

# Cognitive impairment and electroconvulsive therapy in geriatric depression, what could be the role of rivastigmine? A case series

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## Abstract

Electroconvulsive therapy (ECT), albeit highly effective in treating depression, is frequently associated with cognitive impairment, either temporary or more persistent. Especially in older patients, who generally respond even better, serious cognitive impairment during the course of ECT may lead to premature termination of ECT. Treatment of this cognitive impairment is of utmost importance. In this case series report, we present the effect of rivastigmine, an acetylcholinesterase inhibitor, on cognitive impairment in three older, severely depressed patients during or after a course of ECT. An improvement of cognitive functioning, in particular a decline of confusional symptoms, was observed in two patients with structural brain alterations associated with aging. In the other patient, who suffered primarily from amnesia, no effect of rivastigmine was observed. These preliminary results emphasize the need for detailed profiling of cognitive impairment when developing a research design to study the potential benefits of rivastigmine in the prevention or treatment of cognitive impairment in severely depressed patients treated with ECT.

## Introduction

The use of electroconvulsive therapy (ECT) in severe depression has been demonstrated to be a very effective and safe treatment option, especially in older patients.<sup>1,2</sup> However, transient mild to moderate cognitive impairment is

a serious adverse effect that is frequently observed in clinical practice, especially in older patients during and after ECT.<sup>3</sup> ECT-induced cognitive impairment has a broad pallet of different manifestations and usually consists of temporary anterograde (*i.e.*, difficulties in acquiring and retaining new information) and/or retrograde amnesia (*i.e.*, impaired recall of learned information before ECT), or confusional symptoms like disorientation and attention deficits, in some patients during longer periods over days.<sup>4-7</sup> Since these prolonged confusional states might limit the use of ECT, especially for severely depressed older patients, preventing or limiting these cognitive deficits would be of utmost importance.

Pigot *et al.*<sup>8</sup> reviewed the use of pharmacological agents, including acetylcholinesterase inhibitors, in the attenuation of ECT-induced cognitive impairment. As cholinergic processes underlie learning and memory, it seems likely that cholinergic dysfunction may contribute to ECT-induced cognitive impairment. Some studies have shown that there is an increase of acetylcholinesterase during the postictal period after electroconvulsive shock.<sup>9,10</sup> Therefore, treatment with an acetylcholinesterase inhibitor to increase the acetylcholine concentration, might be useful for the prevention or reversion of the cognitive impairment. To our knowledge, only one case study has described the use of rivastigmine during ECT in depressed patients.<sup>11</sup>

In this article first, we describe three patients all with different manifestations of ECT-induced cognitive impairment and the use of the acetylcholinesterase inhibitor rivastigmine, in order to positively influence the course of this ECT-induced cognitive impairment in severely depressed older inpatients with normal premorbid cognitive functioning. Second, we present a hypothesis about the indication of acetylcholinesterase inhibitors to prevent or diminish confusional states during or after ECT in patients with age related alterations of the brain.

## Electroconvulsive therapy protocol

ECT was administered by using a brief-pulse constant-current square-wave device (Thymatron DGx, system IV; Somatics, LLC, Lake Bluff, IL, USA), constant energy 0.9 A, set to deliver a maximum dose of 1008 mC, pulse 0.5 m/s, 10-140 HZ frequency, depending from mC setting. The age dosing protocol was used (*e.g.*, an 80 years old patient is treated with 80% dose corresponding to 403.2 mC). The electrode placement was right unilateral according to D'Elia placement. Bilateral treatment was administered if right unilateral treatment was unsuccessful or when a rapid response was required, *e.g.*, in case of severe catatonia or suicidality. ECT was given twice a week and considered optimal with seizure

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duration of more than 20 s measured by observable tonic-clonic seizure or more than 25 seconds measured by electroencephalogram.

Anesthetic induction was initiated with etomidate, 0.2-0.3 mg/kg. Succinylcholine was administered to provide adequate muscle relaxation, 0.75-1.5 mg/kg.

## Rivastigmine protocol

A dose of rivastigmine 4.6 mg/24 h was given to the patients. Transdermal administration was chosen to reduce possible gastrointestinal side effects. Rivastigmine administration occurred once daily, at 10.00 p.m.

