting.

The Montreal Cognitive Assessment (MOCA) and MMSE are the two most widely used global cognitive screening tests today. Although the MMSE is the most widely used test to assess the impact ECT has on global cognitive functioning,[4,60] the MOCA is superior to the MMSE in that it is more sensitive with detecting MCI in depression, AD dementia, and ECT patients.[60,64,65] The MOCA is also used clinically at times to track cognition changes in ECT patients at YNHH, the primary setting of the study. For these reasons, the MOCA was chosen to be included in the study to measure global cognition changes in the participants, though it has never been used before in the assessment of donepezil or memantine in this setting. Two different versions of the MOCA will be used, one version pre-ECT and a different one post-ECT, so that memories of the specific task questions will not influence results.

The Digit Span Forwards (DSF) is a test that measures attention efficiency, or one's freedom form distractibility. The Digit Span Backwards (DSB) is a measure of working memory, or one's ability to mentally manipulate items in short-term memory.[2,66] These tests have been included in previous ECT studies involving cognitive monitoring

and have been shown to change alongside ECT-induced autobiographical memory changes.[66,67] This along with the ease and speed of its administration is why it will be included in the proposed study.

The Montgomery-Asberg Depression Rating Scale (MADRS) is an objective clinical measuring tool to assess depression severity in patients.[68,69] It along with the HAMD-17 interview are the most commonly used clinical depression scales. The MADRS has demonstrated to have greater sensitivity to treatment-related changes in depression severity than the HAMD-17,[70,71] and has been useful in measuring treatment progression in ECT.[72] For these reasons, the MADRS was chosen to mark ECT treatment progression within the study, while the HAMD-17 will be used to initially screen patients for their depression severity.

The Squire Subjective Memory Questionnaire (SSMQ) is a questionnaire developed to subjectively measure and differentiate any memory complaints related to depression before ECT from any amnesic complaints after ECT.[73,74] It is the most commonly used tool to measure subjective memory change in ECT,[9] and therefore was chosen to measure subjective memory change in this study.

Medication dosages

This study sought to give donepezil/memantine combination therapy the best possible opportunity to demonstrate its efficacy. For this reason, initial medication dosages will be high, followed by quick up-titrations to their maximum or near-maximum dosages. Medication will be started one week before the first ECT session, with the initial doses 5mg/day for donepezil and 10mg/day for memantine. After the first ECT session, medications will be up-titrated to 10mg/day for donepezil and 20mg/day for memantine.

In normal practice for AD, donepezil starts at 5mg/day and is up-titrated to 10mg/day after 4 to 6 weeks. It can further be increased to 23mg/day after being on 10mg/day for at least 3 months.[59] Similarly, memantine typically starts at 5mg/day and is up-titrated by 5mg/day every week until it reaches the max dosages of 20mg/day.[33] These dosages and titrations schedules are listed on their drug labels, since higher initial dosages and quicker titrations led to higher rates of common adverse reactions, including nausea, diarrhea, insomnia, dizziness, and headaches.[33,59] The dosages and titration schedules that this study will be utilizing are different from the label, but mimic previous ECT studies done with these medications. In those studies, there were no significant differences in side effects or adverse events between the high-level medication group and placebo.[18,22,28] By giving higher dosages sooner, this study is promoting the occurrence of any potential effect the medications may give ECT patients in regards to cognitive protection, since higher dosages of these medications have proven to be more efficacious in AD than smaller ones.[33,75] Additionally, starting these medications one week before ECT treatments start allows time for these medications to reach their steady state and take effect within the patient.[26,76] The patients will be titrated off the medications following the conclusion of their acute course of ECT. Patients may report side effects and adverse events at any time by contacting their investigator. Weekly check-ins by the investigator will monitor for safety. Medication adherence will be monitored through MEMS electronic pill bottles, which records the date and times it is open and closed.[77,78]

Sample size

Given that the primary outcome of the study is mean CUAMI-SF scores, the sample size calculation was created based off of one study that measured CUAMI-SF

scores before and after a number of ECT sessions. Only one study, performed by Alvarez-Grandi et al.,[67] was used due to the limited literature and reported data surrounding the CUAMI-SF. In this study, ECT patients received a cognitive battery of 5 different cognitive tests before starting ECT, and then after treatments #3, #6, and #9. The researchers of this study found the mean CUAMI-SF score of 214 patients to be 24.5 +/- 4.37 at baseline, and a mean score of 52 patients to be 21.33 +/- 4.68 after 9 treatments of ECT. Along with these values, the following assumptions were made in order to create an estimated sample size: 1) The predicted "Post-ECT Combo-Therapy" mean will be represented by the baseline mean CUAMI-SF scores mentioned in the study. In other words, it is being presumed that combo-therapy will perfectly retain patient memories from baseline to the post-ECT assessment. 2) The predicted "Post-ECT Placebo" mean will be represented by the post-treatment # 9 mean CUAMI-SF scores. 3) The smaller SD of the predicted means will be replaced by the larger SD of those means. With these assumptions and values, the estimated sample size for this study calculated via Power And Precision 4* with a two-sided hypothesis and a statistical significance of 0.05 for alpha and power of 80% is 70 participants. Based off of previous studies with similar designs where participant drop-out occurred, a predicted 12% drop out rate is expected.[17,18,23,28] Adjusting for the predicted drop-out rate, the new estimated sample size when rounded up to the nearest even number is 80 participants, with 40 participants in each group. Based off of the conservative assumption that 2 patients per facility can be recruited per month, with a recruitment time restraint of 22 months, a total of 44 patients per facility can be recruited for this study. Hence, at least 2 facilities will be needed for this study. All calculations can be found in Appendix III.

The effect size of this study based off of the above estimates is moderate, with a calculated Cohen's d of 0.68. This estimate is rough due to the lack of data surrounding the CUAMI-SF and many differences between this study and the one the estimates are based off of. The issues of this estimation include the following: 1) This study will be administering ECT three times a week, while the referenced study administered ECT twice a week. 2) This study will exclusive administer ECT with BL electrode placement, while the referenced study had a three-to-one ratio of RUL to BL placement. 3) This study will exclusively include MDD patients, while the referenced study included patients of various psychiatric disorders. 4) The referenced study did not score the CUAMI-SF the way it was intended to be scored, using their own custom scoring method. 5) This estimate did not consider the normal rate of forgetting when estimating the "Post-ECT Combo-Therapy" mean. 6) This estimation is assuming the CUAMI-SF scores are normally distributed, but there is no indication whether they are or not.

Conclusion:

The purpose of this review of literature is to acknowledge what is known, what is not known, what has been done before, and what can be done to further expand this branch of psychiatric research. Similar past studies and relevant meta-analyses were discussed and critically analyzed to provide an up to date understanding of where prophylactic pharmacotherapy currently stands in its investigation, as well as provide inspiration towards this proposed study's methodology. Reviews, other meta-analyses, and their cited RCTs provided background information on ECT, memantine, and donepezil to help justify the parameters of the proposed study. By orchestrating a methodology where one of the strongest FDA-approved cognition-preserving medication

combinations[14] is given to patients undergoing the most likely clinical scenario to experience severe ECT-derived cognitive compromise, this study is designed to help determine if there is any true efficacy in the use of prophylactic medications to protect patients from ECT-induced cognitive side effects.

References

1. Porter RJ, Baune BT, Morris G, et al. Cognitive side-effects of electroconvulsive therapy: what are they, how to monitor them and what to tell patients. *BJPsych Open.* 2020;6(3):e40.
2. Semkovska M, McLoughlin DM. Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. *Biol Psychiatry.* 2010;68(6):568-577.
3. Semkovska M, McLoughlin DM. Measuring retrograde autobiographical amnesia following electroconvulsive therapy: historical perspective and current issues. *J ECT.* 2013;29(2):127-133.
4. Landry M, Moreno A, Patry S, Potvin S, Lemasson M. Current Practices of Electroconvulsive Therapy in Mental Disorders: A Systematic Review and Meta-Analysis of Short and Long-Term Cognitive Effects. *J ECT.* 2021;37(2):119-127.
5. McCall WV. Handbook of ECT: A Guide to Electroconvulsive Therapy for Practitioners: Charles H. Kellner. Cambridge University Press, New York. 2019. ISBN 978-1-108-40328-3. *The Journal of ECT.* 2019;35(2):144.
6. Parkinson WL, Rehman Y, Rathbone M, Upadhye S. Performances on individual neurocognitive tests by people experiencing a current major depression episode: A systematic review and meta-analysis. *J Affect Disord.* 2020;276:249-259.
7. Kirov GG, Owen L, Ballard H, et al. Evaluation of cumulative cognitive deficits from electroconvulsive therapy. *Br J Psychiatry.* 2016;208(3):266-270.
8. Hoffmann TC, Del Mar C. Clinicians' Expectations of the Benefits and Harms of Treatments, Screening, and Tests: A Systematic Review. *JAMA Intern Med.* 2017;177(3):407-419.
9. Vann Jones S, McCollum R. Subjective memory complaints after electroconvulsive therapy: systematic review. *BJPsych Bull.* 2019;43(2):73-80.
10. Sienaert PA, Vansteelandt K, Demyttenaere K, Peuskens J. Predictors of patient satisfaction after ultrabrief bifrontal and unilateral electroconvulsive therapies for major depression. *J ECT.* 2010;26(1):55-59.
11. Prudic J, Peyser S, Sackeim HA. Subjective memory complaints: a review of patient self-assessment of memory after electroconvulsive therapy. *J ECT.* 2000;16(2):121-132.
12. Hammershøj LG, Petersen JZ, Jensen HM, Jørgensen MB, Miskowiak KW. Cognitive Adverse Effects of Electroconvulsive Therapy: A Discrepancy Between Subjective and Objective Measures? *J ECT.* 2022;38(1):30-38.
13. Chen R, Chan PT, Chu H, et al. Treatment effects between monotherapy of donepezil versus combination with memantine for Alzheimer disease: A meta-analysis. *PLoS One.* 2017;12(8):e0183586.

14. Guo J, Wang Z, Liu R, Huang Y, Zhang N, Zhang R. Memantine, Donepezil, or Combination Therapy-What is the best therapy for Alzheimer's Disease? A Network Meta-Analysis. *Brain Behav.* 2020;10(11):e01831.
15. DynaMed. Memantine Hydrochloride/Donepezil Hydrochloride. 2022; https://www.dynamed.com/drug-monograph/memantine-hydrochloride-donepezil-hydrochlorideMemantine Accessed 03/11/2022, 2022.
16. Calhoun A, King C, Khoury R, Grossberg GT. An evaluation of memantine ER + donepezil for the treatment of Alzheimer's disease. *Expert Opin Pharmacother.* 2018;19(15):1711-1717.
17. Shams-Alizadeh N, Maroufi A, Sofla AQC, Ghaderi E, Hassanzadeh K. Effect of Donepezil on Cognitive Deficits Associated With Electroconvulsive Therapy: A Randomized Triple-blind Clinical Trial. *Clin Neuropharmacol.* 2019;42(2):27-31.
18. Dutta LCB, Sarkar CP, Andrade C. Efficacy of donepezil for the attenuation of memory deficits associated with electroconvulsive therapy. *Psychiatry Res.* 2020;293:113397.
19. Zarean E, Sedehi M, Heshmati Y. Efficacy of Donepezil in Improving Cognitive Impairment Induced by Electroconvulsive Therapy in Patients with Mood Disorders: A Randomized, Double-blind, Placebo-Controlled Trial. *Iran J Psychiatry Behav Sci.* 2021;15(3):e107598.
20. Nazarinasab M, Behrouzian F, Mahnoo M. Evaluation of donepezil and rivastigmine administration on the cognitive deficits induced by electroconvulsive therapy: a randomized, double-blind clinical trial. *Family Medicine & Primary Care Review.* 2019(3):243-248.
21. Prakash J, Chaudhury S, Chatterjee K, Kotwal A, Srivastava K, Saha A. Therapeutic and prophylactic role of cognitive enhancers in electroconvulsive therapy-induced cognitive deficits. *Ind Psychiatry J.* 2019;28(2):286-293.
22. Prakash J, Kotwal A, Prabhu H. Therapeutic and prophylactic utility of the memory-enhancing drug donepezil hydrochloride on cognition of patients undergoing electroconvulsive therapy: a randomized controlled trial. *J ECT.* 2006;22(3):163-168.
23. Matthews JD, Siefert CJ, Blais MA, et al. A double-blind, placebo-controlled study of the impact of galantamine on anterograde memory impairment during electroconvulsive therapy. *J ECT.* 2013;29(3):170-178.
24. Matthews JD, Blais M, Park L, et al. The impact of galantamine on cognition and mood during electroconvulsive therapy: a pilot study. *J Psychiatr Res.* 2008;42(7):526-531.
25. Stryjer R, Ophir D, Bar F, Spivak B, Weizman A, Strous RD. Rivastigmine treatment for the prevention of electroconvulsive therapy-induced memory deficits in patients with schizophrenia. *Clin Neuropharmacol.* 2012;35(4):161-164.
26. Kumar A, Gupta V, Sharma S. Donepezil. *StatPearls*. Treasure Island FL: © 2022, StatPearls Publishing LLC.; 2022.
27. Sarraf N, Badri T, Keshvari N, Ghassab-Sahebkar A, Qobadighadikolaei R, Abbasinazari M. Comparison of the efficacy and safety of melatonin and memantine in the alleviation of cognitive impairments induced by electroconvulsive therapy: A randomized clinical trial. *J Clin Neurosci.* 2020;74:146-150.
28. Alizadeh NS, Maroufi A, Jamshidi M, Hassanzadeh K, Gharibi F, Ghaderi E. Effect of Memantine on Cognitive Performance in Patients Under Electroconvulsive Therapy: A Double-Blind Randomized Clinical Trial. *Clin Neuropharmacol.* 2015;38(6):236-240.
29. Abbasinazari M, Adib-Eshgh L, Rostami A, Beyraghi N, Dabir S, Jafari R. Memantine in the prevention or alleviation of electroconvulsive therapy induces cognitive disorders: A placebo controlled trial. *Asian J Psychiatr.* 2015;15:5-9.

30. McGirr A, Berlim MT, Bond DJ, Chan PY, Yatham LN, Lam RW. Adjunctive ketamine in electroconvulsive therapy: updated systematic review and meta-analysis. *Br J Psychiatry.* 2017;210(6):403-407.
31. Ainsworth NJ, Sepehry AA, Vila-Rodriguez F. Effects of Ketamine Anesthesia on Efficacy, Tolerability, Seizure Response, and Neurocognitive Outcomes in Electroconvulsive Therapy: A Comprehensive Meta-analysis of Double-Blind Randomized Controlled Trials. *J ECT.* 2020;36(2):94-105.
32. Verdijk J, van Kessel MA, Oud M, et al. Pharmacological interventions to diminish cognitive side effects of electroconvulsive therapy: A systematic review and meta-analysis. *Acta Psychiatr Scand.* 2022.
33. DynaMed. Memantine. 2022; https://www.dynamed.com/drug-monograph/memantine. Accessed 03/11/2022, 2022.
34. Niu Y, Ye D, You Y, Wu J. Prophylactic cognitive enhancers for improvement of cognitive function in patients undergoing electroconvulsive therapy: A systematic review and meta-analysis. *Medicine (Baltimore).* 2020;99(11):e19527.
35. McClintock SM, Choi J, Deng ZD, Appelbaum LG, Krystal AD, Lisanby SH. Multifactorial determinants of the neurocognitive effects of electroconvulsive therapy. *J ECT.* 2014;30(2):165-176.
36. Squire LR, Chace PM. Memory functions six to nine months after electroconvulsive therapy. *Arch Gen Psychiatry.* 1975;32(12):1557-1564.
37. Sackeim HA, Prudic J, Fuller R, Keilp J, Lavori PW, Olfson M. The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology.* 2007;32(1):244-254.
38. Bayless JD, McCormick LM, Brumm MC, Espe-Pfeifer PB, Long JJ, Lewis JL. Pre- and post-electroconvulsive therapy multidomain cognitive assessment in psychotic depression: relationship to premorbid abilities and symptom improvement. *J ECT.* 2010;26(1):47-52.
39. Sobin C, Sackeim HA, Prudic J, Devanand DP, Moody BJ, McElhiney MC. Predictors of retrograde amnesia following ECT. *Am J Psychiatry.* 1995;152(7):995-1001.
40. Loo C, Katalinic N, Mitchell PB, Greenberg B. Physical treatments for bipolar disorder: a review of electroconvulsive therapy, stereotactic surgery and other brain stimulation techniques. *J Affect Disord.* 2011;132(1-2):1-13.
41. Peterchev AV, Rosa MA, Deng ZD, Prudic J, Lisanby SH. Electroconvulsive therapy stimulus parameters: rethinking dosage. *J ECT.* 2010;26(3):159-174.
42. Sackeim HA, Prudic J, Devanand DP, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry.* 2000;57(5):425-434.
43. Sackeim HA, Prudic J, Nobler MS, et al. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimul.* 2008;1(2):71-83.
44. Sackeim HA, Prudic J, Devanand DP, et al. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *N Engl J Med.* 1993;328(12):839-846.
45. Squire SR, Slater PC. Bilateral and unilateral ECT: effects on verbal and nonverbal memory. *Am J Psychiatry.* 1978;135(11):1316-1320.
46. Kellner CH, Knapp R, Husain MM, et al. Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. *Br J Psychiatry.* 2010;196(3):226-234.

