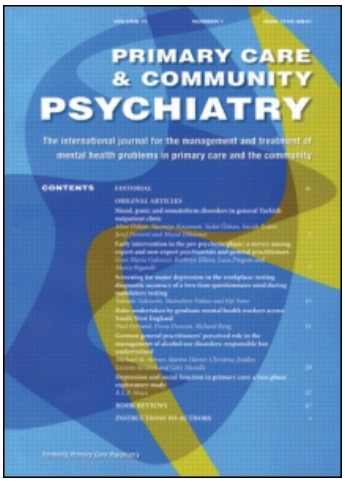

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ORIGINAL ARTICLE

ECT as a 'therapeutic test' to differentiate pharmaco-resistant depression from dementia in the elderly: a pilot study

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Abstract

Objectives: Traditionally, if depression is suspected in elderly patients with cognitive disorders, antidepressant therapy is administered during the first three months of diagnosis, in order to treat a comorbid depression that could ultimately compound cognitive impairments. However, antidepressants are only effective in 50–60% of such cases, and their use in elderly populations should be restricted due to their potential negative side effects. In order to offer an alternative treatment strategy, several cases are described where electroconvulsive therapy (ECT) was used as a 'therapeutic test' for the presence of depression.
Methods: Eight patients with a diagnosis of 'probable dementia; depression remains to be eliminated' were included in the present study. Following a negative 'antidepressant test', an 'ECT test' was performed.
Results: Five patients recovered satisfactorily from depression and cognitive impairments. This improvement persisted for 14 months after the final ECT session.
Conclusions: Results suggest that ECT could be used as a potential therapeutic test in elderly subjects with cognitive impairments when depression is suspected.

***Keywords*: ECT – Pseudo-dementia – Depression – Cognitive impairments**

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Introduction

Depression and dementia are the most frequently occurring pathologies found in elderly individuals. These disorders can exert a highly negative impact on patients' quality of life, autonomy and, most significantly, risk of mortality through suicide, which is significantly elevated in such populations[1]. By treating depression in elderly patients suffering from dementia, their quality of life can be significantly improved[2]. The daily challenge facing practitioners is to differentially diagnose depressed patients (who present with pseudo-dementia) from those with dementia, in order to propose an adapted treatment plan. However, in making such a differential diagnosis, depression is the most frequent cause of error. This is probably due to masked forms of depression, and to the fact that a depressive state can be responsible for behavioural inhibition and attention deficits, suggestive of cognitive deterioration.

The prevalence of depressive disorders in patients suffering from Alzheimer's disease varies between 15% and 50%[3–5] and its incidence in elderly patients without dementia is between 1% and 10%[6–8]. In a recent retrospective study, Klatka et al.[9]

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reported depression associated with Lewy body dementia in 50% of cases. The prevalence of depression in patients over 65 years of age is 15% in the general population[10] and 30% in retirement homes. Within the same patient cohort, dementia occurs in 5% of the general population and in 80% of those in retirement homes. Therefore, there is a high concordance between depression and dementia in elderly individuals and their aetiology is highly complex.

Several phenotypic parallels can be drawn between the two pathologies, with the result that it is often difficult to establish cause and effect in their aetiology and progression. However, in clinical practice priority should be given to treating and eliminating curable states, not identifying causal ones. To this end, many researchers have offered descriptive classification systems based on observations of disorder comorbidity in the elderly. For instance, the concept of 'pseudo-dementia depression' has been used as a key diagnostic variable by Wells[11] and for classification and treatment purposes by Feinberg & Goodman[12], in spite of controversy surrounding its use. However, Burke et al.[13] proposed abandoning the term 'pseudo-dementia depression' in favour of 'potentially reversible cognitive disorder'; while Saez-Fonseca et al.[14] consider the term to be of pragmatic use, regardless of empirical concerns, since it seems to be a strong predictor of dementia.

It is now acknowledged that elderly dementia patients can present with depressive symptoms or outright clinical depression. On the one hand, treating depression or depressive symptoms in such patients can significantly alleviate affective disorders and behavioural problems; on the other hand, it can rule out a potential confound of affective contributions to cognitive decline, facilitating the differential diagnosis of dementia versus depression. Therefore antidepressant treatments used as 'therapeutic tests' help practitioners to make correct diagnoses, even if often-neglected issues surrounding pharmaco-resistance are overlooked.