## Case Reports

### Case 1

An 80-year-old female patient, without any known cognitive impairment, developed a severe psychotic depression shortly after a myocardial infarction and was admitted to our hospital. She was first treated with citalopram without any response. With nortriptyline 50 mg once daily she suffered from adverse side effects as deficits in attention and disorientation, and unilateral ECT was started. During treatment the patient experienced severe cognitive impairment, including deficits in executive functioning, disorientation and confusion. The mini-mental state examination-score (MMSE)<sup>12</sup> was 18/30 during ECT-treatment. Brain magnetic resonance imaging (MRI) showed extensive white matter hyperintensi-

ties (WMH), with medial temporal lobe atrophy (II-III), and no global cortical atrophy. In order to reduce confusional symptoms, 1 mg haloperidol daily was started. However, haloperidol-induced Parkinsonism occurred and was therefore discontinued. After 12 right unilateral ECT-sessions, the depressive disorder remitted and the Montgomery and Åsberg depression rating scale (MADRS)<sup>13</sup> dropped from 45/60 to 6/60. ECT was discontinued. In order to prevent relapse, nortriptyline was started again, once more resulting in cognitive impairment, especially confusional symptoms. Hence, it was decided to refrain from antidepressant treatment and to closely monitor the patient after discharge. On discharge from the hospital the MADRS was 3/60, MMSE-score was 27/30 and the patient did not suffer from confusion or cognitive impairment otherwise.

After 3 months, she experienced a relapse of her depression and a new ECT course was initiated at second admission. To prevent cognitive impairment, that had previously occurred, rivastigmine administration was initiated prior to initiation of the second ECT course. MMSE-score was 15/30 at that time. Gradually the depression remitted, with remarkably less cognitive impairment during ECT and no confusional symptoms. Two weeks after initiating both the second ECT course and rivastigmine treatment, the MMSE-score increased to 25/30. After a long course of 22 ECT sessions with right unilateral stimulation complete remission was achieved (MADRS 5/60). On the second discharge from the hospital the MMSE-score was 27/30. Nortriptyline was administered, under continuation of rivastigmine with no cognitive impairment or confusional episodes during three years of follow-up.

### Case 2

A 65-year-old male patient, with a history of a schizoaffective disorder, was admitted to our in-patients clinic for the treatment of an episode of psychotic depression. At admittance the MADRS and MMSE-score could not be assessed due to the severity of the depressive episode. Since there was a high risk of suicide, involuntary bilateral ECT was initiated. Immediately after ECT was started, disorientation and visual hallucinations were observed. A delirium was suspected. Despite thorough internal and neurological examinations, no somatic cause of the delirium could be detected. Brain MRI showed old ischemic lesions, global atrophy and medial bitemporal lobe atrophy (III). Haloperidol 1 mg daily was initiated for a few days, but was discontinued because of QTc-prolongation. The clinical condition improved during ECT course, although the patient remained disoriented. The delirium observation scale score<sup>14</sup> had dropped from 11/13 to 6/13 after two weeks of treatment, indicating improved cognitive functioning.

After 15 ECT-sessions the MADRS had dropped from 25/60 to 10/60 and ECT was discontinued. The MMSE-score was 23/30 and cognitive impairment, including attention deficits, memory problems and apraxia, persisted after several days. Since the cognitive impairment hampered resocialization, rivastigmine was started. Five weeks after discontinuation of the ECT the depression was still in remission, and his cognitive functioning had improved (MMSE 28/30). After discharge, rivastigmine was tapered out without deterioration in cognitive functioning. The MMSE-score remained 28/30 after three years of follow-up.

### Case 3

A 58-year old female patient, with a long history of recurrent depressive episodes, was admitted to the in-patient ward for a major depressive episode with psychotic features and severe motor agitation (MADRS 46/60). Neuropsychological testing at that time showed normal cognitive functioning with MMSE-score 29/30. Brain MRI showed no abnormalities, especially no cortical atrophy, nor medial temporal lobe atrophy, or white matter hyperintensities. Treatment with respectively citalopram, mirtazapine and nortriptyline, and additional quetiapine were ineffective. The patient refused lithium addition, because of side effects in the past.

Since she had been successfully treated with ECT in another hospital nine years before, right unilateral ECT was started. After 10 sessions, the depression was in remission (MADRS 10/60). However, she still suffered from mild sleeping problems and motor agitation. Also she experienced severe cognitive impairment, including retrograde and anterograde amnesia and also long-term memory loss. The MMSE-score remained 30/30. ECT was discontinued on patient's request. Nortriptyline 50 mg once daily was continued, with adequate blood level. However, within 4 weeks after the last ECT, the motor agitation worsened and a relapse of the major depression was seen. The MADRS rose to 38/60. A second ECT-course with initially unilateral electrode placement was rapidly started, followed by bilateral ECT since suicidal thoughts were prominent.

Considering the cognitive impairment, a trial with rivastigmine was started prior to initiation of the second course. However, the amnesia did not respond. The depressive symptoms responded (MADRS 13/60) after twelve sessions and therefore ECT was discontinued. Since none of the cognitive impairment had improved, rivastigmine was also discontinued. Her memory gradually improved several weeks after discontinuation of ECT, but the patient still claimed minor amnesia at three years of follow-up.