47. Semkovska M, Keane D, Babalola O, McLoughlin DM. Unilateral brief-pulse electroconvulsive therapy and cognition: effects of electrode placement, stimulus dosage and time. *J Psychiatr Res.* 2011;45(6):770-780.
48. Kolshus E, Jelovac A, McLoughlin DM. Bitemporal v. high-dose right unilateral electroconvulsive therapy for depression: a systematic review and meta-analysis of randomized controlled trials. *Psychol Med.* 2017;47(3):518-530.
49. Tor PC, Bautovich A, Wang MJ, Martin D, Harvey SB, Loo C. A Systematic Review and Meta-Analysis of Brief Versus Ultrabrief Right Unilateral Electroconvulsive Therapy for Depression. *J Clin Psychiatry.* 2015;76(9):e1092-1098.
50. Misra S. Randomized double blind placebo control studies, the "Gold Standard" in intervention based studies. *Indian J Sex Transm Dis AIDS.* 2012;33(2):131-134.
51. Sackeim HA. Autobiographical memory and ECT: Don't throw out the baby. *The journal of ECT.* 2014;30(3):177.
52. Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *Clin Interv Aging.* 2008;3(2):211-225.
53. Association As. Medications for Memory, Cognition and Dementia-Related Behaviors. 2022; https://www.alz.org/alzheimers-dementia/treatments/medications-for-memory. Accessed 03/15/2022, 2022.
54. Thirthalli J, Naik SS, Kunigiri G. Frequency and Duration of Course of ECT Sessions: An Appraisal of Recent Evidence. *Indian J Psychol Med.* 2020;42(3):207-218.
55. Wilkinson ST, Agbese E, Leslie DL, Rosenheck RA. Identifying Recipients of Electroconvulsive Therapy: Data From Privately Insured Americans. *Psychiatr Serv.* 2018;69(5):542-548.
56. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23(1):56-62.
57. Zimmerman M, Martinez JH, Young D, Chelminski I, Dalrymple K. Severity classification on the Hamilton Depression Rating Scale. *J Affect Disord.* 2013;150(2):384-388.
58. Pigot M, Andrade C, Loo C. Pharmacological attenuation of electroconvulsive therapy--induced cognitive deficits: theoretical background and clinical findings. *J ECT.* 2008;24(1):57-67.
59. DynaMed. Donepezil. 2022; https://www.dynamed.com/drug-monograph/donepezil#GUID-E7E085F0-A2DA-4F6A-AD7B-9E0756FE9C9B__CITE5. Accessed 03/11/2022, 2022.
60. Hebbrecht K, Giltay EJ, Birkenhäger TK, et al. Cognitive change after electroconvulsive therapy in mood disorders measured with the Montreal Cognitive Assessment. *Acta Psychiatr Scand.* 2020;142(5):413-422.
61. Jelovac A, O'Connor S, McCarron S, McLoughlin DM. Autobiographical Memory Specificity in Major Depression Treated With Electroconvulsive Therapy. *J ECT.* 2016;32(1):38-43.
62. Semkovska M, McLoughlin DM. Retrograde autobiographical amnesia after electroconvulsive therapy: on the difficulty of finding the baby and clearing murky bathwater. *J ECT.* 2014;30(3):187-188; discussion 189-190.
63. Weiss A. *The Electroconvulsive Therapy Workbook: Clinical Applications.* Taylor & Francis; 2018.
64. Moirand R, Galvao F, Lecompte M, Poulet E, Haesebaert F, Brunelin J. Usefulness of the Montreal Cognitive Assessment (MoCA) to monitor cognitive impairments in depressed patients receiving electroconvulsive therapy. *Psychiatry Res.* 2018;259:476-481.

65. Trzepacz PT, Hochstetler H, Wang S, Walker B, Saykin AJ. Relationship between the Montreal Cognitive Assessment and Mini-mental State Examination for assessment of mild cognitive impairment in older adults. *BMC Geriatr.* 2015;15:107.
66. Porter R, Heenan H, Reeves J. Early effects of electroconvulsive therapy on cognitive function. *J ECT.* 2008;24(1):35-39.
67. Alvarez-Grandi SA, Groves SJ, Douglas KM, Porter RJ. Systematic Monitoring of Cognitive Function During Electroconvulsive Therapy: A Retrospective Analysis of Data From a Service Using a Short Cognitive Testing Battery. *J ECT.* 2020;36(1):10-17.
68. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 1979;134:382-389.
69. Quilty LC, Robinson JJ, Rolland JP, Fruyt FD, Rouillon F, Bagby RM. The structure of the Montgomery-Åsberg depression rating scale over the course of treatment for depression. *Int J Methods Psychiatr Res.* 2013;22(3):175-184.
70. Iannuzzo RW, Jaeger J, Goldberg JF, Kafantaris V, Sublette ME. Development and reliability of the HAM-D/MADRS interview: an integrated depression symptom rating scale. *Psychiatry Res.* 2006;145(1):21-37.
71. Carmody TJ, Rush AJ, Bernstein I, et al. The Montgomery Asberg and the Hamilton ratings of depression: a comparison of measures. *Eur Neuropsychopharmacol.* 2006;16(8):601-611.
72. Carstens L, Hartling C, Stippl A, et al. A symptom-based approach in predicting ECT outcome in depressed patients employing MADRS single items. *Eur Arch Psychiatry Clin Neurosci.* 2021;271(7):1275-1284.
73. van Bergen S, Brands I, Jelicic M, Merckelbach H. Assessing trait memory distrust: Psychometric properties of the Squire Subjective Memory Questionnaire. *Legal and Criminological Psychology.* 2010;15(2):373-384.
74. Bennett-Levy J, Powell GE. The Subjective Memory Questionnaire (SMQ). An investigation into the self-reporting of 'real-life' memory skills. *British Journal of Social and Clinical Psychology.* 1980;19(2):177-188.
75. Doody RS, Corey-Bloom J, Zhang R, Li H, Ieni J, Schindler R. Safety and tolerability of donepezil at doses up to 20 mg/day: results from a pilot study in patients with Alzheimer's disease. *Drugs Aging.* 2008;25(2):163-174.
76. Kuns B, Rosani A, Varghese D. Memantine. *StatPearls*. Treasure Island FL: © 2021, StatPearls Publishing LLC.; 2021.
77. Levin JB, Sams J, Tatsuoka C, Cassidy KA, Sajatovic M. Use of automated medication adherence monitoring in bipolar disorder research: pitfalls, pragmatics, and possibilities. *Ther Adv Psychopharmacol.* 2015;5(2):76-87.
78. Olivieri NF, Matsui D, Hermann C, Koren G. Compliance assessed by the Medication Event Monitoring System. *Arch Dis Child.* 1991;66(12):1399-1402.

CHAPTER 3: STUDY METHODS

Study Design:

This study is a double-blind prospective randomized controlled trial. The study begins with a pre-ECT phase, where patients are recruited, screened, interviewed, assessed, randomized, and then begin their assigned pharmacologic treatment course. Next is the ECT treatment phase, in which patients will be given ECT treatments three times per week. Once patients finish their acute series of 6 to 12 ECT treatments, they will undergo the final array of questionnaires and cognitive assessments.

Study Population and Sampling:

Patient referrals to Yale New Haven Psychiatric Hospital & Hartford Hospital's Institute of Living will be monitored daily by participating ECT practitioners for potential study participants. Patients pursuing initial ECT treatment for the primary diagnosis of MDD will be reviewed for eligibility. Patients that meet the inclusion criteria and none of the exclusion criteria will be allowed to participate in the study.

Inclusion criteria includes a current diagnosis of Major Depressive Disorder in accordance to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V), planned ECT treatment for a current major depressive episode, ages 18-65, English as their primary language, moderate-to-severe depression as defined by baseline HAMD-17 scores of 17 or greater, and the informed written consent of the patient.

Exclusion criteria includes an active diagnosis of catatonia, substance abuse disorder, alcohol abuse, schizophrenia, schizoaffective disorder, bipolar disorder, obsessive compulsive disorder, post-traumatic stress disorder, psychosis, or an eating disorder currently or within 3 months of starting the study. Likewise, any past medical

history of neurological disorders, strokes, seizures, cognitive impairment, learning disabilities, brain trauma, brain surgeries, or previous ECT treatments will also meet exclusion criteria. Any medical history of renal or hepatic impairment, obstructive sleep apnea, other sleeping disorders, cardiac disease, gastrointestinal lesions, current pregnancy, current breastfeeding, or recent post-partem will be excluded. Any current or recent use within 3 months of the study of an acetylcholinesterase inhibitor, cholinergic agent, NMDA receptor antagonist, melatonin, dexamethasone, vasopressin, naloxone, piracetam, nitroprusside, thyroid medications, calcium channel blockers, COX-2 inhibitors, or opioids will also meet exclusion criteria. Further exclusion criteria include: inability to give informed written consent, sensitivity to memantine or donepezil, and using ketamine as an anesthetic.

Subject Protection and Confidentiality:

An application for permission to create a study involving human subjects in research will be submitted to the Yale Institutional Review Board (IRB), the Yale Human Investigation Committees (HICs), and the Yale Human Research Protection Program (HRPP) for approval as detailed by Yale IRB Policy 100.1, 100.2, and 100.5. The proposed study's protocol and its ethical considerations will follow the IRB's rules and guidelines for human subject research. Following approval, each facility will receive and review a letter detailing the protocol. After signed approval letters of the protocol are obtained from the facilities, all investigators, researchers, and involved ECT physicians will be required to complete the Health Insurance Portability and Accountability Act (HIPAA) Privacy Training for Research Personnel, the Yale Good Clinical Practice (GCP) training, and the Yale Human Subjects Protection Training. Once completed, all

personnel will be trained for their specific roles; then after this the study may begin.

In order for patients to be enrolled in the study, they must provide written informed consent. The consent form, found in Appendix IV, will be written at a 5th grade reading level and explained to each participant by one of the trained research team members. This form will follow Yale IRB Policy 200 for Informed Consent for Human Research. The consent will include an overview of the purpose of the study, study procedures, expected study duration, potential benefits, potential risks, details of patient confidentiality and HIPPA, the participant's right to withdrawal from the study at any point without penalty, and contact info for the lead investigator, site investigator, Yale IRB, HIC, and HRPP. The patient will also receive instructions on what to do in the case of an emergency, and how to report adverse effects to the research team. When the consent form is signed and dated by the participant with a co-signed witness, then the participant may proceed with the trial. Copies of the consent form will be returned to the patient. Failure to complete the informed consent will result in exclusion from the study.

Because this study uses electronic medical records (EMR) for parts of its data collection, EMR will be deidentified whenever possible to protect patient confidentiality. The EMR will be stored on secure password protected servers, but any non-electronic medical records will be stored in locked cabinets in locked offices. HIPPA protocols will also be practiced by all members of the study team.

Recruitment:

Clinicians at the participating facilities will be informed of the study and what it entails. They will be asked to recruit new referred patients that meet the inclusion criteria. Should the patient give the clinician verbal consent for a researcher to contact them, the

clinician will notify a researcher of the interested patient and contact them through their preferred method of communication. Interested patients will be given an appointment time to meet with the researcher in person or electronically to learn what the study entails and provide written informed consent. Those providing consent will be sent a survey to fill out online. This survey will collect demographic and clinical data, as well as screen for exclusion criteria. Once complete, the participant can start the first phase of the study. Should the interested participant meet any exclusion criteria, they will be reimbursed for their time and travel expenses but will not advance to the first phase of the study.

Subjects that do advance will also be reimbursed for their time and any travel expenses incurred by their participation in the study. Choosing to leave the study before completion, or later becoming an ineligible participant during the study, will not forfeit any financial compensation they have earned up to that point. Participants will be reimbursed in the form of a check for the amount of time they spent at the pre- and post-ECT meetings, but not during the ECT sessions themselves. The patients will be compensated at $20/hr, rounded to the highest 15-minute interval. Each meeting is expected to be 2 hours long, and so participants will receive a $40 minimum per meeting. After a participant has fully completed the study, they will also be given an additional $100 bonus. Travel reimbursement will be applied for every meeting and ECT session the patient goes to. They will be compensated in accordance to the 2022 IRS standard milage rate of 58.5 cents per mile, rounded up to the nearest mile. Travel compensation in the form of a check will be issued at the end of the participant's involvement of the study.

Study Variables and Measures:

Phase 1: Recruitment, Screening, Randomization, Assessment, and Medication

After ensuring none of the exclusion criteria is met, the participants will be given an appointment time to meet with a researcher one week before their first ECT appointment, as well as be randomly allocated to the placebo or combination-therapy group. During the appointment, the researcher will give the patient the SSMQ, and administer the CUAMI-SF, MOCA, DSF, DSB, and MADRS. The assessments in total are expected to take up to 100 minutes. After finishing the questionnaires and tests, the patients will be given their assigned medication with instructions of when and how to take them. Patients will take their first dose with the researcher present to ensure there are no acute allergic reactions. The medication will be given in MEMS pill bottles to better track adherence. Patients will also be given a safety sheet detailing the potential side-effects of the study medications, what to do in an emergency, who to contact in case any adverse events do happen, and how to drop out of the study should the patient wish to.

Phase 2: Electroconvulsive Therapy and Medication up-titration

Patients will undergo their acute series of ECT three times per week, with bilateral electrode placement and brief-pulse width stimulation, under the care of a physician familiar with the study. After their first ECT, participants will have their medication dosage up-titrated. Patients will receive six to twelve ECT treatments during this study. Participating in less than six treatments will result in exclusion from the study. If they require more than twelve ECT treatment to treat their depression, the patient may continue ECT treatments after they undergo their post-ECT follow-up assessments.

Participants will continue their assigned medication regiment and receive morning and nightly reminders of when to take their medication. Pulse amplitude, pulse frequency, stimulus duration, anesthetic choice (except ketamine), and the decision on

when to stop ECT will be up to the discretion of the ECT provider. ECT providers will be instructed to use the dose-titration method and not the half-age method when establishing the patient's proper ECT charge. In addition to their standard op-notes, ECT physicians will also ask the patients if there has been any change in their medical history or in their medications. ECT op-notes will be collected by researchers for later statistical analysis. Providers will inform the researchers of when each patient's final ECT of the study is so the patient can be scheduled to meet with a researcher 24 hours after the final ECT.

During this final meeting, the researcher will again administer the objective and subjective cognitive tests. Patients will also complete another survey asking the patient to rate their tolerability of the medication, and report any adverse effects they experienced during the study. After the interview and tests, patients will be given instructions on how to taper off their medications. The MEMS bottle will then be recollected, and patients will be given their financial compensation for their participation in the study.

Groups with medication regiments

The participants will be allocated in one of the two treatment groups:

Donepezil & Memantine combo-therapy group: One week before starting ECT, participants will take Donepezil 5mg by mouth (PO) once daily and Memantine 5mg PO twice daily. One week later, on the day they start ECT, they will then take Donepezil 10mg PO daily and Memantine 10mg PO twice daily for the remainder of the study.

Pure placebo group: One week before starting ECT, participants will take a placebo PO once daily, and another placebo PO twice daily. On the day they start ECT, they will then take the same drug regiment, but will be told this is an increased dosage.

Participants may continue any of their other regularly prescribed medicine as well

as any over-the-counter medicine so long as they do not meet the exclusion criteria.

Primary and Secondary Outcome Measures

The primary outcome measure of the proposed study is the mean CUAMI-SF score 24 hours after the participants' final ECT. Secondary outcome measures are mean MOCA, DSF, and DSB scores 24 hours after the participants' final ECT. Mean scores for each test will be calculated for both the pre-ECT and post-ECT period of each group. Each group's post-ECT scores will be compared to their pre-ECT scores to assess if there is a significant change in the scores after undergoing the acute series of ECT. The mean post-ECT scores will then be compared between the two groups to assess if there is a significant difference in scores between them. Other outcomes to be measured within and between groups are: MADRS scores, SSMQ scores, the number and characteristics of adverse event occurrences, and the patient's reported medication tolerability.

