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Amnesia Associated with Electroconvulsive Therapy

Progress in Pharmacological Prevention and Treatment

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Summary

Pharmacological treatments have been used in an attempt to improve the memory dysfunction induced by electroconvulsive therapy (ECT). Despite promising results from animal studies, human studies report few successes. Piracetam and physostigmine have been reported to directly improve memory test scores. The use of caffeine and liothyronine (triiodothyronine; T_3) has been reported to reduce the number of ECT treatments required to produce a therapeutic effect, thus indirectly reducing memory deficits. However, the majority of studies on pharmacological treatments report no success.

Some studies suggest that reducing the dosage of medications regularly administered with ECT may reduce memory deficits. However, reducing these medications may not be fruitful as they are necessary to prevent the medical risks associated with ECT. Moreover, at the dosages used during ECT, these medications have not been consistently shown to adversely affect cognition.

At present, better controlled studies are required to assist in the search for effective pharmaceutical agents to reduce the cognitive deficits associated with ECT.

1. Characteristics of Amnesia Associated with Electroconvulsive Therapy (ECT)

Electroconvulsive therapy (ECT) is a very useful and effective treatment for depression and some other psychiatric and medical conditions. However, the adverse cognitive effects of this type of treatment are a cause for concern. Non-memory cognitive effects can occur,[1-3] but the memory effects are the most noteworthy.[3] Since the acute non-memory effects (including disorientation and possibly visuospatial inattention and unilateral neglect) are of very short duration, and the less acute effects are of a lesser magnitude than the memory effects,[2] researchers have focused on the amnestic effects of ECT.[1]

The amnestic effects are characterised as organic amnesia.[1,4-7] They may be induced by the low seizure threshold of brain regions associated with memory such as the hippocampus or the frontotemporal lobe that are commonly used for electrode placement.[1] After ECT, patients rapidly experience an inability to remember new information (anterograde amnesia). They also have difficulty remembering events occurring immediately prior to ECT (retrograde amnesia). Events that occurred earlier in life may be remembered more fully than events that occurred shortly before the treatment,[4,6] while events that occurred during the course of treatment may be permanently lost.[4,6]

These amnestic effects gradually improve, and most researchers agree that at about 6-months post-ECT the negative effects on memory are no longer present. The exception may be persisting memory loss involving the weeks around the time of treatment.[1,3] The amelioration of these effects is a major goal for clinicians who use ECT.

2. Pharmacological Approaches to Preventing and Treating ECT-Induced Amnesia

Several pharmacological agents have been reported to improve memory in humans.[8] These agents were designed to either facilitate neurotransmitter function (e.g. choline, phosphatidyl choline, clonidine) or increase brain metabolism (e.g. piracetam), and have been applied with modest success to memory disorders such as Alzheimer's disease. A number of these agents have been assessed as treatments for patients with the memory dysfunction that occurs post ECT. Tables I and II summarise the available studies. It should be noted that most of the research on the effects of memory-enhancing medications in patients who have received ECT have used rather inadequate trial designs. Sample sizes were usually small and the outcome measures used did not target specific types of memory deficits. The success of some treatments suggest that it is worth studying these effects in better controlled studies.

2.1 Unsuccessful Attempts

Promising results on the effects of corticotrophin [adrenocorticotrophic hormone (ACTH)] and its analogues were reported from animals studies in which animals received electroconvulsive shock (ECS).[20] Subsequently, 3 studies assessed the effect of the corticotrophin analogue $ACTH_{4-10}$ in patients undergoing ECT (see table I).[9,10,14] None of these experimental investigations demonstrated a statistically significant improvement in cognition in patients treated with active drug compared with controls given placebo.

There have been reports of an alteration of cholinergic function in rodents exposed to ECS and in humans after seizures.[25,26] These results provided the impetus for a clinical study in which patients undergoing bilateral ECT received a daily injection of either placebo or cytidine-5-diphosphate choline[11] (a compound involved in the synthesis of phosphatidyl choline, which is involved in the synthesis of lecithin, a precursor of acetylcholine). However, the treatment failed to reduce disorientation or amnesia after ECT. It is not clear whether the assessment measures used in this study were standard and sensitive enough to detect differences between the groups.