Indeed 30% of depressions remain resistant to antidepressant treatment regimens[15]. The most frequently used (and first availed of) antidepressants in elderly patients are selective serotonin reuptake inhibitors (SSRI's)[16,17], serotonin norepinephrine reuptake inhibitors (NSRIs), and, more rarely, tricyclic antidepressants[18], or monoamine oxidase inhibitors (MAOIs)[19,20]. However, antidepressant side effects render them difficult to use in elderly subjects, particularly with regard to the tricyclics (e.g. tachycardia, constipation, urinary retention, confusion and delirium). SSRI and NSRI antidepressants are clearly better tolerated than tricyclics. Nevertheless, SSRIs and NSRIs may cause severe hyponatraemia in elderly subjects, probably due to inappropriate anti-diuretic hormone secretion (SIADH), or possible interactions at the level of cytochrome P450 with other medication[21].

Following negative responses to pharmacological reference treatments (due to intolerance to a given treatment or aggravation of the patient's state), ECT should be recommended for two reasons. First, its efficacy in treating depression in the elderly has received very strong empirical support of late[22,23]. Second, ECT permits assertion of whether observed cognitive deterioration in such patients is secondary or concomitant to the depression. In addition, ECT has been found to be a more efficacious treatment overall than antidepressants in elderly subjects[15,24,25]. Therefore, the aim of the present study was to evaluate the usefulness of ECT in eliminating pharmaco-resistant depression in patients with pseudo-dementia.

Materials and methods

Subjects and assessments

The study population included neurological inpatients referred to the University Hospital of Poitiers, France. During the entire study period (January to December 2006), eight patients (five females) were tested (mean age = 73.2 years; 66–80 years). After having received information on the purposes of the study and potential risks of ECT, all patients gave written consent for participation. The protocol was approved by the local ethics committee (CHU de Poitiers).

At the time of recruitment, all patients suffered from probable dementia with a comorbid ICD-10 diagnosis of either moderate or severe depressive episodes. The eight patients had received a neurological diagnosis of 'probable dementia, depression remains to be eliminated'. Clinically, they all suffered from symptoms presenting as depression, including psychomotor agitation, inability to experience pleasure, sleep changes with insomnia and weight loss (4–8 kg over a six-month period). All patients received an 'antidepressant therapeutic test' at appropriate doses for more than three months, including SSRIs, and four patients additionally received tricyclic antidepressants.

Since tricyclics could not be administered in four patients due to adverse reactions (side effects), a diagnosis of pharmaco-resistant depression first needed to be eliminated before dementia could unproblematically be diagnosed. An anti-cholinesterase treatment was therefore prescribed for two patients, consisting of denopezil (10 mg/day) and galantamine (12 mg/day). In six patients, a history of psychiatric problems was found: bipolar disorder II

($n=3$) and unipolar depression ($n=3$). The other two patients showed no evidence of psychiatric history.

The Montgomery and Asberg Depression rating scale (MADRS 28.5±7.3) and the Mini-Mental State Examination (MMSE 26±3) were conducted prior to any ECT session. The MADRS and MMSE were repeated three months after the final ECT session. All patients were followed up for a period of time between 3 and 14 months after the last ECT session.

ECT was used as a diagnostic tool to confirm the diagnosis of depression. The eight patients who had not responded to standard pharmacotherapy and still suffered from depression associated with cognitive disorders underwent ECT sessions. Patients were treated using the Spectrum 5000 Q Stimulus Ultrabrief 200, from Mecta Corporation. The ECT monitoring and the ictal EEG parameters (e.g. regularity, post-ictal suppression) were manually rated by the same trained psychiatrist. Anaesthetic products used were propofol (1 mg/kg) and succinylcholine (0.5 mg/kg). The titration method was availed of in all patients, and the recording of EEG on two stations by the ECT equipment permitted control of the quality of the shock (duration >25 sec, sudden shock), signifying the efficacy of a session. The dose of a given delivered charge was 370 milicoulombs (128–792). All patients received two ECT sessions each a week, with a mean number of 12.7 (11–18). Six patients underwent ECT sessions on bilateral temporal position whereas two patients underwent ECT sessions on unilateral right temporal position.