Potential Confounding Variables and Secondary Variables

Secondary variables and potential confounders not already controlled in the study will be measured during recruitment and the pre-ECT meeting. Potential confounders include patient age and depression severity. Secondary variables include gender, highest level of education, number of distinct major depressive episodes, and the length of which they have had MDD.

Other potential confounders are recorded during and after the patient's ECT course. These include ECT pulse amplitude, pulse frequency, stimulus duration, and the patient's adherence to their assigned medication. Secondary variables include the number of ECT treatments needed and the anesthetic used for each session.

Blinding of Intervention and Outcome:

Participants will be blinded to their group allocation by researchers not labeling the medications given to them. Participants will be randomized to the combination therapy group or placebo group. Research assistants will be in charge of the randomization of patients and medication distribution, while the investigators will be in charge of the study's recruitment, assessment, and interviewing. The investigator will not be involved in the research assistant's duties, and vice versa to ensure blinding. Both investigator and research assistant will not be involved with the ECT treatment, nor the statistical analysis. The ECT providers will be blind to participant group allocation.

Assignment of Intervention:

Participants will be evenly and randomly allocated to one of the two study groups via a computer-generated algorithm. To take into account the use of multiple facilities and ensure equal assignment to each treatment, the algorithm will practice block randomization. 20 blocks of 4 participants will be used, each with a randomly generated sequence of even participant allocation. 10 blocks will then be randomly distributed to each facility in a random order. All study staff, besides the research assistants in charge of the randomization and allocation of participants, will be blind to the size of the blocks.

Adherence:

Adherence to ECT treatments will be monitored by the clinicians through filling out sign-in sheets. Medication adherence will be tracked through the use of MEMS medication bottles, which records the time and date each bottle is opened and closed. Medication adherence will further be promoted with morning and nightly reminders to participants to take their assigned medication. Medication adherence will be further monitored through weekly check-ins by the investigators.

Monitoring of Adverse Events:

Information sheets about donepezil and memantine will be given to patients, including a list of possible side effects. Participants can self-report adverse events by calling their investigator, by telling their investigator during weekly check-in, and by reporting them at their post-ECT meeting. During ECT sessions, vitals are routinely attained when visiting the treatment centers, and ECT clinicians will also conduct their own interviews with the patient at this time. ECT clinicians may also report any known or suspected adverse events experienced by the patients to their respective investigator.

Data Collection:

Recruiters will send consented participants a survey to fill out online. The online survey will serve to collect demographic and clinical information. An example of this survey can be found in Appendix V. Recruiters will vet the information to ensure the patient does not meet any of the exclusion criteria before advancing to the first phase, and the survey information will be saved for later analysis.

After being cleared, the patient will meet with one of the investigators about one week before their first ECT. The date and time will be recorded, and the patient will complete a SSMQ, CUAMI-SF, MOCA, DSF, DSB, and a MADRS. Examples of all these can be found in Appendix VI. The recorded results will serve as baseline scores.

During the ECT phase, provider notes will be collected and saved for later analysis. These reports will include variables such as the ECT treatment number, pulse frequency, pulse amplitude, stimulus duration, and which anesthetic was used. When the patient is finished with their acute series of ECT, the patient will meet again with an investigator approximately 24 hours after the final treatment. The patient will again

complete a SSMQ, CUAMI-SF, MOCA, DSF, DSB, and a MADRS. These scores will serve as the post-ECT scores. They will also report on their perceived tolerability of the medications, as well as report any adverse events they experienced during the study. A sample of this survey can be found in Appendix VII. Data from the weekly check-ins and the MEMS bottles will also be saved for analysis.

Sample Size Calculation:

The estimated sample size was calculated via Power And Precision 4* for this study with a two-sided hypothesis and a statistical significance of 0.05 for alpha and a power of 80% is 70 participants. Adjusting for a predicted 12% drop-out rate, the new estimated size is 80 participants, with 40 in the combo-therapy group and 40 in the placebo group. It is estimated that 2 facilities are needed to perform this study. The estimated effect size of this study is moderate, with a calculated Cohen's d of 0.68. Calculations can be found in Appendix II.

Analysis:

Data analysis will be performed by the Yale JDAT. Individual patient factors, baseline questionnaire and cognitive assessment scores, and ECT administration information will be used to detect for any statistically significant difference between the groups and identify any possible confounders to the study's results. Post-ECT questionnaire and cognitive assessments scores, adverse event reports, and drop-out rates will be analyzed with an intent-to-treat protocol in regards to medication compliance. However, per-protocol analysis will be used with respect to the patient's attendance and completion of their ECT sessions and investigator meetings. Data will be analyzed using the Statistical Package for the Social Sciences (SPSS). P-values ≤ 0.05 will be considered

statistically significant with a power of 80%.

CUAMI-SF scores are the primary outcome of the study. A CUAMI-SF score is a quantitative continuous variable and will be represented in means with standard deviations. Before and after ECT mean CUAMI-SF scores will be presumed to be parametric, and will be compared within groups via paired t-tests, and between groups via student t-tests. The secondary outcomes are the MOCA, DSF, and DSB scores. The MOCA is quantitative non-parametric continuous variable, while the DSF and DSB are quantitative parametric continuous variables. Each of these tests will be represented in means with standard deviations. Before and after ECT mean MOCA scores will be compared within groups via Wilcoxon signed-rank tests, and between groups via Mann-Whitney U tests. Both before and after ECT mean DSF and mean DSB scores will be compared within groups via paired t-tests, and between groups via student t-tests.

Many other variables require analysis in this study. Both before and after ECT mean MADRS and mean SSMQ scores will be compared within groups via Wilcoxon signed-rank tests, and between groups via Mann-Whitney U tests. Patient demographic information, adverse event occurrences, medication compliance, and study drop-out rate will be compared between groups using student-t tests and Chi-square tests. ECT variables will be compared between groups using student-t tests. Patient reported medication tolerability will be compared between groups via the Mann-Whitney U test.

Table 1. Schedule of study interventions and assessments

		Phase			
		Screening	Phase I: Baseline Scores and Medication	Phase 2: ECT Treatment	
		Before the study begins	*Start of the study*	*The first day of ECT*	*24 hours after the last day of ECT*
	Day	(-∞) - 1	1	8 – (22-36)	(22-36) + 1
Consent	Written informed consent	**X**			
Interviews, Assessments	Demographic & Clinical Survey	**X**			
	SSMQ		**X**		**X**
	CUAMI-SF		**X**		**X**
	MOCA		**X**		**X**
	DSF		**X**		**X**
	DSB		**X**		**X**
	MADRS		**X**		**X**
	Tolerability and Adverse Event Survey				**X**
Depression Treatment	ECT x3 per week			**X**	
Medication	Initiate randomized group medication		**X**		
	Medication up-titration			**X**	
	Initiate medication taper				**X**
	Weekly check-ins			**X**	**X**

This table lays out the schedule of events a patient will experience during the study

Abbreviations: SSMQ – *Squire Subjective Memory Questionnaire*, CUAMI-SF – *Columbia University Autobiographical Memory Interview - Short Form*, MOCA – *Montreal Cognitive Assessment*, DSF – *Digit Span Forwards*, DSB – *Digit Span Backwards*, MADRS – *Montgomery–Åsberg Depression Rating Scale*, ECT – *Electroconvulsive Therapy*

* Numbers within parenthesis (__) are the range of days possible

Timeline and Resources:

The participating facilities for this study will be the Yale New Haven Psychiatric Hospital & Hartford Hospital's Institute of Living. The participating staff includes a lead chief investigator, one data and safety monitoring investigator, as well as one investigator and one research assistant per participating facility. Investigators and research assistants will be trained to administer the various assessments being conducted in the study to

ensure proper data collection and scoring consistency. One to two ECT clinicians at the participating facilities will be recruited to aid in the study. They will be familiarized with the study so that they know to induce ECT within the needed parameters. Participant recruitment will begin January 2024, and continue up till October 2025 or whenever the sample size goals are met if met earlier. After the final participant's post-ECT meeting, data analysis will be performed. Data analysis will be performed by a third party, specifically the Yale JDAT. Funding study expenses will be obtained through grants.

CHAPTER 4: CONCLUSION

Strengths:

This proposed study has many advantages in its design compared to previous studies investigating a pharmacological means to protect memory and cognition in ECT patients. Randomized double-blind placebo-control studies are considered the "gold standard" studies to determine causality in the clinical setting, and they help limit both selection and information bias.[1] Using high dosages, along with starting medication regiments earlier before ECT initiation, gives donepezil and memantine the best the chance to showcase their efficacy. Through the use of bilateral ECT with brief-pulse width stimulus, the study creates a scenario where cognitive deficits would most likely occur clinically.[2-5] By measuring post-ECT effects 24 hours after the final test, this study focuses its investigation on the most likely time ECT-induced cognitive deficits would present themselves within a patient.[2,6,7] Using the CUAMI-SF to measure ECT-induced amnesic effects will best target a key patient concern regarding ECT treatment. Use of the MOCA over the MMSE as a global cognitive measure will both be more sensitive to mild cognitive impairments[8-10] and better mimic clinical practice at YNHH. To limit confounding and maximize internal validity, extensive exclusion criteria will be used and the population will be restricted to restricted to MDD patients only.

Limitations:

Although strong in design for its purpose, this study is not without limitations. The foremost limitation is its inability to compare results to donepezil and memantine monotherapies. Therefore, this study is unable to determine if a specific medication is more influential, nor can it determine if any additive or synergistic effect took place.

Performing these comparisons would have made the estimated sample size needed for the study much too large to be feasible. Continuing on the topic of sample size, the current sample size presented in this proposal is based off of many assumptions. Part of this is due to the study's novelty, but it is mostly due to the lack of data within the literature surrounding the CUAMI-SF. Another shortcoming of this study is that it does not measure for any cognitive deficits seen in other common clinical scenarios, such as chronic ECT usage. Likewise, this study accepts only unipolar MDD patients, reducing generalizability by leaving out other ECT patient populations.

For the participants of this study, ECT treatments may end up being delayed in order to fit them within the study parameters. However, there is often a natural delay prior to ECT treatment because patients need to receive pre-procedural medical clearance. It is anticipated that the delay caused by the study would not be more than a few days for most patients. Further, restricting ECT parameters limits the optimalization of their overall treatment. The high dosages and quick up-titrations of the medications being used also puts participants at a greater risk of experiencing donepezil and memantine side effects. Lastly, the length of the assessment battery within the pre- and post-ECT meetings can create lower than average scores due to fatigue.

Clinical Significance:

The primary implication of this study is to further investigate a possible pharmacologic means of protecting memories and cognitive functioning in ECT patients. This would be the first study to investigate the use of an AChEI and NMDAr antagonist in combination to protect patients from ECT-induced cognitive side effects. Should the results of this study support the stated hypothesis, it could lead to an alteration of current

ECT protocols, improve the quality of life of the patients undergoing ECT, and make ECT a more appealing, approachable, and accessible treatment modality in the United States. Lastly, it will also add to the existing literature regarding the theorized ECT mechanisms of action and the influence of medications in ECT outcomes.

References:

1. Misra S. Randomized double blind placebo control studies, the "Gold Standard" in intervention based studies. *Indian J Sex Transm Dis AIDS.* 2012;33(2):131-134.
2. Porter RJ, Baune BT, Morris G, et al. Cognitive side-effects of electroconvulsive therapy: what are they, how to monitor them and what to tell patients. *BJPsych Open.* 2020;6(3):e40.
3. Peterchev AV, Rosa MA, Deng ZD, Prudic J, Lisanby SH. Electroconvulsive therapy stimulus parameters: rethinking dosage. *J ECT.* 2010;26(3):159-174.
4. McClintock SM, Choi J, Deng ZD, Appelbaum LG, Krystal AD, Lisanby SH. Multifactorial determinants of the neurocognitive effects of electroconvulsive therapy. *J ECT.* 2014;30(2):165-176.
5. Tor PC, Bautovich A, Wang MJ, Martin D, Harvey SB, Loo C. A Systematic Review and Meta-Analysis of Brief Versus Ultrabrief Right Unilateral Electroconvulsive Therapy for Depression. *J Clin Psychiatry.* 2015;76(9):e1092-1098.
6. Semkovska M, McLoughlin DM. Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. *Biol Psychiatry.* 2010;68(6):568-577.
7. Landry M, Moreno A, Patry S, Potvin S, Lemasson M. Current Practices of Electroconvulsive Therapy in Mental Disorders: A Systematic Review and Meta-Analysis of Short and Long-Term Cognitive Effects. *J ECT.* 2021;37(2):119-127.
8. Hebbrecht K, Giltay EJ, Birkenhäger TK, et al. Cognitive change after electroconvulsive therapy in mood disorders measured with the Montreal Cognitive Assessment. *Acta Psychiatr Scand.* 2020;142(5):413-422.
9. Moirand R, Galvao F, Lecompte M, Poulet E, Haesebaert F, Brunelin J. Usefulness of the Montreal Cognitive Assessment (MoCA) to monitor cognitive impairments in depressed patients receiving electroconvulsive therapy. *Psychiatry Res.* 2018;259:476-481.
10. Trzepacz PT, Hochstetler H, Wang S, Walker B, Saykin AJ. Relationship between the Montreal Cognitive Assessment and Mini-mental State Examination for assessment of mild cognitive impairment in older adults. *BMC Geriatr.* 2015;15:107.

APPENDIX

I. Database Search Terms

ECT, electroconvulsive therapy, cognition, cognitive, memory, amnesia, amnesic, cholinesterase inhibitor, acetylcholinesterase inhibitor, AChEI, ChEI, N-methyl-D-aspartate receptor antagonist, N-methyl-D-aspartate antagonist, NMDA antagonist, NMDAr antagonist, NMDA receptor antagonist, memantine, Namenda, donepezil, Aricept, Namzaric, galantamine, rivastigmine, ambenonium, neostigmine, dextromethorphan, ketamine, esketamine, amantadine, major depressive disorder, depression, depressive, MDD, resistant, treatment resistant depression, TRD, mood disorder, objective, subjective, mechanism, MOA, practice, practicing, monitor, autobiographical, autobiographic, autobiographical memory index, autobiographical memory inventory, AMI, AMI-SF, CUAMI, CUAMI-SF, Montreal Cognitive Assessment, MoCA, digit span, DGS, DS, DSB, history, stigma, perspective, perception, Alzheimer's, Alzheimer's disease, Alzheimer's dementia, AD

II. Mentioned Cognition and Depression Assessment Tools with Abbreviations

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3MS – *Modified Mini-Mental State Examination*

