Efficacy and Safety of the Thymatron System IV ECT Device, a Comprehensive Review

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This is a comprehensive review of the clinical research literature on electroconvulsive therapy (ECT) as it relates to the risks and benefits of the most widely-used Thymatron ECT device models: the DG, DGx, and System IV. The review is limited to controlled studies that typically contain the key elements of random assignment, "blind" outcome evaluation, and statistical analysis to a specified criterion. Such studies have generally replaced those in the older literature that were often characterized by impressionistic reports based on anecdotal observations without objective verification.

Several reports in the older literature not specific to the Thymatron have expressed concern on potential adverse effects of induced seizures on brain function, but the technique of ECT and the design features of modern devices have advanced substantially over the years to mitigate those concerns. For example, it is instructive to compare one of the oft-cited older studies purporting to demonstrate brain damage in cats receiving electrically-induced convulsions (Alpers and Hughes, 1942) with a prospective study in patients receiving modern ECT that employed blindly-analyzed serial magnetic resonance images obtained before, 2-3 days after ECT, and 6 months later, and revealed no such evidence for brain damage (Coffey et al, 1991).

The problem with Alpers and Hughes (1942) and other older neuropathological studies of electrically-induced seizures in animals (ECS) is that they failed to use muscle-relaxant drugs before stimulation and did not include untreated animals for comparison. Breggin (1979) has emphasized the cerebral petechial hemorrhages (small blood spots on the brain surface) found in such animals, but when animals were restrained from banging their head during the seizure no such petechiae were found (Siekert, Williams, and Windle, 1950). Moreover, Breggin's opinions on ECT were rejected in court as biased, unqualified, and without rational basis in fact (Lightner v. Alessi, 22 February 1995).

Efficacy of the Thymatron ECT Device

Abbott CC, Lemke NT, Gopal S et al (2013) reported twelve DSM-IV manic-depressive depressed patients treated with a Thymatron System IV who were rated on the Hamilton scale before and after a course of ECT and exhibited a significant mean depression scale improvement of 27.6 points.

Azuma H, Fujita A, Sato K et al (2007) studied 14 treatment-resistant depressives received bilateral ECT with a Thymatron System IV. Highly significant improvement in Hamilton Depression Scale scores was achieved, with 43% scoring less than 8 post-ECT. Postictal suppression as measured by the Thymatron System IV was a significant predictor of therapeutic outcome.

Heikman et al (2002) used a Thymatron DGx ECT device to treat 24 major depressives who were randomly assigned to high-dose right unilateral ECT, moderate-dose right unilateral ECT, or low-dose bifrontal ECT. Blindly-obtained Hamilton Depression scale scores at baseline and after the ECT course showed an overall 66% improvement, with the best improvement (73%) recorded for the high-dose right unilateral group.

Huang CJ et al (2017) studied 95 inpatients with depression receiving at least 6 ECT sessions with a Thymatron device. Quality of life, symptom severity, and functioning were assessed before and after ECT on the Hamilton Depression scale and the Modified Work and Social Adjustment Scale CT. All measures improved significantly after treatment without significant adverse effects.

Kellner et al (2005) used a Thymatron DGx to treat 131 unipolar major depressives who expressed high suicidal intent as recorded on item 3 of the Hamilton depression scale. 81% of these patients' suicide ratings ultimately dropped to zero, including the 13 patients who had made an actual suicide attempt.

Kellner CH et al (2017) present the case of a 25-year-old woman hospitalized for a major depressive episode and suicidality in the context of bipolar 1 disorder, whose symptoms fully remitted with 1 ECT.

Lin CH, Chen MC, Lee WK et al (2013) studied fifty-five treatment-resistant depressives who received ECT administered with a Thymatron System IV. Hamilton depression scale scores and Clinical Global Impression-Severity scores obtained at baseline and after every 3 treatments showed significant reductions after the treatment course.