Other investigators have used vasopressin (antidiuretic hormone) in patients undergoing ECT, following its application in the treatment of post-

Table I. Studies reporting unsuccessful pharmacotherapy of the cognitive dysfunction associated with electroconvulsive therapy (ECT)

Reference	Year of study	No. patients	Study design	Drug regimen [dose (mg) and route]	Outcome measures
Small et al.[9]	1977	20 (study I), 30 (study II; 15 drug, 15 placebo)	db, co (study I); db (study 2)	$ACTH_{4-10}$ [15-30, SC] single dose 0.5h and 24h after ECT session (study I) or single dose 28.5h after fifth or sixth ECT session (study II)	Paired Associate Words and Pictures (study I); memory for tape recorded sounds and visually presented faces (study II)
D'Elia & Frederiksen[10]	1980	20 ECT (study I), 20 healthy (study II)	db, co	$ACTH_{4-10}$ [30, SC] single dose 90 min after second or third ECT session	Verbal memory of word pairs and figures. Nonverbal memory of geometric figures and faces
Ayuso-Gutierrez & Saiz-Ruiz[11]	1982	22 (11 drug, 11 placebo)	db, pc	Cytidine-5-diphosphate choline [800] before ECT session	Numeric and Associative Memory from a Spanish test (the TEA), which is similar to the Wechsler Memory Scale
Lerer et al.[12]	1983	9	db, co	1-desamino-8-D-arginine vasopressin [25μg, IN] single dose 2-3h after fourth or fifth ECT session	Wechsler Memory Scale
Horne et al.[13]	1984	48 (12 bilateral ECT + drug, 12 bilateral ECT + placebo; 12 right unilateral ECT + drug, 12 right unilateral ECT + placebo)	db, pc	Dexamethasone [1.0ml, IM] 2h before and 2h after each ECT session	Digit Span; Trails B, Paired Associate Learning; Story Recall (immediate and delayed); Complex Figure Test
Frederiksen et al.[14]	1985	38	db, co	$ACTH_{4-10}$ [30, SC] single dose 90 min after second or third ECT session	Immediate and delayed recall of bisyllabic words
Nasrallah et al.[15]	1985	9	db, co	Naloxone [0.1 mg/kg, IV] single dose 1 day after a course of ECT	Digit Span; Digit Symbol; Oral Word Association; Digit Sequence Learning; Visual Retention (geometric figures)
Nasrallah et al.[16]	1986	10	db, co	Naloxone [0.1 mg/kg, IV] single dose 3 to 5 days after a course of ECT	Digit Span; Digit Symbol; Oral Word Association; Digit Sequence Learning; Visual Retention (geometric figures)
Sachs et al.[17]	1989	10 (5 drug, 5 placebo)	db, pc	Ergoloid mesylates [2, PO] 45 min before each ECT session	Immediate and delayed (3-4h) recall of words and geometric shapes
Mattes et al.[18]	1990	33 (16 drug, 17 placebo)	db, pc	Vasopressin [0.01, IN] 4 daily doses before and after each ECT session	Digit Span and Paired Associates (Wechsler Memory Scale); Rey-Osterreith and Taylor Complex Figure; Television Test of Retrograde Memory; Subjective Memory Rating
Cohen & Swartz[19]	1991	8	sb, co	Nimodipine [30-60, PO] 2h before each ECT session	Orientation to place and time; recognition of previously presented words belonging to a specific category
Krueger et al.[20]	1992	>50	db, pc	Piracetam [12.5, 50 or 200 tid[a]) before and after each ECT	Bushke Selective Reminding Learning and Recall, Story Recall, Paired Associates, Subjective Memory, delayed retesting after about 24h

a Route of administration not stated.

Abbreviations: ACTH = adrenocorticotrophic hormone; co = crossover; db = double-blind; IM = intramuscularly; IN = intranasally; IV = intravenously; pc = placebo-controlled; PO = orally; SC = subcutaneously; sb = single-blind; tid = 3 times daily.

traumatic amnesia.[27] However, the results in ECT patients have been disappointing. Lerer et al.[12] used an analogue of arginine-vasopressin in a double-blind placebo-controlled trial and found that it had no effect on memory function in patients given a series of ECT. Memory function was assessed using the Wechsler Memory Scale. In another study,[18] lysine-8-vasopressin was used. A more extensive battery of memory tests, including both anterograde and retrograde amnesic measures, was applied. Neither patients who had undergone unilateral or bilateral ECT benefited from this treatment.