## Discussion and Conclusions

We describe three patients with different manifestations of ECT-induced cognitive impairment, and present the use of an acetylcholinesterase inhibitor, rivastigmine, as adjuvant treatment during or immediately after ECT in order to prevent or treat ECT-induced cognitive impairment. Different results were observed, most probably due to different patient-characteristics. The first patient showed good improvement of the cognitive impairment, particularly confusional symptoms, after adjuvant rivastigmine treatment during ECT course. This patient suffered from extensive WMH and medial temporal lobe atrophy. The second patient, suffering from old ischemic lesions, global atrophy and medial bitemporal lobe atrophy on brain MRI, also experienced cognitive impairment and confusional symptoms during the ECT course, but they persisted after discontinuation of ECT. Satisfactory results were observed after addition of rivastigmine. The third patient did not experience confusional symptoms such as disorientation or attention deficits. However she complained of short- and long-term amnesia. She did not benefit from rivastigmine addition concomitant ECT. The brain MRI of the third patient did not show any abnormalities.

Acetylcholinesterase inhibitors were developed for the treatment of Alzheimer's disease, since a decrease of cholinergic neurotransmission seemed to explain the clinical phenomena.<sup>15</sup> The cholinergic system contributes significantly to the fundamental processing of attention and concentration, flexibility and the speed of information gathering.<sup>16</sup> Likewise, impaired cholinergic neurotransmission can induce delirium.<sup>17</sup> Therefore, acetylcholinesterase inhibitors might improve confusional or delirious-like symptoms associated with ECT.

To date, four clinical trials have assessed the anti-amnesic effects of acetylcholinesterase inhibitors in the context of ECT.<sup>19-21</sup> In three trials patients were relatively young and in all four trials no information was present about brain alterations identified by brain computed tomography or MRI.

These trials differ in study design (one cross-over double blind design, and three placebo randomized controlled trials), studied pharmacotherapy (galantamine, rivastigmine, physostigmine and donepezil) and duration of administration. All trials focus on cognitive functioning as primary outcome, but time of cognitive assessments varies widely from directly after ECT till 4 weeks after the last ECT. Also, to assess the primary outcome, a large battery of various cognitive tests was used. Despite these considerable differences, they all detect a favorable effect of the study

medication on cognitive functioning.

In our three patients, the first two patients suffering from confusional symptoms, such as postictal disorientation and confusion, showed brain alterations associated with old age, such as WMH and medial temporal lobe atrophy. Notably, they did not fulfill the criteria for dementia prior to ECT or after three years of follow-up. A recent naturalistic cohort study among 81 elderly depressed inpatients demonstrated, that WMH - not medial temporal lobe atrophy or global cortical atrophy - are associated with cognitive impairment during ECT in severely depressed elderly.<sup>22</sup> Patients with WMH who switched to bilateral ECT showed a mean decline of 7.2 points on the MMSE-score compared to a mean decline of 1.8 point in patients without WMH during the course of ECT. This suggests that especially elderly patients with WMH are at risk to develop cognitive impairment during an ECT course. Since WMH - as well as dementia - are associated with more cognitive impairment during ECT, including prolonged postictal disorientation or confusional and/or delirious states,<sup>23</sup> these patients might benefit best from rivastigmine addition.

The dosage of rivastigmine seemed well tolerated by all three patients. This might be a reflection of the fact that the brain-blood barrier is known to have an increased permeability during ECT, permitting lower dosage.<sup>24</sup> In our patients no side effects were observed. This is particularly important, since in one trial there was evidence that rivastigmine might have increased mortality.<sup>25</sup> However, the study population in this trial included delirious patients, admitted to an intensive care unit for severe somatic illnesses. Hence, these results cannot be generalized to depressed in-patients. Finally, adjuvant rivastigmine administration did not cause additional anesthetic side effects, as prolonged muscle paralysis and apnea, in our patients.<sup>26</sup>

Several limitations should be noted. First, MMSE-scores of our patients were not assessed prior to their current depressive episode. A pre-ECT MMSE-score would have improved our report, since a decline of cognitive functioning can also be attributed to the depression treatment. However, the course of cognitive improvement after start of rivastigmine in the first patient strongly suggests a beneficial effect of rivastigmine. Second, the MMSE does not test potential cognitive impairment in specific cognitive domains. For example, the third patient reported cognitive impairment as retro- and anterograde amnesia and long-term memory loss, but MMSE-score remained 30/30. Also there was a potential learning effect from measurements of the MMSE. Finally, two patients suffered from neurodegenerative brain alternations (*e.g.*, WMH and atrophy). Hence, the predictive value of

specific brain alterations on rivastigmine response needs to be determined.

To conclude, our case report suggests a putative beneficial effect of rivastigmine on - in particular - confusional and/or delirious symptomatology during ECT without considerable side-effects. Unfortunately, rivastigmine did not have an impact on retrograde and anterograde amnesia in our third patient. Randomized controlled trials are needed, including an extensive cognitive test battery for detailed assessment of cognitive deficits during ECT. Further subtyping of cognitive impairment is needed and may facilitate early identification of patients that may benefit of adjuvant rivastigmine treatment during ECT as a tailored treatment.

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