ACE-R – *Addenbrooke's Cognitive Examination-Revised*

ADAS-Cog – *Alzheimer's Disease Assessment Scale-Cognition subscale*

ADL – *Activities of Daily Living*

CGI – *Clinical Global Impression*

CUAMI – *Columbia University Autobiographical Memory Inventory*

CUAMI-SF – *Columbia University Autobiographical Memory Inventory – Short Form*

DSB – *Digit Span Backwards*

DSF – *Digit Span Forwards*

HAMD-17 – *Hamilton Depression Rating Scale - 17*

MADRS – *Montgomery–Åsberg Depression Rating Scale*

MMSE – *Mini Mental State Examination*

MOCA – *Montreal Cognitive Assessment*

NPI – *Neuropsychiatric Inventory*

PGI-MS – *Postgraduate Institute Memory Scale*

RBANS – *Repeatable Battery for the Assessment of Neuropsychological Status*

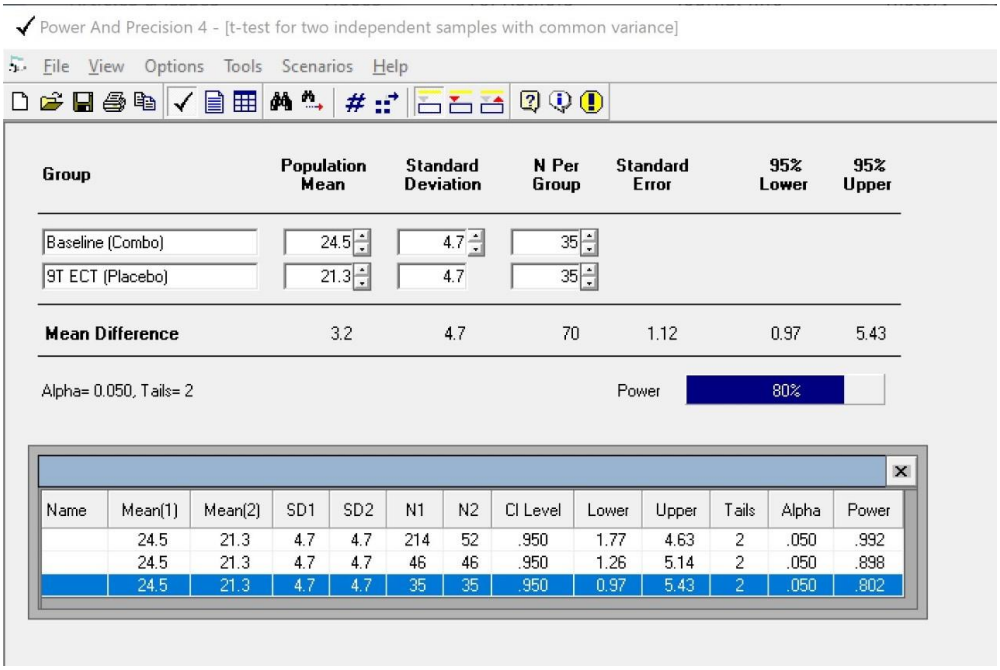
SIB – *Severe Impairment Battery*

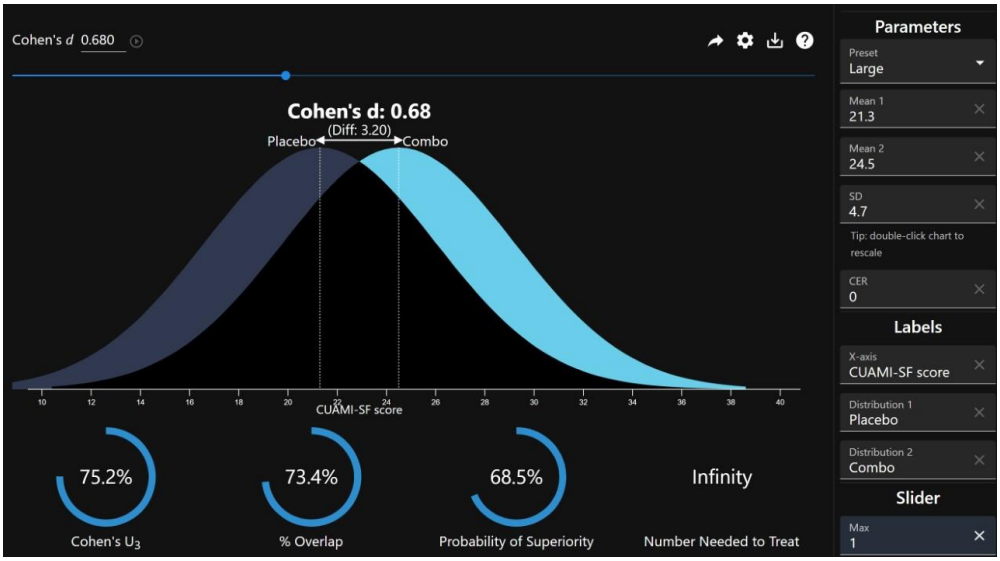
SSMQ – *Squire Subjective Memory Questionnaire*

WAIS - *Wechsler Adult Intelligence Scale*

WMS-III – Wechsler Memory Scale – 3rd Edition

III. Sample Size Calculations





22 participants of 190 participants dropped out of studies involving donepezil or memantine as a potential cognitive protector in ECT patients. (if dropout occurred)

22/190 = 11.5% → rounded up to the nearest percent is 12%

A 12% drop out of 70 needed participants is 8.4 (0.12 x 70 = 8.4)

70 participants + 8.4 extra participants to account for dropouts is 78.4 (70 + 8.4 = 78.4)

78.4 rounded up to the nearest even number is 80

80 participants divided evenly between 2 groups is 40 participants per group (80/2 = 40)

IV. Consent Form

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE

Study Title: COMBINATION OF DONEPEZIL & MEMANTINE TO MITIGATE ELECTROCONVULSIVE THERAPY INDUCED COGNITIVE EFFECTS
Principal Investigators: Samuel Wilkinson, MD & Ryan Rogers, PA-SII

Invitation to Participate and Description of Project

You are invited to participate in a research study designed to look at the efficacy of donepezil and memantine combination therapy to protect patients from potential temporary cognitive deficits following electroconvulsive therapy (ECT). You have been asked to participate in this study because your provider identified you as being an adult age 18-65, who is classified as someone with Major Depressive Disorder (MDD) and as a suitable candidate for ECT. There will be approximately 80 participants in this study across 2 clinical sites in Connecticut.

To decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you are interested in this study, you will be asked questions about your health to determine if you are eligible for this study. Information will be collected about your age, gender, level of education, level of income, primary language, marital status, past medical history, current medications, history with depression, and allergies. Depending on the information you give us, you will then be asked to participate in the study. One week before you start ECT, you will complete a series of interviews and tests with a trained assessor. These interviews and tests are expected to take about 100 minutes to complete, and they will assess your cognitive functioning and depressive symptoms. You will then be given either donepezil and memantine or placebos to take every day throughout the rest of the study. The assignment of the real medication or the placebo is random, and will be unknown to you and the people interviewing you. Instructions will be included for your reference.

When you begin ECT, your medication dosages will be increased. ECT will be administered under specific parameters given to your provider. You will be given ECT 3 times per week during this study. Attendance will be monitored, as it is expected you attend each session. After finishing your acute course of ECT within 6 to 12 treatments, you will be asked to return 24 hours after your last ECT session to re-take the interviews and tests you took at the beginning of the study, along with one additional questionnaire asking about your experience

during the study. Following the end of these tests, you will be given instructions on how to taper off your medications.

The interviews and tests you will be subject to are as follows:

The Montgomery-Åsberg Depression Rating Scale (MADRS) to measure depression severity and determine if you are a responder to ECT.
The Squire Subjective Memory Questionnaire (SSMQ) to give us a sense of how you view your memory and cognitive abilities.

The Columbia University Autobiographical Memory Interview, Short Form (CUAMI-SF) to measure your ability to recall personal memories of your past after finishing ECT.

The Montreal Cognitive Assessment (MOCA) to test your overall cognitive functioning abilities.

The Digit Span Forwards (DSF) will test your attention abilities.

The Digit Span Backwards (DSB) will test your working memory, or your ability to mentally manipulate items in your short-term memory.

In this study we are evaluating if adults who receive donepezil/memantine combination during ECT will experience less cognitive deficits and memory loss after ECT than those who receive ECT with no potentially protective medication. Donepezil and memantine used together is an effective treatment in slowing the cognitive decline of Alzheimer's disease patients. The results we see from the tests and interviews listed above will be how we will determine if this medication has a similar protective effect in the ECT setting.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Risks and Inconveniences

We do not anticipate any significant risks in either group. Adverse effects can be seen in some patients with the use of donepezil and memantine. These include the following:
Common:

- Diarrhea, Loss of appetite, Vomiting
- Bruising
- Fevers
- Dizziness, Headache, Insomnia

Rare, but Serious:

- Heart block, Bradycardia
- Stevens-Johnson syndrome
- Gastrointestinal ulcers, Nausea
- Syncope, Seizures
- Suicidal thoughts

Side effects from ECT may also be experienced. Common side effects from ECT include: nausea, headache, fatigue, confusion, and slight memory loss.

Participation in this study may involve risks that are currently not known.

Benefits

We anticipate that adults with MDD that receive donepezil/memantine combination therapy during ECT will have higher overall memory and cognitive scores on various tests when compared to similar patients not receiving any such medication during ECT.

Economic Considerations

You will be reimbursed for their time and any travel expenses incurred by their involvement in the study. Choosing to leave the study before completion, or later becoming an ineligible participant during the study, will not forfeit you from any financial compensation you have earned up to that point. You will be reimbursed in the form of a check for the amount of time you spent in the meetings involving the tests and interviews, but not during the ECT sessions themselves. You will be compensated at $20/hr, rounded to the highest 15-minute interval. Each meeting is expected to be 2 hours long, as such you will receive a $40 minimum per meeting. After you fully complete the study, you will also be given an additional $100 bonus. Travel reimbursement will be applied for every meeting and ECT session you go to. You will be compensated in accordance to the 2022 IRS standard milage rate of 58.5 cents per mile, rounded up to the nearest mile. Travel compensation in the form of a check will be issued at the end of your involvement of the study.

There are no costs associated with donepezil/memantine combination therapy as the intervention will be offered free of charge. Since ECT is used in standard clinical practice, you will be still responsible for any deductibles or copays required by your insurance company for standard treatment. If you have any questions regarding your insurance coverage, please contact your insurance company directly. There will be no financial penalty for withdrawing for the study.

Confidentiality

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

Information about your study participation will be entered under a unique identification number in a password-protected software and stored on a secure Yale server until needed for statistical analysis. Health Insurance Portability and Accountability Act (HIPAA) standards will be met and maintained for all devices and personnel. Only approved research personnel will have access to your medical records in order to verify information required for the study. Any information that in not relevant will not be extracted from your medical records. Data

auditing will be performed at random points throughout the trial to ensure no inappropriate viewing or disclosure of protected health information has occurred All records no longer needed for research purposes will be shredded and destroyed in accordance with HIPAA requirements. All data and records used in the study will be kept for 10 years after data analysis has concluded.

Representatives from the Yale Human Research Protection Program, the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). You will not be able to enroll in this study and will not receive study procedures as a participant if you do not allow use of your information as part of this study.

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. The researchers may withdraw you from participating in the research if necessary. Withdrawing from the study will involve no penalty or 61
loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own providers or with Yale School of Medicine.

When you withdraw from the study, no new health information identifying you will be gathered. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to ensure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully, as long as you feel is necessary, before you decide.

Authorization

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject:_____

Signature:_____

Relationship:_____

Date:_____

_____

Signature of Principal Investigator Date

or

_____

Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator Samuel Wilkinson, MD.

If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

V. Demographic & Clinical Information Survey (Example)

Name:_____ Date & Time:_____

Age:_____

Gender: (Male / Female / Other) Marital Status: (Single / Married / Other)

Highest level of Education: (No schooling / grade school / high school or equivalent / Undergraduate Bachelor's degree / Graduate Master's degree / Doctorate)

Is English your first language? (Yes / No)

Level of Income (approximate):_____

Medical History (include diagnosis and the year of onset):

_____
_____
_____
_____

Surgical History (include name of surgery and year it was performed):

_____
_____
_____
_____

Psychiatric History (include diagnosis, treatment, and the year of onset):

_____
_____
_____
_____

Past Hospitalizations (include the reason and the year it occurred):

_____
_____
_____
_____

Current Medications (include name, dosages, and when you began taking them):

Allergies (also include what your reaction is):

How many Major Depressive Episodes have you experienced? When?

Have you ever attempted suicide? If so, how many times?

Have you ever been hospitalized for your depression? If so, when and how many times?

What medications have you tried to help with your depression? Please list the name, dosage, if it worked for you, month and year of its start and end, and the number of trials attempted.

What else has been done, or is being done, to help with your depression?

Is there anything else you would like us to know about you?

Have you had, or do you have any of the following? If so, write when it started and ended if applicable, or write “present”:

- Catatonia
- Substance abuse disorder (SAD)
- Alcohol abuse
- Schizophrenia
- Schizoaffective disorder
- Bipolar disorder (BPD)
- Obsessive compulsive disorder (OCD)
- Post-traumatic stress disorder (PTSD)
- Psychosis
- Eating disorder
- Neurological disorders
- Stroke
- Seizures
- Cognitive impairment
- Learning disabilities
- Brain trauma
- Brain surgeries
- Previous ECT treatments
- Kidney issues
- Liver issues
- Obstructive sleep apnea (OSA)
- Other sleeping disorders
- Heart issues
- Gastrointestinal lesions
- Current pregnancy
- Current breastfeeding
- Recent post-partem
- Allergies to acetylcholinesterase inhibitors (donepezil [Aricept, Adlarity] galantamine [Razadyne, Reminyl], rivastigmine [Exelon], tacrine [Cognex])
- Allergies to NMDA receptor antagonists (memantine [Namenda], ketamine, Esketamine [Spavato], Nudexta, dextromethorphan)
- Allergies to Namzaric (donepezil/memantine)

VI. Study Assessments

VI.1 – SSMQ - *Squire Subjective Memory Questionnaire*

For this questionnaire, please read each question and mark your rating on the right		**Disastrous**								**Perfect**
		-4	**-3**	**-2**	**1**	**0**	**1**	**2**	**3**	**4**
1	My ability to search through my mind and recall names or memories I know are there is…	○	○	○	○	○	○	○	○	○
2	I think my relatives and acquaintances judge my memory to be …	○	○	○	○	○	○	○	○	○
3	My ability to recall things when I really try is …	○	○	○	○	○	○	○	○	○
4	My ability to hold in my memory things I have learned is …	○	○	○	○	○	○	○	○	○
5	If I were asked about it a month from now, my ability to remember facts about this form I am filling out would be …	○	○	○	○	○	○	○	○	○
6	My ability to make a past memory that is 'on the tip of my tongue' available is…	○	○	○	○	○	○	○	○	○
7	My ability to recall things that happened a long time ago is…	○	○	○	○	○	○	○	○	○
8	My ability to remember names and faced of people I meet is…	○	○	○	○	○	○	○	○	○
9	My ability to remember what I was doing after I have taken my mind off it for a few minutes is…	○	○	○	○	○	○	○	○	○
10	My ability to remember things that have happened during my childhood is…	○	○	○	○	○	○	○	○	○
11	My ability to remember what I read and what I watch on television is…	○	○	○	○	○	○	○	○	○
12	My ability to recall things that happened during my childhood is…	○	○	○	○	○	○	○	○	○

13	My ability to know when the things I am paying attention to are going to stick in my memory is…	○	○	○	○	○	○	○	○	○
14	My ability to make sense out of what people explain to me is…	○	○	○	○	○	○	○	○	○
15	My ability to reach back in my memory and recall what happened a few minutes ago is…	○	○	○	○	○	○	○	○	○
16	My ability to pay attention to what goes on around me is…	○	○	○	○	○	○	○	○	○
17	My general alertness to things happening around me is…	○	○	○	○	○	○	○	○	○
18	My ability to follow what people are saying is…	○	○	○	○	○	○	○	○	○

PART 1: FAMILY MEMBER (1)

Interviewer: You will begin this section by asking the subject to name a relative about whom five questions will be asked. If several relatives are mentioned, ask regarding the relative with whom the subject has the most frequent contact. If the subject has no relative, ask regarding his/her closest friend.

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT A FAMILY MEMBER: WHAT IS THE FIRST AND NAME OF THE RELATIVE WHO IS THE MOST IMPORTANT TO YOU BUT WHO DOES NOT LIVE WITH

NOTES:

PRE: name provided	POST: name provided

NOTES:

WHAT IS HIS/HER RELATION TO YOU

NOTES:

PRE: relationship

Interviewer: At POST, if the name recalled is different than the name given at PRE, remind the subject of the original name and relation, and proceed with questions 1-5.

QUESTION 1: WHAT IS THE MONTH AND DAY OF HIS/HER BIRTHDAY?

NOTES:

PRE: month & day	score	POST: month & day	score

QUESTION 2: WHAT WAS HIS/HER AGE AT THE TIME YOU ENTERED THIS PROGRAM?

NOTES:

PRE: age	score	POST: age	score

QUESTION 3: WHAT WAS HIS/HER COMPLETE ADDRESS AT THE TIME YOU ENTERED THIS PR(

NOTES:

PRE: address	score	POST: address	score
number, street, & apt.		number, street, & apt.	
city: state:		city: state:	
zip code:		zip code:	

QUESTION 4: WHAT WAS HIS/HER PHONE NUMBER WITH AREA CODE AT THE TIME YOU ENTERED T PROGRAM?

NOTES:

PRE: phone number	score	POST: phone number	score

QUESTION 5: LIST THE FULL NAMES OF THE PERSON OR PERSONS LIVING WITH YOUR RELATIV TIME YOU ENTERED THIS PROGRAM?

NOTES:

PRE: house mates	score	POST: house mates	score

PRE: total score	POST: total score

PAGE 1

PART 1: FAMILY MEMBER (2)

Interviewer: You will begin this section by asking the subject to name a relative about whom five questions will be asked. If several relatives are mentioned, ask regarding the relative with whom the subject has the most frequent contact. If the subject has no relative, ask regarding his/her closest friend.

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT A FAMILY MEMBER: WHAT IS THE FIRST AND NAME OF THE RELATIVE WHO IS THE MOST IMPORTANT TO YOU BUT WHO DOES NOT LIVE WITH

2 MOS POST: name provided	4 MOS POST: name provided	6 MOS POST: name provided
NOTES:	NOTES:	NOTES:

*Interviewer: At **all** POST testing sessions, if the name recalled is different than the name given at PRE, remind the subject of the original name and relation provided, and proceed with questions 1-5.*

QUESTION 1: WHAT IS THE MONTH AND DAY OF HIS/HER BIRTHDAY?