Several other agents have also been assessed, with equally disappointing results. Dexamethasone, a corticosteroid, was of no benefit and even produced slight deficits in attention and short term memory after ECT.[13] Nasrallah et al.[15,16] conducted 2 studies using naloxone, an opioid receptor antagonist, in patients undergoing ECT following reports of memory improvement in animal studies[28] and in studies of patients with Alzheimer's disease.[29] The investigators did not find any improvement in cognitive function compared with placebo. However, the battery of tests in this study, as in some others (see table I), was not specifically designed to be sensitive to the memory deficits caused by ECT.

Cohen and Swartz[19] administered nimodipine, a calcium antagonist, orally to patients 2 to 2.5 hours before ECT. The treatment was not effective in reversing the cognitive deficits associated with ECT.

A more appropriate battery of tests, that included measures of rapid memory loss, was used by Sachs et al.[17] who administered ergoloid mesylates to patients undergoing ECT. This study showed a trend towards an effect with the drugs, although the results were not significant. This study raises the possibility that a failure to detect a reversal of memory deficits following ECT may be due to methodological deficiencies. First, memory assessment in many studies seems not to have been specific to the types of memory deficits seen after ECT. Researchers have only begun to agree in the last 2 to 5 years on the tasks that are sensitive for cognitive research in ECT. Secondly, since the amnesic effect of ECT is relatively mild (compared with that seen in organic conditions such as Alzheimer's disease), it may be difficult to observe slight or partial improvement. Thirdly, the cause of memory deficits in ECT (i.e. seizures and the electrical stimulus) differ from that of other organic conditions. As a result, any improvement in memory may be different to and more mild than that seen in other amnesic conditions.

These points were taken into consideration in a study in which the effects of piracetam in patients undergoing ECT were assessed using an appropriate battery of tests, including both anterograde and retrograde measures (see review by Krueger et al.[20]). Piracetam is a γ-aminobutyric acid (GABA) analogue that is expected to enhance brain metabolism. However, this study also failed to show any significant improvement of memory.

2.2 Successful Attempts

It is encouraging, yet puzzling, that success in reversing memory deficits after ECT has been reported with similar agents to those used in studies that have failed to report an effect (see table II).

Physostigmine, like vasopressin, enhances cholinergic activity, and has been reported to improve memory (acquisition and retrieval) in healthy volunteers.[30] Subsequently, Levin et al.[22] used physostigmine as a treatment for ECT-induced cognitive deficits in a crossover placebo-controlled trial. Significant improvement was reported in 4 tests: (i) orientation (place, date of birth, and physician's name); (ii) visual memory (for previously presented pictures of daily events); (iii) story repetition; and (iv) retrieval (of as many items as possible belonging to a semantic category). These tests have not been previously reported to be particularly sensitive to post-ECT deficits. Although not all cognitive measures used in this study assessed memory, the findings are positive.

Despite the negative findings reported in section 2.1, piracetam has been used with some success. Ezzat et al.[21] assessed the effect of intravenously administered piracetam in a placebo-controlled study. The total score on the Wechsler Memory

Table II. Studies reporting successful pharmacotherapy of the cognitive dysfunction associated with electroconvulsive therapy (ECT). It should be noted that some drugs may reduce memory problems by increasing seizure efficacy and so reducing the number of treatments required

Reference	Year of study	No. patients	Study design	Drug regimen [dose (mg), route]	Outcome measures	Probable reason for efficacy	Significance level
Ezzat et al.[21]	1985	30 (15 drug, 15 placebo)	Between group[a]	Piracetam [5g, IV] before each ECT session	Wechsler Memory Scale	Direct effect on memory	$p < 0.01$
Levin et al.[22]	1987	17	db, co	Physostigmine [0.5, IV] after fifth or sixth ECT as a single dose	Orientation; Digit Repetition; Story Repetition; memory for pictures	Direct effect on memory	Not reported (authors only report that significance level was reached)
Stern et al.[23]	1991	20 (11 drug, 9 placebo)	db	Liothyronine [50μg[b]] before each ECT session	CVLT - total number correct; CVLT Delayed Recognition; Squire's Personal Events Test	Decrease in the number of ECT treatments	Only remote memory test reached statistical significance ($p < 0.05$)
Calev et al.[24]	1993	21 (8 drug, 13 placebo)	Open	Caffeine [500, IV] before each ECT session	Complex figure reproduction; story recall; paired associations recall; famous public events recall; personal memory	Decrease in the number of ECT treatments	Personal memory ($p < 0.02$); Story Recall ($p < 0.07$)

a Blindness not stated.

b Route of administration not stated.