Niemantsverdriet L et al (2009) studied 65 patients with major depression who received bilateral ECT administered with a Thymatron System IV using either brief pulse or ultra-brief pulse stimulation. Significant and equivalent improvement in depression scale scores was achieved with both electrode placements.

Petrides et al (2001) used a Thymatron DGx ECT device to treat 253 patients with unipolar major depression with bilateral ECT at 50% above threshold. The overall remission rate for the sample as determined by blindly-obtained Hamilton Depression Scale ratings was 87%, with patients with psychotic depression enjoying a remarkable 95% remission rate.

Ranjkesh, Barekatain, and Akuchakian (2005) randomly assigned 39 DSM-IV patients with major depression to receive courses of 8 bifrontal, bitemporal, or right ORIGINAL unilateral ECT administered with a Thymatron DGx ECT device. Blindly-obtained Hamilton Depression scale ratings at baseline and after the 8th ECT revealed 73% improvement for the entire sample, with no significant difference among the treatment groups.

Williams et al (2008) used a Thymatron DGx ECT device to administer 1.5 times threshold bitemporal ECT to 515 patients with DSM-IV unipolar major depression, obtaining a 68% reduction in Hamilton Depression scale scores at the end of their course of treatment.

Somatics' safety experience with the Thymatron ECT device

Since September 27, 1984, when FDA cleared the Somatics Thymatron ECT device for marketing, more than 4,300 Thymatron devices have been sold worldwide. During that time Somatics has maintained complete safety files on the Thymatron device, including those required by the FDA's Good Manufacturing Practice regulation, the Canadian Standards Association, the German TüV testing agency, and KEMA Registered Quality. The latter three agencies regularly make on-site inspection visits to review manufacturing practices, documentation, and established quality control procedures for compliance with applicable published standards.

Risk reduction components of the Thymatron ECT Device

a) Risk of prolonged seizures and cardiac arrhythmias

The two most frequent complications during an ECT treatment session are excessively long seizures and irregular heart rhythms (Nuttall et al, 2004), both of which can be detected by routine monitoring during the treatment. The Thymatron's integral brain-wave monitor (electroencephalogram, EEG) enhances the safety of ECT by allowing the treating doctor to detect a prolonged seizure as it occurs so that it can be terminated with intravenous medication. Likewise, a heart monitor (electrocardiogram, ECG) allows the treating doctor to detect irregular heartbeat patterns as they occur so that they can be managed with intravenous medication. These Somatics Thymatron monitors start recording automatically as soon as the ECT stimulus is delivered and continue until they are turned off by the doctor.

In addition to the paper EEG record the Somatics Thymatron device has an auditory EEG monitor that allows the user to tell without looking at the patient or the paper EEG whether or not the seizure has stopped. In a study of 82 consecutive ECTs the auditory EEG of the Thymatron device allowed the investigators to determine the occurrence and the duration of the induced EEG seizure with a high degree of accuracy when tested against the paper EEG standard (Swartz and Abrams, 1986).

Risk reduction of Thymatron component failure

In the extremely rare event of catastrophic failure of an ECT device component there exists the remote possibility for an ECT device to deliver an electrical stimulus dose substantially in excess of that set by the operator, potentially causing excessive memory disturbance. To prevent such an occurrence the Somatics Thymatron device includes an independent separate redundant safety circuit that automatically measures the electrical charge at the output terminals each time the stimulus button is pressed and prevents delivery of any stimulus charge that exceeds by more than 5% that set by the operator. To test the integrity of the electrical connection to the patient, the Somatics Thymatron device includes a static impedance test initiated by a button press. The test current is too small to be felt by a fully awake person. This test helps assure good electrode contact and prevent excessive heat release onto the skin.

Published risk assessments of the Thymatron

a) Brain damage risk

Bai T et al (2019) studied 61 depressed patients receving ECT with a Thymatron System IV device compared with 23 healthy controls. ECT increased local activity of the dorsomedial prefrontal cortex and enhanced connectivity with the posterior cingulate cortex that was positively correlated with clinical improvement. These findings provide strong evidence to support the functional plasticity of the dorsomedial prefrontal cortex and its reorganization by ECT that putatively underlies its antidepressant effect.