All patients underwent a standard physical examination that included brain scan, an EEG and a TPHA-VDRL serology; these all returned as negative. Red blood cell folate and plasma vitamin B12 were both measured at baseline. Functional SPECT imagery was not carried out.

Data analyses

The significance of 'general improvement' (post-treatment versus pre-treatment) was tested by paired *t*-tests. Differences between groups on single, continuous variables were evaluated with *t*-tests or analysis of variance (ANOVA). Analyses were performed using SPSS version 10.0. The significance level was set at $P<0.05$ for two-tailed tests.

Results

All patients responded positively to ECT treatment, with an overall recovery from depression (MADRS < 5, $P<0.05$). The affective improvement persisted for 14 months after the final ECT session (Figure 1). The cognitive improvement measured by MMSE was not significant in all patients, being significant in only five (MMSE = 28, $P<0.05$), while three patients still presented retrograde memory lacunae that persisted for 14 months after the end of ECT sessions (MMSE = 24). However, none of the patients showed evidence of cognitive deterioration that was more significant post-ECT versus pre-ECT, at either 3 or 14 months.

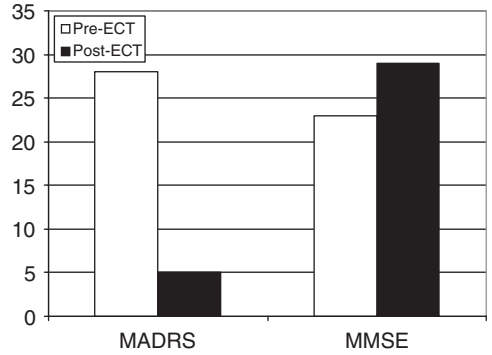

Figure 1. Comparison of mood (MADRS mean score) and cognitive changes (MMSE mean score) in patients ($n=8$) before and after ECT sessions

No significant side effects were observed due to participation in ECT sessions; although two patients did develop psychomotor agitation following a single session, necessitating sedation by midazolam (5 mg). Another patient developed a delirium after the final ECT session, associated with cognitive decline as evaluated by the MMSE.

Discussion

This study investigates the usefulness of ECT for distinguishing between dementia and depression in elderly patients who suffer from resistant depression that mimics dementia. Depression improved significantly for all patients that received ECT treatment ($n=8$). No significant effect on cognitive impairment was reported.

Depression and dementia occur frequently and are often comorbid in elderly patients. However no specific biological marker permits a confident, differential diagnosis of either one of these pathologies. A precise diagnosis of dementia (with Lewy bodies or Alzheimer's disease) can be made only through autopsy; no definitive marker exists to confirm the diagnosis of depression[26]. In elderly patients, depression and dementia share common clinical features, especially concerning cognitive impairments. Thus, in order to aid diagnosis, an antidepressant test is usually performed. Yet antidepressants may be inefficient in treating

presenting problems, or produce unwanted side effects in the elderly. The results of the present study suggest that ECT may be helpful in this regard, when antidepressant test results in such patients return negative.

Alternatively, some studies report the use of complementary examinations to provide evidence of diverse anomalies in subjects suffering from dementia or depression. In dementia the following techniques are often used: functional MRI, monophotonic emission tomography (MPET or SPECT), and positron emission tomography (PET). SPECT has a sensitivity of 89% in diagnosing Alzheimer's disease and a specificity of 80%[27]. In spite of this apparent efficacy, the scintigraphic profile of Alzheimer's disease is neither sensitive nor specific enough for two reasons. First, approximately 25% of patients have abnormalities in predominantly anterior regions; second, this posterior hypometabolism can be observed in other pathologies. SPECT can provide other useful information[28], but cannot provide a differential diagnosis of depression or dementia.

The most investigated of the potential biological causes for depression is cortisol and the Hypothalamic–Pituitary–Adrenocortical (HPA) axis. Mannie et al.[29] reported that the level of salivary cortisol in the waking state (reflecting global HPA functioning) is increased in subjects from a depressive family. Other studies showed that the Dexamethasone Suppression Test[30–34] is perturbed in depressed subjects, and free urinary cortisol[35–38] is abnormally diminished in depressed subjects, while it is increased in subjects with dementia.