2 MOS POST: month & day	score	4 MOS POST: month & day	score	6 MOS POST: month & day	score

QUESTION 2: WHAT WAS HIS/HER AGE AT THE TIME YOU ENTERED THIS PROGRAM?

2 MOS POST: age	score	4 MOS POST: age	score	6 MOS POST: age	score

QUESTION 3: WHAT WAS HIS/HER COMPLETE ADDRESS AT THE TIME YOU ENTERED THIS PR(

2 MOS POST: address	score	4 MOS POST: address	score	6 MOS POST: address	score
number, street, & apt. #:		number, street, & apt. #:		number, street, & apt. #:	
city: state:		city: state:		city: state:	
zip code:		zip code:		zip code:	

QUESTION 4: WHAT WAS HIS/HER PHONE NUMBER WITH AREA CODE AT THE TIME YOU ENTERED T PROGRAM?

2 MOS POST: phone number	score	4 MOS POST: phone number	score	6 MOS POST: phone number	score

QUESTION 5: LIST THE FULL NAMES OF THE PERSON OR PERSONS LIVING WITH YOUR RELATIV TIME YOU ENTERED THIS PROGRAM?

2 MOS POST: house mates	score	4 MOS POST: house mates	score	6 MOS POST: house mates	score

2 MOS POST: total score	4 MOS POST: total score	6 MOS POST: total score

PAGE 2

PART 2: TRAVEL (3)

Interviewer: You will begin this section by asking the subject to recall the LAST major trip that he/she took before entering the program. If the subject has never traveled farther than 100 miles, ask regarding the most recent overnight trip away from home.

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT THE LAST MAJOR TRIP YOU TOOK BEFORE YOU ENTERED THIS PROGRAM: WHERE DID YOU GO ON YOUR LAST OVERNIGHT TRIP OF 100 MI OR MORE AWAY FROM HOME?

NOTES:

PRE: trip destination	POST: trip destination

NOTES:

IN WHAT MONTH AND YEAR DID YOU TAKE THIS TRI

NOTES:

PRE: month & year of trip

Interviewer: At POST, if the trip recalled is different than the trip given at PRE, remind the subject of the original trip and date, and proceed with questions 1-5.

QUESTION 1: COUNTING THE DAYS YOU SPENT TRAVELING, HOW MANY DAYS WERE YOU AWA

NOTES:

PRE: days away	score	POST: days away	score

QUESTION 2: WHAT IS THE FULL NAME OF THE HOTEL AT WHICH (OR PERSON WITH WHOM) YOU STAYED DURING THE MAJORITY OF THIS TRIP?

NOTES:

PRE: name of lodging	score	POST: name of lodging	score

QUESTION 3: LIST THE FULL NAMES OF THE PERSON OR PERSONS WHO WENT WITH YOU ON T

NOTES:

PRE: travel companion(s)	score	POST: travel companion	score

QUESTION 4: WHAT WAS THE MAIN REASON FOR TAKING THIS TRIP?

NOTES:

PRE: reason for trip	score	POST: reason for trip	score

QUESTION 5: WHAT DID YOU ENJOY MOST ABOUT THIS TF

NOTES:

PRE: enjoyed about trip	score	POST: enjoyed about trip	score

PRE: total score	POST: total score

Page 3

PART 2: TRAVEL (4)

Interviewer: You will begin this section by asking the subject to recall the LAST major trip that he/she took before entering the program. If the subject has never traveled farther than 100 miles, ask regarding the most recent overnight trip away from home.

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT THE LAST MAJOR TRIP YOU TOOK BEFORE YOU ENTERED THIS PROGRAM: WHERE DID YOU GO ON YOUR LAST OVERNIGHT TRIP OF 100 MI OR MORE AWAY FROM HOME?

2 MOS POST: trip destination	4 MOS POST: trip destination	6 MOS POST: trip destination
NOTES:	NOTES:	NOTES:

*Interviewer: At **all** POST testing sessions, if the trip recalled is different than the trip given at PRE, remind the subject of the original trip and date provided, and proceed with questions 1-5.*

QUESTION 1: COUNTING THE DAYS YOU SPENT TRAVELING, HOW MANY DAYS WERE YOU AWA

2 MOS POST: days away	score	4 MOS POST: days away	score	6 MOS POST: days away	score

QUESTION 2: WHAT IS THE FULL NAME OF THE HOTEL AT WHICH (OR PERSON WITH WHOM) YOU STAYED DURING THE MAJORITY OF THIS TRIP?

2 MOS POST: name of lodging	score	4 MOS POST: name of lodging	score	6 MOS POST: name of lodging	score

QUESTION 3: LIST THE FULL NAMES OF THE PERSON OR PERSONS WHO WENT WITH YOU ON T

2 MO POST: travel companion(s)	score	4 MO POST: travel companion(s)	score	6 MO POST: travel companion	score

QUESTION 4: WHAT WAS THE MAIN REASON FOR TAKING THIS TRIP?

2 MOS POST: reason for trip	score	4 MOS POST: reason for trip	score	6 MOS POST: reason for trip	score

QUESTION 5: WHAT DID YOU ENJOY MOST ABOUT THIS TF

2 MO POST: enjoyed about trip	score	4 MO POST: enjoyed about trip	score	6 MO POST: enjoyed about trip	score

2 MOS POST: total score	4 MOS POST: total score	6 MOS POST: total score

Page 4

PART 3: NEW YEAR'S

5

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT LAST NEW YEAR'S EVE: WHAT WAS THE YEA
THE LAST NEW YEAR'S EVE BEFORE YOU ENTERED THIS PROGRAM (I.E. THAT YEAR IT WAS ON DECEMBER 31ST) ?

NOTES:

PRE: year	POST: year

Interviewer: At POST, if the year recalled is different than the year given at PRE, remind the subject of the original year, and proceed with questions 1-5. Emphasize that you are asking about the last New Year's Eve BEFORE he/she entered the program.

QUESTION 1: LIST THE FULL NAMES OF THE PERSON OR PERSONS YOU WERE WITH THAT E

NOTES:

PRE: companion(s)	score	POST: companion(s)	score

QUESTION 2: WHERE DID YOU EAT DINNER THAT EVENING?

NOTES:

PRE: dinner location	score	POST: dinner location	score

QUESTION 3: WHERE DID YOU GO THAT NIGHT?

NOTES:

PRE: location	score	POST: location	score

QUESTION 4: WHAT DID YOU DO THERE

NOTES:

PRE: activity	score	POST: activity	score

QUESTION 5: WHAT DID YOU DO AT MIDNIGH

NOTES:

PRE: midnight	score	POST: midnight	score

PRE: total score	POST: total score

Page 5

PART 3: NEW YEAR'S

6

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT LAST NEW YEAR'S EVE: WHAT WAS THE YEA
THE LAST NEW YEAR'S EVE BEFORE YOU ENTERED THIS PROGRAM **(I.E. THAT YEAR IT WAS ON DECEMBER 31ST) ?**

2 MOS POST: year	4 MOS POST: year	6 MOS POST: year
NOTES:	NOTES:	NOTES:

Interviewer: At all POST testing sessions, if the year recalled is different than the year given at PRE, remind the subject of the original year, and proceed with questions 1-5. Emphasize that you are asking about the last New Year's Eve BEFORE he/she entered the program, and not necessarily the most recent New Year's Eve.

QUESTION 1: LIST THE FULL NAMES OF THE PERSON OR PERSONS YOU WERE WITH THAT E

2 MOS POST: companion(s)	score	4 MOS POST: companion(s)	score	6 MOS POST: companion(s)	score

QUESTION 2: WHERE DID YOU EAT DINNER THAT EVENING?

2 MOS POST: dinner location	score	4 MOS POST: dinner location	score	6 MOS POST: dinner location	score

QUESTION 3: WHERE DID YOU GO THAT NIGHT?

2 MOS POST: location	score	4 MOS POST: location	score	6 MOS POST: location	score

QUESTION 4: WHAT DID YOU DO THERE

2 MOS POST: activity	score	4 MOS POST: activity	score	6 MOS POST: activity	score

QUESTION 5: WHAT DID YOU DO AT MIDNIGH

2 MOS POST: midnight	score	4 MOS POST: midnight	score	6 MOS POST: midnight	score

2 MOS POST: total score	4 MOS POST: total score	6 MOS POST: total score

Page 6

PART 4: BIRTHDAY (7)

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT YOUR BIRTHDAY: WHAT IS THE DATE OF YOUR BIRTH (MONTH/DAY/YEAR) ?

NOTES:

PRE: birth date (mo/dy/yr)	POST: birth date (mo/dy/yr)

HOW OLD DID YOU BECOME ON YOUR LAST BIRTHDAY BEFORE I ENTERED THIS PROGRAM?

NOTES:

PRE: age

NOTES:

Interviewer: At POST, if the age recalled is different than the age given at PRE, remind the subject of the original age, and proceed with questions 1-5.

QUESTION 1: LIST THE FULL NAMES OF THE PERSON OR PERSONS WHO HELPEI CELEBRATE ON YOUR LAST BIRTHDAY:

NOTES:

PRE: companion(s)	score	POST: companion(s)	score

QUESTION 2: WHERE DID YOU CELEBRATE YOUR BIRTHDAY?

NOTES:

PRE: location	score	POST: location	score

QUESTION 3: WHAT DID YOU DO THERE

NOTES:

PRE: activity	score	POST: activity	score

QUESTION 4: FROM WHOM DID YOU RECEIVE GIFTS (IF NO GIFTS, ASK REGARDING CARDS)

NOTES:

PRE: received gifts from	score	POST: received gifts from	score

QUESTION 5: WHAT DID YOU RECEIVE

NOTES:

PRE: gifts received	score	POST: gifts received	score

PRE: total score	POST: total score

Page 7

PART 4: BIRTHDAY (8)

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT YOUR BIRTHDAY: WHAT IS THE DATE OF YOUR BIRTH (MONTH/DAY/YEAR) ?

2 MOS POST: birth date	4 MOS POST: birth date	6 MOS POST: birth date

NOTES: NOTES: NOTES:

*Interviewer: At **all** POST testing sessions, if the age recalled is different than the age given at PRE, remind the subject of the original age, and proceed with questions 1-5. Emphasize that you are asking about the subject's last birthday BEFORE he/she entered the program, which may not necessarily be his/her most recent birthday.*

QUESTION 1: LIST THE FULL NAMES OF THE PERSON OR PERSONS WHO HELPEI CELEBRATE ON YOUR LAST BIRTHDAY:

2 MOS POST: companion(s)	score	4 MOS POST: companion(s)	score	6 MOS POST: companion(s)	score

QUESTION 2: WHERE DID YOU CELEBRATE YOUR BIRTHDAY?

2 MOS POST: location	score	4 MOS POST: location	score	6 MOS POST: location	score

QUESTION 3: WHAT DID YOU DO THERE

2 MOS POST: activity	score	4 MOS POST: activity	score	6 MOS POST: activity	score

QUESTION 4: FROM WHOM DID YOU RECEIVE GIFTS? (IF NO GIFTS, ASK REGARDING CARDS)

2 MO POST: received gifts from	score	4 MO POST: received gifts from	score	6 MO POST: received gifts from	score

QUESTION 5: WHAT DID YOU RECEIVE

2 MOS POST: gifts received	score	4 MOS POST: gifts received	score	6 MOS POST: gifts received	score

2 MOS POST: total score	4 MOS POST: total score	6 MOS POST: total score

Page 8

PART 5: 9

Interviewer: You will begin this section by asking the subject to recall the LAST job that he/she held before entering the program. If the subject has never been formally employed, ask about volunteer work or the job of his/her spouse. If the subject is self-employed, ask him/her to recall the last job held before becoming self-employed.

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT YOUR MOST RECENT EMPLOYMENT BEFO YOU ENTERED THIS PROGRAM: WHAT WAS THE NAME OF THE COMPANY OR ORGANIZATION WHICH YOU WERE AFFILIATED?

NOTES:

PRE: name of company	POST: name of company

NOTES:

BEFORE YOU ENTERED THIS PROGRAM, IN WHAT MONTH AND Y DID YOU LAST WORK FOR THIS EMPLOYEF

NOTES:

PRE: month & year last worked

Interviewer: At POST, if the job recalled is different than the job given at PRE, remind the subject of the original job and date provided, and proceed with questions 1-5.

QUESTION 1: WHAT WAS YOUR TITLE WHEN LAST WORKING AT THIS JOB?

NOTES:

PRE: job title	score	POST: job title	score

QUESTION 2: WHAT WAS THE FIRST AND LAST NAME OF YOUR SUPERVISOR?

NOTES:

PRE: supervisor's name	score	POST: supervisor's name	score

QUESTION 3: WHAT WAS THE COMPLETE ADDRESS OF THE BUILDING WHERE YOU WC

NOTES:

PRE: address	score	POST: address	score
number & street:		number & street:	
city: state:		city: state:	
zip code:		zip code:	

QUESTION 4: WHAT WAS YOUR PHONE NUMBER WITH AREA CODE AT THIS JOB?

NOTES:

PRE: phone number	score	POST: phone number	score

QUESTION 5: IN WHAT MONTH AND YEAR DID YOU FIRST START WORKING FOR THIS EMPL

NOTES:

PRE: mo & yr job began	score	POST: mo & yr job began	score

PRE: total score	POST: total score

Page 9

PART 5: 10

Interviewer: You will begin this section by asking the subject to recall the LAST job that he/she held before entering the program. If the subject has never been formally employed, ask about volunteer work or the job of his/her spouse. If the subject is self-employed, ask him/her to recall the last job held before becoming self-employed.

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT YOUR MOST RECENT EMPLOYMENT BEFO YOU ENTERED THIS PROGRAM: WHAT WAS THE NAME OF THE COMPANY OR ORGANIZATION W WHICH YOU WERE AFFILIATED?

2 MOS POST: name of company	4 MOS POST: name of company	6 MOS POST: name of company
NOTES:	NOTES:	NOTES:

*Interviewer: At **all** POST testing sessions, if the job recalled is different than the job given at PRE, remind the subject of the original job and date provided, and proceed with questions 1-5.*

QUESTION 1: WHAT WAS YOUR TITLE WHEN LAST WORKING AT THIS JOB?

2 MOS POST: job title	score	4 MOS POST: job title	score	6 MOS POST: job title	score

QUESTION 2: WHAT WAS THE FIRST AND LAST NAME OF YOUR SUPERVISOR?

2 MO POST: supervisor's name	score	4 MO POST: supervisor's name	score	6 MO POST: supervisor's name	score

QUESTION 3: WHAT WAS THE COMPLETE ADDRESS OF THE BUILDING WHERE YOU WC

2 MOS POST: address	score	4 MOS POST: address	score	6 MOS POST: address	score
number & street:		number & street:		number & street:	
city: state:		city: state:		city: state:	
zip code:		zip code:		zip code:	

QUESTION 4: WHAT WAS YOUR PHONE NUMBER WITH AREA CODE AT THIS JOB?

2 MOS POST: phone number	score	4 MOS POST: phone number	score	6 MOS POST: phone number	score

QUESTION 5: IN WHAT MONTH AND YEAR DID YOU FIRST START WORKING FOR THIS EMPL

2 MO POST: mo & yr job began	score	4 MO POST: mo & yr job began	score	6 MO POST: mo & yr job began	score

2 MOS POST: total score	4 MOS POST: total score	6 MOS POST: total score

Page 10

PART 6: PHYSICAL

11

Interviewer: You will begin this section by asking the subject to recall the MOST RECENT physical illness for which he/she consulted a physician, before entering the program. If the subject's most recent doctor's visit was for a check-up, ask him/her to recall the most recent visit that involved a physical complaint.

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT THE LAST TIME YOU CONSULTED A PHYS FOR A PHYSICAL COMPLAINT OR ILLNESS BEFORE YOU ENTERED THIS PROGRAM. WHY DID YO GO TO SEE A DOCTOR; WHAT WERE YOUR COMPLAINTS?

NOTES:

PRE: complaint	POST: complaint

NOTES:

IN WHAT MONTH AND YEAR DID THIS CONSULTATION TAKE PLA

NOTES:

PRE: month & year of visit

Interviewer: At POST, if the illness recalled is different than the one given at PRE, remind the subject of the original illness and date, and proceed with questions 1-5.

QUESTION 1: WHAT WAS THE FIRST AND LAST NAME OF THE DOCTOR WHOM YOU SAW AT THI

NOTES:

PRE: Dr.'s name	score	POST: Dr.'s name	score

QUESTION 2: WHAT WAS THE NAME AND ADDRESS OF THE BUILDING OR HOSPITAL WHERE Y(YOUR DOCTOR?