Doddi SR et al (2018) A 72 yo man with severe depression following a subarachnoid hemorrhage demonstrated on CT received 9 bifrontal ECTs 33 days post-hemorrhage with a Thymatron System IV device, with dramatic improvement in sequential Montgomery-Asberg Depression Scale scores, and Mini-Mental State Scores that ranged from 28-30, all within the normal range. A repeat CT scan after the first ECT showed no intracranial hemorrhage or any other acute intracranial process. 5 months later he remained in full remission.

Ende et al (2000) used proton magnetic resonance spectroscopic imaging to study hippocampal effects of the Thymatron DG ECT device as reflected in N-acetylaspartate signals. In 17 patients receiving either unilateral or bilateral ECT (all of whom improved with treatment), no differences were found from 30 control subjects in hippocampal N-acetylaspartate signals, and thus providing no evidence for ECT-induced hippocampal atrophy or cell death.

Gryglewski G et al (2018) carried out Magnetic Resonance Imaging scans in 14 patients with unipolar treatment-resistant depression before and after courses of right unilateral ECT administered with a Thymatron System IV device. Increases in volume of the right hippocampus, right amygdala, and right putamen by were observed, localised in the basal and lateral nuclei, and the corticoamygdaloid transition area of the amygdala, the hippocampal-amygdaloid transition area and the granule cell and molecular layer of the dentate gyrus. Cortical thickness increased in the temporal, parietal and insular cortices of the right hemisphere. These lateralized ECT-induced structural changes occurred in hippocampal subfields and amygdala nuclei that have been specifically implicated in the pathophysiology of depression and that retain a high potential for neuroplasticity in adulthood.

Kranaster L et al (2014) analyzed serum levels of the established brain damage markers protein S-100 and neuron-specific enolase in 19 patients with depression at baseline and throughout courses of ECT administered with a Thymatron System IV ECT device. Protein S-100 and enolase levels remained stable throughout the treatment course, in accordance with previous studies failing to demonstrate elevated brain damage markers in patients receiving ECT.

Bouckaert et al (2016) obtained structural magnetic resonance images in 88 severely depressed elderly patients who received courses of ECT with a Thymatron System IV device. Following ECT there was a significant improvement in depression scale scores, a significant but short-lived increase in hippocampal volume, and no change in serum levels of brain-derived neurotrophic

factor. The authors concluded that ECT-induced hippocampal growth is a transient phenomenon possibly related to ECT-induced normalization of physical activity levels.

Hirano et al (2017) used task-related functional near-infrared spectroscopy to compare 108 healthy controls with 30 patients with major depressive disorder or bipolar depression before and after an ECT series administered with a Thymatron System IV device. Pre-ECT, patients exhibited significantly smaller oxyhemoblobin values in the bilateral frontal cortex during a verbal fluency task than healthy controls, values that increased significantly after ECT. A decrease in depression severity was significantly correlated with an increase in oxyhemoglobin values in the right ventrolateral prefrontal cortex. ECT normalized the impaired functional responses during the cognitive task, demonstrating that the acute therapeutic effects of ECT may restore abnormal functional responses to cognitive tasks in the frontal brain regions of depressives.

Cano et al (2017 studied 12 patients with treatment-resistant depression who received bilateral ECT with a Thymatron System IV device and compared them with 10 healthy controls on high-resolution structural MRI and hippocampal metabolite concentrations before and after a course of treatment. ECT-induced regional gray matter volume increases in the left medial temporal lobe revealed a significant positive association with clinical improvement, which was not true for neuroinflammatory changes as measured by hippocampal metabolites. The authors concluded that structural, but not metabolic, changes in the left medial temporal lobe are useful neuroimaging biomarkers of ECT-induced clinical improvement in treatment-resistant depression.