In terms of imaging, fMRI is more often used in depression research[39,40] than nuclear magnetic resonance imaging. Recognition of expressed joy is slower in depressed individuals, but antidepressant treatment normalised performance on this test, paralleled by an improvement in depressive symptomatology as evidenced by Hamilton's evaluation scale. Electroencephalography[41] can also bring informative elements to the diagnosis of depression through evaluation of cerebral activity. For instance, when depressed patients conduct a detection error task, EEG recordings show that they recruit more cerebral resources than normal subjects, complemented by the fact that they recognise their faults better than normal subjects. This 'auto-critic' faculty is exacerbated in melancholy which could lead to suicidal tendencies.

However, no definitive biological marker of depression exists, so the diagnosis of dementia or depression is based on a tableau of heterogeneous clinical and biological arguments. Nor is there a specific test for diagnosing depression, outside of clinical interview with the patient and his/her carers. Therefore in the majority of cases when depression associated with dementia is suspected, antidepressant treatment is prescribed, but secondary effects and pharmaco-resistant forms limit their use.

ECT could act as an alternative, precise diagnostic tool to aid in distinguishing between depression and dementia. In our patients, ECT sessions resulted in disappearance of behavioural problems of psychomotor agitation and a global improvement in affective problems. Fourteen months after the final ECT session, the diagnosis of dementia was eliminated in five patients, and remained in three patients. In the latter group, the diagnosis of dementia and Alzheimer's disease was retained for two patients and Lewy body dementia for one patient.

Elsewhere, Bourgeois et al. 42 reported 3 cases of dementia associated with depression that was significantly improved by ECT sessions – to such an extent that the diagnosis of dementia was eventually abandoned. These patients did not develop memory problems, anterograde or retrograde. Rasmussen et al.[43] reported seven cases (five males, two females) of Lewy body dementia associated with depression. Following ECT sessions, no changes in dementia symptoms were observed in these patients, but there was an overall improvement in affective problems. In a five-year retrospective study (1991–1996), Rao et al.[44] reported 31 cases of 'dementia with depression', where a significant improvement of the affective state was found following ECT sessions. In this study, 55% of patients suffered from a vascular dementia, 13% from Alzheimer's disease and 32% from an uncertain aetiology. This significant improvement was measured on the affective plane by the MADRS, and on the cognitive plane by the MMSE, showing an improvement of 1.62 (non-significant improvement).

Patient age and ECT

The age of patients was not a contra-indication for conducting ECT sessions, as confirmed by previous reports. In our study the average age was 73.5 years. It is 75.6 in Rao et al.'s study[44], with the eldest patient aged 97 years. Two other studies reported the age of patients as being 94[39] and 96[40] years. The risk of using ECT in the elderly relates to possible osteoarticular fractures caused by bone decalcification; however, this is no longer a concern since the introduction of anaesthesia and curare products. Nowadays the principal risk to patients is cardiac complication. Cattan et al.[41] reported that this risk increases after the 80th year of life. However, Burd et al.[48] reported that patients aged less than 72 years showed significantly more asystole during ECT sessions relative to patients aged more than 77 years. Cardiac complications are not very

frequent, and we have not witnessed them in our patients tested here. By contrast, they all tolerated ECT sessions well. Other studies confirm this trend[49,50].

Anticholinesterasic

In the case of using ECT with patients treated by anticholinesterasics, medication should temporarily be suspended during ECT sessions, due to the potential adverse effects of prolonging succinylcholine action[51]. Anticholinesterasic medication can then be recommenced at the end of ECT treatment. Here we asked patients to stop taking anticholinesterasics one week before beginning ECT sessions. In contrast, Rasmussen et al.[43] reported the absence of secondary effects in two patients under donepezil. They recommended conserving treatment during ECT if it proves efficacious in treating hallucinations (e.g. in Lewy body dementia), interrupting medication one day before the ECT session only.