NOTES:

PRE: Dr.'s address	score	POST: Dr.'s address	score
name of building or hospital:		name of building or hospital:	
number & street:		number & street:	
city: state:		city: state:	
zip code:		zip code:	

QUESTION 3: ON WHAT FLOOR OF THIS BUILDING OR HOSPITAL WAS YOUR APPOINTM

NOTES:

PRE: floor	score	POST: floor	score

QUESTION 4: WHAT TREATMENTS OR MEDICATIONS WERE PRESCRIBED FOR YOU?

NOTES:

PRE: treatment	score	POST: treatment	score

QUESTION 5: IN WHAT MONTH AND YEAR DID YOU FIRST NOTICE YOUR SYMPT

NOTES:

PRE: mo & yr symps	score	POST: mo & yr symps	score

PRE: total score	POST: total score

Page 11

PART 6: PHYSICAL

12

Interviewer: You will begin this section by asking the subject to recall the MOST RECENT physical illness for which he/she consulted a physician before entering the program. If the subject's most recent doctor's visit was for a check-up, ask him/her to recall the most recent visit that involved a physical complaint.

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT THE LAST TIME YOU CONSULTED A PHYSI FOR A PHYSICAL COMPLAINT OR ILLNESS BEFORE YOU ENTERED THIS PROGRAM. WHY DID GO TO SEE A DOCTOR; WHAT WERE YOUR COMPLAINTS?

2 MOS POST: complaint	4 MOS POST: complaint	6 MOS POST: complaint
NOTES:	NOTES:	NOTES:

*Interviewer: At **all** POST testing sessions, if the illness recalled is different than the one given at PRE, remind the subject of the original illness and date, and proceed with questions 1-5.*

QUESTION 1: WHAT WAS THE FIRST AND LAST NAME OF THE DOCTOR WHOM YOU SAW AT THI

2 MOS POST: Dr.'s name	score	4 MOS POST: Dr.'s name	score	6 MOS POST: Dr.'s name	score

QUESTION 2: WHAT WAS THE NAME AND ADDRESS OF THE BUILDING OR HOSPITAL WHERE Y(YOUR DOCTOR?

2 MOS POST: Dr.'s address	score	4 MOS POST: Dr.'s address	score	6 MOS POST: Dr.'s address	score
name of building or hospital:		name of building or hospital:		name of building or hospital:	
number & street:		number & street:		number & street:	
city: state:		city: state:		city: state:	
zip code:		zip code:		zip code:	

QUESTION 3: ON WHAT FLOOR OF THIS BUILDING OR HOSPITAL WAS YOUR APPOINTM

2 MOS POST: floor	score	4 MOS POST: floor	score	6 MOS POST: floor	score

QUESTION 4: WHAT TREATMENTS OR MEDICATIONS WERE PRESCRIBED FOR YOU?

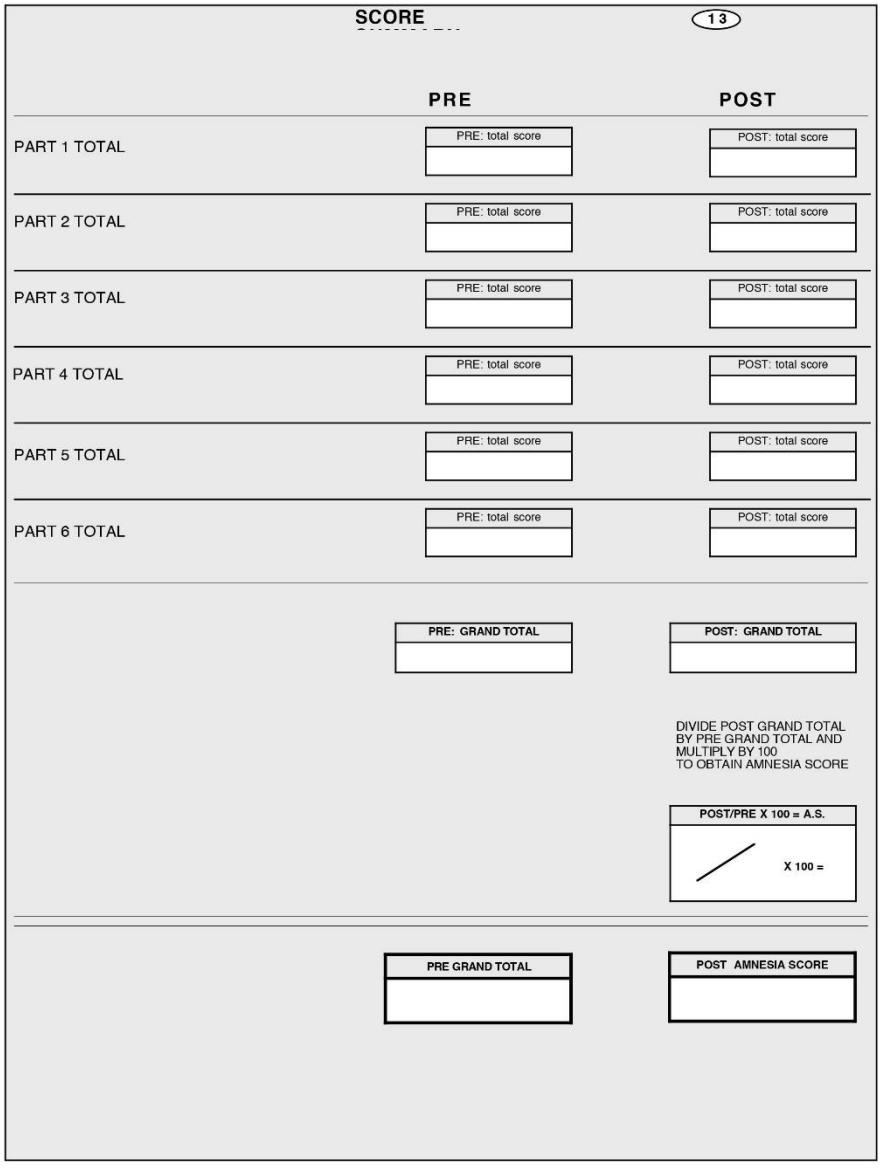
2 MOS POST: treatment	score	4 MOS POST: treatment	score	6 MOS POST: treatment	score

QUESTION 5: IN WHAT MONTH AND YEAR DID YOU FIRST NOTICE YOUR SYMPT

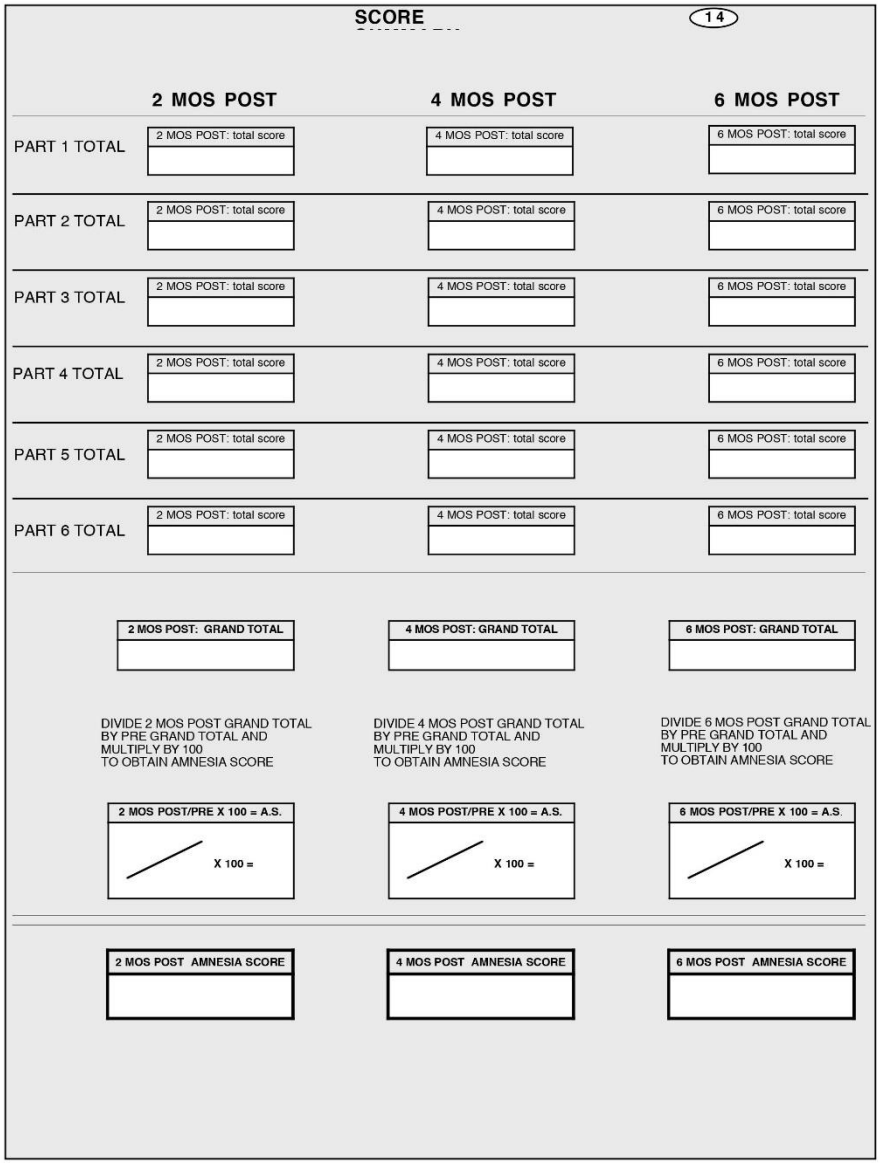
2 MOS POST: mo & yr symps	score	4 MOS POST: mo & yr symps	score	6 MOS POST: mo & yr symps	score

2 MOS POST: total score	4 MOS POST: total score	6 MOS POST: total score

Page 12


SCORE
13
PRE
POST
PART 1 TOTAL
PRE: total score
POST: total score
PART 2 TOTAL
PRE: total score
POST: total score
PART 3 TOTAL
PRE: total score
POST: total score
PART 4 TOTAL
PRE: total score
POST: total score
PART 5 TOTAL
PRE: total score
POST: total score
PART 6 TOTAL
PRE: total score
POST: total score
PRE: GRAND TOTAL
POST: GRAND TOTAL
DIVIDE POST GRAND TOTAL
BY PRE GRAND TOTAL AND
MULTIPLY BY 100
TO OBTAIN AMNESIA SCORE
POST/PRE X 100 = A.S.
X 100 =
PRE GRAND TOTAL
POST AMNESIA SCORE

Page 13


SCORE
14
2 MOS POST
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6 MOS POST
PART 1 TOTAL
2 MOS POST: total score
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PART 6 TOTAL
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6 MOS POST: total score
2 MOS POST: GRAND TOTAL
4 MOS POST: GRAND TOTAL
6 MOS POST: GRAND TOTAL
DIVIDE 2 MOS POST GRAND TOTAL BY PRE GRAND TOTAL AND MULTIPLY BY 100 TO OBTAIN AMNESIA SCORE
DIVIDE 4 MOS POST GRAND TOTAL BY PRE GRAND TOTAL AND MULTIPLY BY 100 TO OBTAIN AMNESIA SCORE
DIVIDE 6 MOS POST GRAND TOTAL BY PRE GRAND TOTAL AND MULTIPLY BY 100 TO OBTAIN AMNESIA SCORE
2 MOS POST/PRE X 100 = A.S.
X 100 =
4 MOS POST/PRE X 100 = A.S.
X 100 =
6 MOS POST/PRE X 100 = A.S.
X 100 =
2 MOS POST AMNESIA SCORE
4 MOS POST AMNESIA SCORE
6 MOS POST AMNESIA SCORE

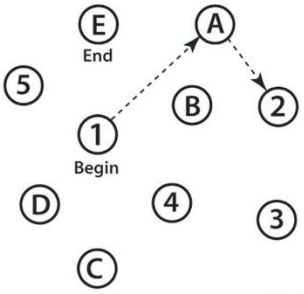
Page 14

V.3 – MOCA - *Montreal Cognitive Assessment*, V.8.1 & V.8.2

MONTREAL COGNITIVE ASSESSMENT (MOCA®)
Version 8.1 English

Name:
Education:
Sex:
Date of birth:
DATE:

VISUOSPATIAL/EXECUTIVE — POINTS



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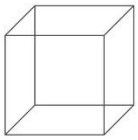
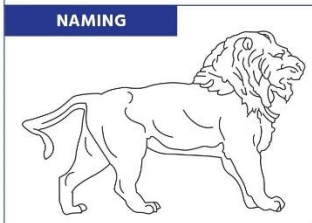


Draw CLOCK (Ten past eleven)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING



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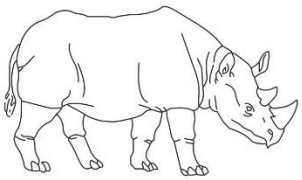

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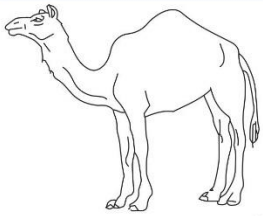

[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1ST TRIAL					
2ND TRIAL					

NO POINTS

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order. [ ] 2 1 8 5 4
Subject has to repeat them in the backward order. [ ] 7 4 2 — __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B — __/1

Serial 7 subtraction starting at 100. [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0** — __/3

LANGUAGE Repeat: I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] — __/2

Fluency: Name maximum number of words in one minute that begin with the letter F. [ ] _____ (N ≥ 11 words) — __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train - bicycle [ ] watch - ruler — __/2

DELAYED RECALL — __/5

(MIS)	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
X3							
X2	Category cue						MIS = ____ /15
X1	Multiple choice cue						

Memory Index Score (MIS)

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City — __/6

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Administered by: _____

Training and Certification are required to ensure accuracy

MIS: /15
(Normal ≥ 26/30)
Add 1 point if ≤ 12 yr edu

TOTAL __/30

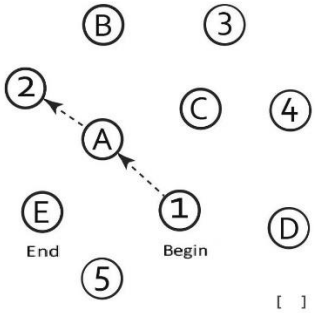
MONTREAL COGNITIVE ASSESSMENT (MoCA®)

Version 8.2 English

Name:
Education:
Sex:
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE

Copy chair



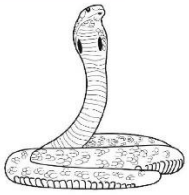
[ ] [ ]

Draw CLOCK (Ten past nine)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS __/5

NAMING



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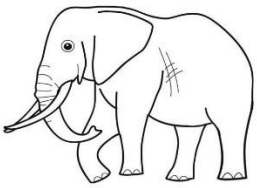

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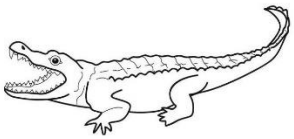

[ ]

__/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	HAND	NYLON	PARK	CARROT	YELLOW
1st TRIAL					
2nd TRIAL					

NO POINTS

ATTENTION

Read list of digits (1 digit / sec.).

Subject has to repeat them in the forward order. [ ] 8 1 5 2 4

Subject has to repeat them in the backward order. [ ] 2 4 7

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors.

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 70. [ ] 63 [ ] 56 [ ] 49 [ ] 42 [ ] 35

4 or 5 correct subtractions: **3 pts,** 2 or 3 correct: **2 pts,** 1 correct: **1 pt,** 0 correct: **0 pt**

__/3

LANGUAGE

Repeat: The robber of the gray car was stopped by the police. [ ]

The student went back to school without his books and pencils. [ ]

__/2

Language Fluency. Name maximum number of words in one minute that begin with the letter S. [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] bed - table [ ] letter - telephone

__/2

DELAYED RECALL

Memory Index Score (MIS)

(MIS)	Has to recall words WITH NO CUE	HAND [ ]	NYLON [ ]	PARK [ ]	CARROT [ ]	YELLOW [ ]	Points for UNCUED recall only
X3							
X2	Category cue						MIS = ____ /15
X1	Multiple choice cue						

__/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

www.mocatest.org

Administered by: _____

Training and Certification are required to ensure accuracy.