Abbreviations: co = crossover; CVLT = Californian Verbal Learning Test; db = double-blind; IV = intravenously.

Scale improved significantly in piracetam-treated patients.

Two other studies reported pharmacologically induced improvement in the cognitive deficits associated with ECT, but attributed this to the effectiveness of the drug used in reducing the number of ECT treatments required. Since the number of treatments in a series is directly related to the degree of memory impairment,[4,6] this approach seems worthwhile. Stern et al.[23] administered liothyronine (triiodothyronine; T_3) 50μg nightly during the course of ECT. The drug had an antidepressant effect, as assessed by the Hamilton Depression Rating Scale. As a result, patients receiving the drug required fewer ECT treatments. The measures used in this study were of learning, rapid memory loss and remote memory using the California Verbal Learning Test and Squire's Personal Events Test. These are most relevant to the measurement of ECT-induced memory deficit. The mechanism of the antidepressant effect of liothyronine is not clear, but its ability to reduce seizure threshold may be involved.

Pretreatment with caffeine before each ECT treatment has also been found to reduce the number of required treatments in an ECT series.[24] Memory function, as assessed by 4 memory tests relevant to ECT-induced amnesia, was better in patients receiving a shorter series of ECT treatment. Caffeine may reduce the number of treatments required through an increase in seizure duration, or by induction of neurotransmitter changes that mimic the effect of tricyclic antidepressants, as has been observed in rats.[31]

3. Role of Medications Commonly Used During ECT

ECT is now routinely administered together with certain medications. An anaesthetic such as thiopental sodium and a muscle relaxant such as suxamethonium chloride (succinylcholine) are almost always given, in addition to oxygen. Atropine

or glycopyrronium bromide (glycopyrrolate) is often administered.

There is evidence that these drugs contribute to the memory deficits observed after ECT. Miller et al.[32] reported that doses of suxamethonium chloride and methoxital were positively related to the severity of memory problems. These results suggest that reducing the dosages of these medications might contribute to reductions in ECT-related memory impairments. However, reducing the dosages of these medications can result in medical adverse effects such as bone fractures, heart problems and personal discomfort. Further, findings such as those reported by Miller et al.[32] are not always replicated. For example, Calev et al.[33] did not find memory impairment to be associated with the low doses of these medications commonly used during ECT. In addition, Calev et al.[34] and Sommer et al.[35] did not find that the low dose of atropine used in ECT significantly affected memory performance, despite its presumed anticholinergic effect.

This suggests that there is little indication for a reduction in the dosage of these drugs in order to improve memory function after ECT, and, to the best of our knowledge, practitioners do avoid reducing the dosage of these medications. Furthermore, total exposure to these medications is reduced if fewer ECT treatments are needed, a situation which may occur if drugs are coadministered that reduce the number of ECT treatments required (e.g. liothyronine and caffeine). This can also occur if a treatment schedule requiring fewer ECT treatments can be used, e.g. a course of twice weekly ECT may be as effective as that given 3 times weekly and can produce less pronounced memory deficits.[36]

4. Conclusions

This review reveals that studies of approaches to pharmacologically improving memory after ECT have so far produced equivocal results. A possible reason for such contradictory data is the poor methodology used in past research. Nevertheless, it is not clear why certain drugs improve memory in healthy volunteers and patients with Alzheimer's disease, but not in patients with ECT-induced memory deficits. The difference between the mechanisms producing memory deficits associated with ECT compared with those in other conditions, and the milder nature of the deficit, may be factors that affect the chances of pharmacological improvement. It may therefore be wise to look at drugs other than those that are recommended for other conditions. The next step should be to research new agents, and those that have already showed promise with ECT patients, in studies with more rigorous methodology.

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