Cognitive problems post-ECT

In this study, cognitive difficulties were totally reversed in four patients, slightly improved in two patients, and remained identical in the other two patients following ECT treatment. Memory was evaluated by the MMSE. Liang et al.[52] reported the absence of aggravated cognitive problems after ECT in patients with dementia. Some studies supported the idea that pre-existing cognitive problems before ECT treatment can be aggravated by ECT sessions[47,53]. Other studies[43,44,46] report an improvement in cognitive performance in patients measured by the MMSE post-ECT as compared with pre-ECT. Two randomised studies in elderly people[48,49] reported the absence of significant cognitive problems after treatment by ECT, as measured by MMSE and by Folstein and Weschler's memory scale, independent of ECT method used (titration, moderated dose, elevated dose, unilateral ECT or bilateral ECT).

Generally speaking, the most frequently reported undesirable cognitive effects reported by patients are those of temporary memory problems[57]. These take the form of an anterograde amnesia which progressively disappears, and a retrograde amnesia which can persist several weeks after completion of ECT treatment[58]. Freeman et al.[59] and Frith et al.[60] noted that post-ECT secondary cognitive effects disappear within an average of 72 days after the end of ECT sessions. Mid- and long-term cognitive effects can have a significant impact on memory performance. According to Squire[61], both implicit and procedural semantic memories are ordinarily preserved, whereas autobiographical and episodic memories are affected. Perturbations in remembering events that happened prior to the ECT sessions can be durable in certain patients, and can cover a period lasting from several hours to 2 years sometimes[62–67]. However, Vaughn McCall et al.[68] reported that this mnemonic deficit does not have deleterious consequences on patients' quality of life. Although ECT perturbs the learning of events acquired just after treatment, the literature is unanimous in showing that this deficit is transitory, very often disappearing after several weeks.

ECT and cerebral structures

ECT does not produce cerebral tissue damage. A literature review by Devanand et al.[69] concludes that no empirical evidence supports the notion that ECT causes cerebral lesions. No objective cerebral lesions were observed in patients who showed benefits from ECT treatment, as examined by post mortem autopsy or cerebral imaging. Agelink et al.[70] reported the absence of deleterious effects on cerebral tissue in 14 patients by measuring neuronal specific enolase and protein S-100. Several post-ECT histological studies[71–74] on rat hippocampus show neurogenesis and the appearance of synaptic connections.

Strengths of this study

This is the first pilot study to address the question of the utility of ECT in order to rule out the depressive aetiology miming dementia. All the patients were given by a neurologist the diagnosis of 'dementia; depression remains to be eliminated'. All of them suffered from resistant depression to current antidepressant treatments. Therefore, ECT sessions were used as a therapeutic test which led to a significant improvement of depression with no side effect on cognitive abilities. Moreover, cognitive improvement was observed in four patients. Our study thus demonstrates the ability of ECT to be used as an efficacious and safe 'therapeutic test' for the presence of depression in the elderly, without leading to increased cognitive impairment.

Limitations of this study

However, results from this study must be interpreted with caution. First, the small number of patients in our sample and the 3- to 14-month follow-up limit conclusions that can be drawn. Before these reported results can be generalized, a larger sample size and longer follow-up period should be used. Second, assessment of cognition in the present study was restricted to the MMSE, a tool that provides a reliable global metric of performance but not

an extensive and precise evaluation of patient's individual cognitive status.

Future directions

Before any generalization of the reported results, more research into this area is warranted, particularly studies that use a larger sample size, more reliable assessment tools, and a longer follow-up period. If our results are confirmed by such studies, then the status of ECT as a 'therapeutic test' to facilitate differential diagnoses (dementia versus resistant depression) would be strengthened. We anticipate that ECT will be used in this practical capacity in the near future.

Conclusion

Antidepressants seem to function as potent 'diagnostic' or 'therapeutic' tests for treating depression in dementia patients; their potential in this regard may be far from realised[75]. However, the diagnostic 'weight' which antidepressants are granted is often exaggerated, and we believe it important to bear in mind that 30–40% of elderly patients do not respond to such treatments. Our results suggest that ECT represents a compelling alternative as 'diagnostic test', especially for depressed elderly patients with cognitive problems who respond negatively to pharmacological treatments.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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