Cano et al (2018) used MRI to assess whole-brain gray matter volume in 24 subjects with treatment-resistant depression before and after courses of bilateral or right-unilateral ECT given with a Thymatron System IV device. Bilateral ECT induced bilateral gray matter volume increases in the limbic system, compared with gray matter volume increases limited to the right hemisphere after right-unilateral ECT.

Sartorius et al (2016) conducted a prospective study of whole brain gray matter volume in a sample of 18 patients with treatment-resistant manic-depressive illness who received ECT with a Thymatron System IV device. Highly significant gray matter increases were observed in the hippocampus, amygdyla, and temporal regions, adding further support to the hypothesis that ECT enables cerebral plasticity, and falsifying older claims that ECT induces brain damage

Sartorius et al (2018) obtained whole brain magnetic resonance imaging scans in 92 major depressives before and after ECT administered with a Thymatron System IV device. Significant gray matter volume increases were observed in the hippocampus and amygdala that did not correlate with psychopathology, age, gender or number of ECT sessions, thus demonstrating regionally dependent ECT-induced neuroplasticity effects on the brain.

b) Memory and cognitive risks

Ng et al (2000) used a Thymatron DGx to treat 32 major depressives with courses of right-unilateral ECT (mean=9.4). The mean percentage recall of Personal Memory test items recorded

at baseline was 68% after 6 ECTs, 72% at treatment endpoint, and 87% one month later. Wechsler Adult Intelligence Scale scores did not change with ECT.

Obbels J et al (2018) examined 110 unipolar late-life depressives treated with a Thymatron System IV ECT device on a neuropsychological test battery prior to ECT and 6 months after the last ECT. There were no statistically significant changes from baseline to 6 months post-ECT in any of the neuropsychological measurements obtained.

Schat et al (2007) used a Thymatron DGx ECT device to treat 83 DSM-IV medication-free patients with unipolar depression who had been evaluated at baseline on tests of behavioral (everyday) memory and semantic memory (word fluency). One year after a course of bilateral or unilateral ECT neither everyday memory scores nor semantic memory scores were reduced from baseline—in fact, bilateral ECT was associated with significantly improved semantic (but not everyday) memory scores.

Smith GE et al (2010) conducted a randomized controlled trial in unipolar major depressives comparing multiple memory test effects after 12 and 24 weeks of ECT with the Thymatron System IV device and pharmacotherapy with a nortriptyline-lithium combination. 12-week objective anterograde memory scores and 24-week subjective memory scores were significantly improved for both treatment groups compared with baseline, failing to reveal clinically important memory outcome differences between ECT and drug therapy for depression.

van Oostrom et al (2018) studied 19 medication-free treatment-resistant major depressives underwent a whole-brain magnetic resonance imaging scan and a neuropsychological examination one week before and within 1 week after the course of ECT with a Thymatron System IV device. Hippocampal volumes increased significantly with ECT, correlating with a decrease in cognitive functioning, suggesting that the neurotrophic processes thought to be crucial for the antidepressive effect of ECT are also related to the temporary cognitive side effects of ECT.

Verwijk et al (2014) assessed global cognitive function, memory, and executive functions in 42 depressed patients before and one week and 6 months after courses of ECT administered with a Thymatron System IV device. There was no decline for any of the neurocognitive tests after ECT. Medium to large post-ECT improvements in neurocognitive functioning one week post-ECT were statistically significant for the Mini-Mental State Examination, Visual Association Test, 10 Words Verbal Learning Test, and Expanded Mental Control Test.

Ziegelmayer C et al (2017) examined neurocognitive performance in a sample of 20 treatment-resistant ECT-naive subjects. Cognitive functioning was assessed at baseline), 1 week, and 6 months after 12 to15 unilateral ECTs with a Thymatron System IV device. No adverse cognitive effects were observed in any of the cognitive domains examined.

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