MIS: / 15

(Normal ≥ 26/30)

Add 1 point if ≤ 12 yr education

TOTAL __ /30

VI.4 - DSF & DSB – Digit Span Forwards & Digit Span Backwards

DIGIT SPAN TEST - - *FORWARD*

- After saying the instructions administer the digit spans in order.
- Do not repeat a span once read.
- Administer both spans of the same length regardless of how the participant performs.
- Say the digits at a rate of 1 digit about every 1 sec.
- Use a monotonic voice; without inflections at the end
- Discontinue after failure on both trials of any item (e.g., 5a and 5b)

Examiner: *"I am going to say some numbers. Listen carefully, and when I am through say them right after me. For example, if I say 7-1-9, what would you say?"*

- If the participant responds correctly (7-1-9), say: *"That's right,"* and proceed to Item 1.
- If the participant fails the example, say: *"No, you would say 7-1-9. I said 7-1-9, so to say it forwards you would say 7-1-9. Now try these numbers. Remember, you are to say them forwards. 3-4-8."*
- Whether the participant succeeds or fails with the second example (3-4-8), proceed to Item 1. Give no help on this second example or any of the items that follow.

Scoring: Each span is scored '1' (Pass) or '0' (Fail). Only discontinue test when participant has failed both trials of the same span length (e.g., 5a and 5b)

Item	Digit Span	Pass	Fail
1 a.	1 - 7	O 1	O 0
b.	6 - 3	O 1	O 0
2 a.	5 - 8 - 2	O 1	O 0
b.	6 - 9 - 4	O 1	O 0
3 a.	6 - 4 - 3 - 9	O 1	O 0
b.	7 - 2 - 8 - 6	O 1	O 0
4 a.	4 - 2 - 7 - 3 - 1	O 1	O 0
b.	7 - 5 - 8 - 3 - 6	O 1	O 0
5 a.	6 - 1 - 9 - 4 - 7 - 3	O 1	O 0
b.	3 - 9 - 2 - 4 - 8 - 7	O 1	O 0
6 a.	5 - 9 - 1 - 7 - 4 - 2 - 8	O 1	O 0
b.	4 - 1 - 7 - 9 - 3 - 8 - 6	O 1	O 0
7 a.	5 - 8 - 1 - 9 - 2 - 6 - 4 - 7	O 1	O 0
b.	3 - 8 - 2 - 9 - 5 - 1 - 7 - 4	O 1	O 0
8 a.	2 - 7 - 5 - 8 - 6 - 2 - 5 - 8 - 4	O 1	O 0
b.	7 - 1 - 3 - 9 - 4 - 2 - 5 - 6 - 8	O 1	O 0

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DIGIT SPAN TEST - - *BACKWARD*

- Administer the digit spans in order.
- Do not repeat a span once read.
- Administer both spans of the same length regardless of how the participant performs.
- Say the digits at a rate of 1 digit about every 1 sec.
- Use a monotonic voice; without inflections at the end

Examiner: *"Now I am going to say some numbers, but this time when I stop I want you say them backwards. For example, if I say 7-1-9, what would you say?"*

- If the participant responds correctly (9-1-7), say: *"That's right,"* and proceed to Item 1.
- If the participant fails the example, say: *"No, you would say 9-1-7. I said 7-1-9, so to say it backwards you would say 9-1-7. Now try these numbers. Remember, you are to say them backwards. 3-4-8."*
- Whether the participant succeeds or fails with the second example (3-4-8), proceed to Item 1. Give no help on this second example or any of the items that follow.
- Discontinue after failure on both trials of any item (e.g., 5a and 5b)

Scoring: Each span is scored '1' (Pass) or '0' (Fail). Only discontinue test when participant has failed both trials of the same span length (e.g., 5a and 5b)

Item	Digit Span	Pass	Fail
1 a.	2 - 4	O 1	O 0
b.	5 - 7	O 1	O 0
2 a.	6 - 2 - 9	O 1	O 0
b.	4 - 1 - 5	O 1	O 0
3 a.	3 - 2 - 7 - 9	O 1	O 0
b.	4 - 9 - 6 - 8	O 1	O 0
4 a.	1 - 5 - 2 - 8 - 6	O 1	O 0
b.	6 - 1 - 8 - 4 - 3	O 1	O 0
5 a.	5 - 3 - 9 - 4 - 1 - 8	O 1	O 0
b.	7 - 2 - 4 - 8 - 5 - 6	O 1	O 0
6 a.	8 - 1 - 2 - 9 - 3 - 6 - 5	O 1	O 0
b.	4 - 7 - 3 - 9 - 1 - 2 - 8	O 1	O 0
7 a.	9 - 4 - 3 - 7 - 6 - 2 - 5 - 8	O 1	O 0
b.	7 - 2 - 8 - 1 - 9 - 6 - 5 - 3	O 1	O 0

MONTGOMERY-ASBERG DEPRESSION RATING SCALE (MADRS)

OVERALL SEVERITY

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

It is important to remember that it is only on rare occasions when a depressed patient is encountered who cannot be rated on the items on the scale. If definite answers cannot be elicited from the patient all relevant clues as well as information from other sources should be used as a basis for the rating in line with customary clinical practice.

The scale may be used for any time interval between ratings, be it weekly or otherwise but this must be recorded.

Specify **one** of the reasons listed below by putting appropriate number in adjacent box.

1. APPARENT SADNESS

Representing despondency, gloom, and despair (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

☐

0 - No sadness
1
2 - Looks dispirited but does brighten up without difficulty
3
4 - Appears sad and unhappy most of the time
5
6 - Looks miserable all the time. Extremely despondent

2. REPORTED SADNESS

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

☐

0 - Occasional sadness in keeping with the circumstances
1
2 - Sad or low but brightens up without difficulty
3
4 - Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances
5
6 - Continuous or unvarying sadness, misery, or despondency

3. INNER TENSION

Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish.

Rate according to intensity, frequency, duration, and the extent of reassurance called for.

☐

0 - Placid. Only fleeting inner tension
1
2 - Occasional feelings of edginess and ill-defined discomfort
3
4 - Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty
5
6 - Unrelenting dread or anguish. Overwhelming panic

4. REDUCED SLEEP

Representing the experience of reduced duration or depth of sleep compared to the patient's own normal pattern when well.

☐

0 - Sleeps as usual
1
2 - Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep
3
4 - Sleep reduced or broken by at least 2 hours
5
6 - Less than 2 or 3 hours sleep

5. REDUCED APPETITE

Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

☐

0 - Normal or increased appetite
1
2 - Slightly reduced appetite
3
4 - No appetite. Food is tasteless
5
6 - Needs persuasion to eat at all

6. CONCENTRATION DIFFICULTIES

Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

Rate according to intensity, frequency, and degree of incapacity produced.

☐

0 - No difficulties in concentrating
1
2 - Occasional difficulties in collecting one's thoughts
3
4 - Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation
5
6 - Unable to read or converse without great difficulty

7. LASSITUDE

Representing a difficulty getting started or slowness initiating and performing everyday activities.

☐

0 - Hardly any difficulty in getting started. No sluggishness
1
2 - Difficulties in starting activities
3
4 - Difficulties in starting simple routine activities which are carried out with effort
5
6 - Complete lassitude. Unable to do anything without help

8. INABILITY TO FEEL

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

☐

0 - Normal interest in surroundings and in other people
1
2 - Reduced ability to enjoy usual interests
3
4 - Loss of interest in the surroundings. Loss of feelings for friends and acquaintances
5
6 - The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends

9. PESSIMISTIC THOUGHTS

Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin.

☐

0 - No pessimistic thoughts
1
2 - Fluctuating ideas of failure, self-reproach, or self-depreciation
3
4 - Persistent self-accusations or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future
5
6 - Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable

10. SUICIDAL THOUGHTS

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicide attempts should not in themselves influence the rating.

☐

0 - Enjoys life or takes it as it comes
1
2 - Weary of life. Only fleeting suicidal thoughts
3
4 - Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention
5
6 - Explicit plans for suicide when there is an opportunity. Active preparations for suicide

VII. Tolerability and Adverse Event Survey (Example)

During your time in this study, did you experience any side effects that you believe was due to the medication? If so, what did you experience? How often?

_____
_____
_____
_____

Did anything significant happen to you medically during your time in this study? If so, what happened and when?

_____
_____
_____
_____

Did any of your home medications change while you were in this study? If so, what changed? When?

_____
_____
_____
_____

On a scale from 1 to 9, how would you say you tolerated the medication assigned to you?

1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
They were completely tolerable								They were completely intolerable
○	○	○	○	○	○	○	○	○

Why?_____

On a scale from 1 to 9, how would you say you tolerated your ECT treatment?

1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
It was completely tolerable								It was completely intolerable
○	○	○	○	○	○	○	○	○

Why?_____

BIBLIOGRAPHY – *Alphabetical Order*

1. Abbasinazari M, Adib-Eshgh L, Rostami A, Beyraghi N, Dabir S, Jafari R. Memantine in the prevention or alleviation of electroconvulsive therapy induces cognitive disorders: A placebo controlled trial. *Asian J Psychiatr.* 2015;15:5-9.
2. Ainsworth NJ, Sepehry AA, Vila-Rodriguez F. Effects of Ketamine Anesthesia on Efficacy, Tolerability, Seizure Response, and Neurocognitive Outcomes in Electroconvulsive Therapy: A Comprehensive Meta-analysis of Double-Blind Randomized Controlled Trials. *J ECT.* 2020;36(2):94-105.
3. Alizadeh NS, Maroufi A, Jamshidi M, Hassanzadeh K, Gharibi F, Ghaderi E. Effect of Memantine on Cognitive Performance in Patients Under Electroconvulsive Therapy: A Double-Blind Randomized Clinical Trial. *Clin Neuropharmacol.* 2015;38(6):236-240.
4. Alvarez-Grandi SA, Groves SJ, Douglas KM, Porter RJ. Systematic Monitoring of Cognitive Function During Electroconvulsive Therapy: A Retrospective Analysis of Data From a Service Using a Short Cognitive Testing Battery. *J ECT.* 2020;36(1):10-17.
5. Andrade C. Molecular mechanisms underlying electroconvulsive therapy-induced amnestic deficits: A decade of research. *Indian J Psychiatry.* 2008;50(4):244-252.
6. Association As. Medications for Memory, Cognition and Dementia-Related Behaviors. 2022; https://www.alz.org/alzheimers-dementia/treatments/medications-for-memory. Accessed 03/15/2022, 2022.
7. Bassa A, Sagués T, Porta-Casteràs D, et al. The Neurobiological Basis of Cognitive Side Effects of Electroconvulsive Therapy: A Systematic Review. *Brain Sci.* 2021;11(10).
8. Bayless JD, McCormick LM, Brumm MC, Espe-Pfeifer PB, Long JJ, Lewis JL. Pre- and post-electroconvulsive therapy multidomain cognitive assessment in psychotic depression: relationship to premorbid abilities and symptom improvement. *J ECT.* 2010;26(1):47-52.
9. Bennett-Levy J, Powell GE. The Subjective Memory Questionnaire (SMQ). An investigation into the self-reporting of 'real-life' memory skills. *British Journal of Social and Clinical Psychology.* 1980;19(2):177-188.
10. Brus O, Nordanskog P, Båve U, et al. Subjective Memory Immediately Following Electroconvulsive Therapy. *J ECT.* 2017;33(2):96-103.
11. Calhoun A, King C, Khoury R, Grossberg GT. An evaluation of memantine ER + donepezil for the treatment of Alzheimer's disease. *Expert Opin Pharmacother.* 2018;19(15):1711-1717.
12. Carmody TJ, Rush AJ, Bernstein I, et al. The Montgomery Asberg and the Hamilton ratings of depression: a comparison of measures. *Eur Neuropsychopharmacol.* 2006;16(8):601-611.
13. Carstens L, Hartling C, Stippl A, et al. A symptom-based approach in predicting ECT outcome in depressed patients employing MADRS single items. *Eur Arch Psychiatry Clin Neurosci.* 2021;271(7):1275-1284.

14. Chakrabarti S, Grover S, Rajagopal R. Electroconvulsive therapy: a review of knowledge, experience and attitudes of patients concerning the treatment. *World J Biol Psychiatry.* 2010;11(3):525-537.
15. Chen R, Chan PT, Chu H, et al. Treatment effects between monotherapy of donepezil versus combination with memantine for Alzheimer disease: A meta-analysis. *PLoS One.* 2017;12(8):e0183586.
16. David L. Perez EDM, Brent P. Forester, Bruce H. Price. Depression and Psychosis in Neurological Practice. *Bradley and Daroff's Neurology in Clinical Practice*. Eighth ed: Elsevier Inc; 2022:97-119.
17. Doody RS, Corey-Bloom J, Zhang R, Li H, Ieni J, Schindler R. Safety and tolerability of donepezil at doses up to 20 mg/day: results from a pilot study in patients with Alzheimer's disease. *Drugs Aging.* 2008;25(2):163-174.
18. Dutta LCB, Sarkar CP, Andrade C. Efficacy of donepezil for the attenuation of memory deficits associated with electroconvulsive therapy. *Psychiatry Res.* 2020;293:113397.
19. DynaMed. Memantine Hydrochloride/Donepezil Hydrochloride. 2022; https://www.dynamed.com/drug-monograph/memantine-hydrochloride-donepezil-hydrochlorideMemantine Accessed 03/11/2022, 2022.
20. DynaMed. Memantine. 2022; https://www.dynamed.com/drug-monograph/memantine. Accessed 03/11/2022, 2022.
21. DynaMed. Donepezil. 2022; https://www.dynamed.com/drug-monograph/donepezil#GUID-E7E085F0-A2DA-4F6A-AD7B-9E0756FE9C9B__CITE5. Accessed 03/11/2022, 2022.
22. Fink M. Convulsive therapy: a review of the first 55 years. *J Affect Disord.* 2001;63(1-3):1-15.
23. Fink M. What was learned: studies by the consortium for research in ECT (CORE) 1997-2011. *Acta Psychiatr Scand.* 2014;129(6):417-426.
24. Folch J, Busquets O, Ettcheto M, et al. Memantine for the Treatment of Dementia: A Review on its Current and Future Applications. *J Alzheimers Dis.* 2018;62(3):1223-1240.
25. Greenberg RM, Kellner CH. Electroconvulsive therapy: a selected review. *Am J Geriatr Psychiatry.* 2005;13(4):268-281.
26. Guo J, Wang Z, Liu R, Huang Y, Zhang N, Zhang R. Memantine, Donepezil, or Combination Therapy—What is the best therapy for Alzheimer's Disease? A Network Meta-Analysis. *Brain and Behavior.* 2020;10(11):e01831.
27. Guo J, Wang Z, Liu R, Huang Y, Zhang N, Zhang R. Memantine, Donepezil, or Combination Therapy-What is the best therapy for Alzheimer's Disease? A Network Meta-Analysis. *Brain Behav.* 2020;10(11):e01831.
28. Haake A, Nguyen K, Friedman L, Chakkamparambil B, Grossberg GT. An update on the utility and safety of cholinesterase inhibitors for the treatment of Alzheimer's disease. *Expert Opin Drug Saf.* 2020;19(2):147-157.
29. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23(1):56-62.
30. Hammershøj LG, Petersen JZ, Jensen HM, Jørgensen MB, Miskowiak KW. Cognitive Adverse Effects of Electroconvulsive Therapy: A Discrepancy Between Subjective and Objective Measures? *J ECT.* 2022;38(1):30-38.

31. Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *Clin Interv Aging.* 2008;3(2):211-225.
32. Hebbrecht K, Giltay EJ, Birkenhäger TK, et al. Cognitive change after electroconvulsive therapy in mood disorders measured with the Montreal Cognitive Assessment. *Acta Psychiatr Scand.* 2020;142(5):413-422.
33. Henstra MJ, Jansma EP, van der Velde N, Swart EL, Stek ML, Rhebergen D. Acetylcholinesterase inhibitors for electroconvulsive therapy-induced cognitive side effects: a systematic review. *Int J Geriatr Psychiatry.* 2017;32(5):522-531.
34. Hoffmann TC, Del Mar C. Clinicians' Expectations of the Benefits and Harms of Treatments, Screening, and Tests: A Systematic Review. *JAMA Intern Med.* 2017;177(3):407-419.
35. Iannuzzo RW, Jaeger J, Goldberg JF, Kafantaris V, Sublette ME. Development and reliability of the HAM-D/MADRS interview: an integrated depression symptom rating scale. *Psychiatry Res.* 2006;145(1):21-37.
36. Jelovac A, O'Connor S, McCarron S, McLoughlin DM. Autobiographical Memory Specificity in Major Depression Treated With Electroconvulsive Therapy. *J ECT.* 2016;32(1):38-43.
37. Kadiyala PK, Kadiyala LD. Anaesthesia for electroconvulsive therapy: An overview with an update on its role in potentiating electroconvulsive therapy. *Indian J Anaesth.* 2017;61(5):373-380.
38. Kellner CH, Adams DA, Benferhat A. Further improving the cognitive effect profile of electroconvulsive therapy (ECT): the case for studying carbamylated erythropoietin. *Med Hypotheses.* 2015;84(3):258-261.
39. Kellner CH, Knapp R, Husain MM, et al. Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. *Br J Psychiatry.* 2010;196(3):226-234.
40. Kellner CH, Obbels J, Sienaert P. When to consider electroconvulsive therapy (ECT). *Acta Psychiatr Scand.* 2020;141(4):304-315.
41. Kirov GG, Owen L, Ballard H, et al. Evaluation of cumulative cognitive deficits from electroconvulsive therapy. *Br J Psychiatry.* 2016;208(3):266-270.
42. Kolshus E, Jelovac A, McLoughlin DM. Bitemporal v. high-dose right unilateral electroconvulsive therapy for depression: a systematic review and meta-analysis of randomized controlled trials. *Psychol Med.* 2017;47(3):518-530.
43. Koola MM. Galantamine-Memantine Combination for Cognitive Impairments Due to Electroconvulsive Therapy, Traumatic Brain Injury, and Neurologic and Psychiatric Disorders: Kynurenic Acid and Mismatch Negativity Target Engagement. *Prim Care Companion CNS Disord.* 2018;20(2).
44. Kumar A, Gupta V, Sharma S. Donepezil. *StatPearls*. Treasure Island FL: © 2022, StatPearls Publishing LLC.; 2022.
45. Kuns B, Rosani A, Varghese D. Memantine. *StatPearls*. Treasure Island FL: © 2021, StatPearls Publishing LLC.; 2021.
46. Landry M, Moreno A, Patry S, Potvin S, Lemasson M. Current Practices of Electroconvulsive Therapy in Mental Disorders: A Systematic Review and Meta-Analysis of Short and Long-Term Cognitive Effects. *J ECT.* 2021;37(2):119-127.

47. Lerer B. Studies on the role of brain cholinergic systems in the therapeutic mechanisms and adverse effects of ECT and lithium. *Biol Psychiatry.* 1985;20(1):20-40.
48. Lerer B, Stanley M, McIntyre I, Altman H. Electroconvulsive shock and brain muscarinic receptors: relationship to anterograde amnesia. *Life Sci.* 1984;35(26):2659-2664.
49. Levin JB, Sams J, Tatsuoka C, Cassidy KA, Sajatovic M. Use of automated medication adherence monitoring in bipolar disorder research: pitfalls, pragmatics, and possibilities. *Ther Adv Psychopharmacol.* 2015;5(2):76-87.
50. Lisanby SH. Electroconvulsive therapy for depression. *N Engl J Med.* 2007;357(19):1939-1945.
51. Lisanby SH, Maddox JH, Prudic J, Devanand DP, Sackeim HA. The effects of electroconvulsive therapy on memory of autobiographical and public events. *Arch Gen Psychiatry.* 2000;57(6):581-590.
52. Liu J, Chang L, Song Y, Li H, Wu Y. The Role of NMDA Receptors in Alzheimer's Disease. *Front Neurosci.* 2019;13:43.
53. Loo C, Katalinic N, Mitchell PB, Greenberg B. Physical treatments for bipolar disorder: a review of electroconvulsive therapy, stereotactic surgery and other brain stimulation techniques. *J Affect Disord.* 2011;132(1-2):1-13.
54. Luchini F, Medda P, Mariani MG, Mauri M, Toni C, Perugi G. Electroconvulsive therapy in catatonic patients: Efficacy and predictors of response. *World J Psychiatry.* 2015;5(2):182-192.
55. Magnezi R, Aminov E, Shmuel D, Dreifuss M, Dannon P. Comparison between neurostimulation techniques repetitive transcranial magnetic stimulation vs electroconvulsive therapy for the treatment of resistant depression: patient preference and cost-effectiveness. *Patient Prefer Adherence.* 2016;10:1481-1487.
56. Mankad MV, Beyer JL, Weiner RD, Krystal AD. *Clinical manual of electroconvulsive therapy.* Arlington, VA: American Psychiatric Publishing, Inc ; US; 2010.
57. Mathew SJ, Wilkinson ST, Altinay M, et al. ELEctroconvulsive therapy (ECT) vs. Ketamine in patients with Treatment-resistant Depression: The ELEKT-D study protocol. *Contemp Clin Trials.* 2019;77:19-26.
58. Matthews JD, Blais M, Park L, et al. The impact of galantamine on cognition and mood during electroconvulsive therapy: a pilot study. *J Psychiatr Res.* 2008;42(7):526-531.
59. Matthews JD, Siefert CJ, Blais MA, et al. A double-blind, placebo-controlled study of the impact of galantamine on anterograde memory impairment during electroconvulsive therapy. *J ECT.* 2013;29(3):170-178.
60. McCall WV. Handbook of ECT: A Guide to Electroconvulsive Therapy for Practitioners: Charles H. Kellner. Cambridge University Press, New York. 2019. ISBN 978-1-108-40328-3. *The Journal of ECT.* 2019;35(2):144.
61. McClintock SM, Choi J, Deng ZD, Appelbaum LG, Krystal AD, Lisanby SH. Multifactorial determinants of the neurocognitive effects of electroconvulsive therapy. *J ECT.* 2014;30(2):165-176.

62. McGirr A, Berlim MT, Bond DJ, Chan PY, Yatham LN, Lam RW. Adjunctive ketamine in electroconvulsive therapy: updated systematic review and meta-analysis. *Br J Psychiatry.* 2017;210(6):403-407.
63. McIntyre RS, Filteau MJ, Martin L, et al. Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. *J Affect Disord.* 2014;156:1-7.
64. Mehlman MJ. Cognition-enhancing drugs. *Milbank Q.* 2004;82(3):483-506, table of contents.
65. Misra S. Randomized double blind placebo control studies, the "Gold Standard" in intervention based studies. *Indian J Sex Transm Dis AIDS.* 2012;33(2):131-134.
66. Moirand R, Galvao F, Lecompte M, Poulet E, Haesebaert F, Brunelin J. Usefulness of the Montreal Cognitive Assessment (MoCA) to monitor cognitive impairments in depressed patients receiving electroconvulsive therapy. *Psychiatry Res.* 2018;259:476-481.
67. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 1979;134:382-389.
68. Nazarinasab M, Behrouzian F, Mahnoo M. Evaluation of donepezil and rivastigmine administration on the cognitive deficits induced by electroconvulsive therapy: a randomized, double-blind clinical trial. *Family Medicine & Primary Care Review.* 2019(3):243-248.
69. Niu Y, Ye D, You Y, Wu J. Prophylactic cognitive enhancers for improvement of cognitive function in patients undergoing electroconvulsive therapy: A systematic review and meta-analysis. *Medicine (Baltimore).* 2020;99(11):e19527.
70. Njau S, Joshi SH, Espinoza R, et al. Neurochemical correlates of rapid treatment response to electroconvulsive therapy in patients with major depression. *J Psychiatry Neurosci.* 2017;42(1):6-16.
71. Obbels J, Verwijk E, Bouckaert F, Sienaert P. ECT-Related Anxiety: A Systematic Review. *J ECT.* 2017;33(4):229-236.
72. Olivieri NF, Matsui D, Hermann C, Koren G. Compliance assessed by the Medication Event Monitoring System. *Arch Dis Child.* 1991;66(12):1399-1402.
73. Park MJ, Kim H, Kim EJ, et al. Recent Updates on Electro-Convulsive Therapy in Patients with Depression. *Psychiatry Investig.* 2021;18(1):1-10.
74. Parkinson WL, Rehman Y, Rathbone M, Upadhye S. Performances on individual neurocognitive tests by people experiencing a current major depression episode: A systematic review and meta-analysis. *J Affect Disord.* 2020;276:249-259.
75. Peterchev AV, Rosa MA, Deng ZD, Prudic J, Lisanby SH. Electroconvulsive therapy stimulus parameters: rethinking dosage. *J ECT.* 2010;26(3):159-174.
76. Petrides G, Malur C, Braga RJ, et al. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. *Am J Psychiatry.* 2015;172(1):52-58.
77. Petrides G, Tobias KG, Kellner CH, Rudorfer MV. Continuation and maintenance electroconvulsive therapy for mood disorders: review of the literature. *Neuropsychobiology.* 2011;64(3):129-140.

78. Pigot M, Andrade C, Loo C. Pharmacological attenuation of electroconvulsive therapy--induced cognitive deficits: theoretical background and clinical findings. *J ECT.* 2008;24(1):57-67.
79. Porter R, Heenan H, Reeves J. Early effects of electroconvulsive therapy on cognitive function. *J ECT.* 2008;24(1):35-39.
80. Porter RJ, Baune BT, Morris G, et al. Cognitive side-effects of electroconvulsive therapy: what are they, how to monitor them and what to tell patients. *BJPsych Open.* 2020;6(3):e40.
81. Prakash J, Chaudhury S, Chatterjee K, Kotwal A, Srivastava K, Saha A. Therapeutic and prophylactic role of cognitive enhancers in electroconvulsive therapy-induced cognitive deficits. *Ind Psychiatry J.* 2019;28(2):286-293.
82. Prakash J, Kotwal A, Prabhu H. Therapeutic and prophylactic utility of the memory-enhancing drug donepezil hydrochloride on cognition of patients undergoing electroconvulsive therapy: a randomized controlled trial. *J ECT.* 2006;22(3):163-168.
83. Prudic J. Strategies to minimize cognitive side effects with ECT: aspects of ECT technique. *J ECT.* 2008;24(1):46-51.
84. Prudic J, Peyser S, Sackeim HA. Subjective memory complaints: a review of patient self-assessment of memory after electroconvulsive therapy. *J ECT.* 2000;16(2):121-132.
85. Quilty LC, Robinson JJ, Rolland JP, Fruyt FD, Rouillon F, Bagby RM. The structure of the Montgomery-Åsberg depression rating scale over the course of treatment for depression. *Int J Methods Psychiatr Res.* 2013;22(3):175-184.
86. Sackeim HA. Autobiographical memory and ECT: Don't throw out the baby. *The journal of ECT.* 2014;30(3):177.
87. Sackeim HA. Modern Electroconvulsive Therapy: Vastly Improved yet Greatly Underused. *JAMA Psychiatry.* 2017;74(8):779-780.
88. Sackeim HA, Prudic J, Devanand DP, et al. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *N Engl J Med.* 1993;328(12):839-846.
89. Sackeim HA, Prudic J, Devanand DP, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry.* 2000;57(5):425-434.
90. Sackeim HA, Prudic J, Fuller R, Keilp J, Lavori PW, Olfson M. The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology.* 2007;32(1):244-254.
91. Sackeim HA, Prudic J, Nobler MS, et al. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimul.* 2008;1(2):71-83.
92. Sarraf N, Badri T, Keshvari N, Ghassab-Sahebkar A, Qobadighadikolaei R, Abbasinazari M. Comparison of the efficacy and safety of melatonin and memantine in the alleviation of cognitive impairments induced by electroconvulsive therapy: A randomized clinical trial. *J Clin Neurosci.* 2020;74:146-150.

93. Semkovska M, Keane D, Babalola O, McLoughlin DM. Unilateral brief-pulse electroconvulsive therapy and cognition: effects of electrode placement, stimulus dosage and time. *J Psychiatr Res.* 2011;45(6):770-780.
94. Semkovska M, McLoughlin DM. Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. *Biol Psychiatry.* 2010;68(6):568-577.
95. Semkovska M, McLoughlin DM. Measuring retrograde autobiographical amnesia following electroconvulsive therapy: historical perspective and current issues. *J ECT.* 2013;29(2):127-133.
96. Semkovska M, McLoughlin DM. Retrograde autobiographical amnesia after electroconvulsive therapy: on the difficulty of finding the baby and clearing murky bathwater. *J ECT.* 2014;30(3):187-188; discussion 189-190.
97. Shams-Alizadeh N, Maroufi A, Sofla AQC, Ghaderi E, Hassanzadeh K. Effect of Donepezil on Cognitive Deficits Associated With Electroconvulsive Therapy: A Randomized Triple-blind Clinical Trial. *Clin Neuropharmacol.* 2019;42(2):27-31.
98. Sienaert PA, Vansteelandt K, Demyttenaere K, Peuskens J. Predictors of patient satisfaction after ultrabrief bifrontal and unilateral electroconvulsive therapies for major depression. *J ECT.* 2010;26(1):55-59.
99. Singh A, Kar SK. How Electroconvulsive Therapy Works?: Understanding the Neurobiological Mechanisms. *Clin Psychopharmacol Neurosci.* 2017;15(3):210-221.
100. Sobin C, Sackeim HA, Prudic J, Devanand DP, Moody BJ, McElhiney MC. Predictors of retrograde amnesia following ECT. *Am J Psychiatry.* 1995;152(7):995-1001.
101. Squire LR, Chace PM. Memory functions six to nine months after electroconvulsive therapy. *Arch Gen Psychiatry.* 1975;32(12):1557-1564.
102. Squire SR, Slater PC. Bilateral and unilateral ECT: effects on verbal and nonverbal memory. *Am J Psychiatry.* 1978;135(11):1316-1320.
103. Stryjer R, Ophir D, Bar F, Spivak B, Weizman A, Strous RD. Rivastigmine treatment for the prevention of electroconvulsive therapy-induced memory deficits in patients with schizophrenia. *Clin Neuropharmacol.* 2012;35(4):161-164.
104. Thirthalli J, Naik SS, Kunigiri G. Frequency and Duration of Course of ECT Sessions: An Appraisal of Recent Evidence. *Indian J Psychol Med.* 2020;42(3):207-218.
105. Tor PC, Bautovich A, Wang MJ, Martin D, Harvey SB, Loo C. A Systematic Review and Meta-Analysis of Brief Versus Ultrabrief Right Unilateral Electroconvulsive Therapy for Depression. *J Clin Psychiatry.* 2015;76(9):e1092-1098.
106. Trzepacz PT, Hochstetler H, Wang S, Walker B, Saykin AJ. Relationship between the Montreal Cognitive Assessment and Mini-mental State Examination for assessment of mild cognitive impairment in older adults. *BMC Geriatr.* 2015;15:107.
107. van Bergen S, Brands I, Jelicic M, Merckelbach H. Assessing trait memory distrust: Psychometric properties of the Squire Subjective Memory Questionnaire. *Legal and Criminological Psychology.* 2010;15(2):373-384.

108. van Diermen L, van den Ameele S, Kamperman AM, et al. Prediction of electroconvulsive therapy response and remission in major depression: meta-analysis. *Br J Psychiatry.* 2018;212(2):71-80.
109. Vann Jones S, McCollum R. Subjective memory complaints after electroconvulsive therapy: systematic review. *BJPsych Bull.* 2019;43(2):73-80.
110. Verdijk J, van Kessel MA, Oud M, et al. Pharmacological interventions to diminish cognitive side effects of electroconvulsive therapy: A systematic review and meta-analysis. *Acta Psychiatr Scand.* 2022.
111. Weiss A. *The Electroconvulsive Therapy Workbook: Clinical Applications.* Taylor & Francis; 2018.
112. Wilkinson ST, Agbese E, Leslie DL, Rosenheck RA. Identifying Recipients of Electroconvulsive Therapy: Data From Privately Insured Americans. *Psychiatr Serv.* 2018;69(5):542-548.
113. Wilkinson ST, Kitay BM, Harper A, et al. Barriers to the Implementation of Electroconvulsive Therapy (ECT): Results From a Nationwide Survey of ECT Practitioners. *Psychiatr Serv.* 2021;72(7):752-757.
114. Woo SW, Do SH. Tongue laceration during electroconvulsive therapy. *Korean J Anesthesiol.* 2012;62(1):101-102.
115. Zarean E, Sedehi M, Heshmati Y. Efficacy of Donepezil in Improving Cognitive Impairment Induced by Electroconvulsive Therapy in Patients with Mood Disorders: A Randomized, Double-blind, Placebo-Controlled Trial. *Iran J Psychiatry Behav Sci.* 2021;15(3):e107598.
116. Zhdanava M, Pilon D, Ghelerter I, et al. The Prevalence and National Burden of Treatment-Resistant Depression and Major Depressive Disorder in the United States. *J Clin Psychiatry.* 2021;82(2).
117. Zimmerman M, Martinez JH, Young D, Chelminski I, Dalrymple K. Severity classification on the Hamilton Depression Rating Scale. *J Affect Disord.* 2013;150(2):384-388.
118. Zisook S, Ganadjian K, Moutier C, Prather R, Rao S. Sequenced Treatment Alternatives to Relieve Depression (STAR*D): lessons learned. *J Clin Psychiatry.* 2008;69(7):1184-1185.