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The anticholinergic burden is not associated with cognitive impairments in patients treated by electroconvulsive therapy for treatment-resistant depression

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1 Introduction

Depression is a frequent and disabling illness with a lifetime prevalence of 24% in France (Lepine et al., 2005). Major depressive disorder (MDD) is associated with cognitive impairments of executive functions, attention, working memory and episodic memory (Trivedi & Greer, 2014). Neurobiological abnormalities underlie these cognitive deficits, such as the lesser hippocampal volume observed in patients suffering from chronic or recurrent depression (Kaymak et al., 2010)(McKinnon et al., 2009). Antidepressant treatments improve cognitive performance (Wagner et al., 2012). However, it is estimated that 40% of patients are non-responders to antidepressant treatment and 20% of patients suffer from chronic depression (Cleare et al., 2015). Because of its numerous mechanisms of action - whether by increasing brain plasticity and neurogenesis (Kubicki et al., 2018), by regulating the stress axis (Li et al., 2020)(Giacobbe et al., 2020), by activating microglia and astrocytes (An & Shi, 2020)(Giacobbe et al., 2020), by its anti-inflammatory effects (An & Shi, 2020)(Giacobbe et al., 2020), by releasing neurotransmitters (GABA, monoamines) (Li et al., 2020) or by synthesizing neurotrophic factors necessary for brain plasticity (Luan et al., 2020) - electroconvulsive therapy (ECT) is the gold-standard non-pharmacological treatment for treatment-resistant depression (TRD). ECT can also improve cognitive impairments related to depression (Vann Jones & McCollum, 2019)(R. J. Porter et al., 2020)(Hebbrecht et al., 2020). In this sense, some studies highlight a correlation between the perception of improved cognition by patients and the improvement of depression clinical scales (Ferne et al., 2014).

25 Currently, ECT is considered as the most effective non-pharmacological treatment
26 for TRD (absence of remission despite two antidepressant treatments at an effective dose
27 for at least 6 weeks) (UK ECT Review Group, 2003) particularly in cases of depression
28 with psychotic symptoms or with a high risk of suicide (Milev et al., 2016). The
29 effectiveness of ECT is also confirmed among older people (Geduldig & Kellner, 2016),
30 notably in cases of intolerance to psychotropic treatments or in emergency situations
31 (Kerner & Prudic, 2014). Moreover, ECT is a safe treatment with a mortality rate
32 estimated at 2.1/100,000 according to a meta-analysis based on 766,180 ECT carried out
33 in 32 countries (Tørring et al., 2017). Although ECT is a safe and effective treatment
34 allowing a reduction of depression-related cognitive impairment, ECT can also be the
35 source of short- and medium-term cognitive disturbances (Basso et al., 2020). These
36 complaints are frequent since a study carried out on 1212 patients revealed a 26% rate
37 of subjective memory disorder after ECT, affecting mainly women and young subjects
38 (Brus et al., 2017). In the elderly, white matter lesions are probably associated with
39 poorer cognitive tolerance of ECT (Oudega et al., 2014). These cognitive complaints are
40 not trivial since they can reduce the patient's compliance to ECT (Vann Jones & McCollum,
41 2019). Subjective memory impairments are predictive of satisfaction with ECT. If a first
42 ECT course was associated with subjective memory disorder, a refusal or strong
43 reluctance is to be expected when a second course is suggested (Sienaert et al., 2010).
44 However, cognitive disorders might be over-attributed to ECT rather than to pre-existing
45 or residual depression, primarily because of the negative image ECT still has (Sigström et
46 al., 2020). In any case, studies have confirmed that ECT can induce acute cognitive
47 impairments, such as confusion and disorientation, and short-term cognitive
48 impairments, such as anterograde or retrograde memory impairments (Semkovska &
49 McLoughlin, 2013). Although short-term memory problems are generally resolved within

50 3 months after the end of the ECT courses (Hebbrecht et al., 2020)(Nuninga et al., 2018),
51 alterations in long-term autobiographical memory may persist in the longer term (6
52 months and beyond) (Sackeim, 2014).

53

54 At the technical level, numerous studies have been conducted to identify ECT
55 parameters associated with a better cognitive tolerance such as: number of sessions
56 (increased risk beyond 12 sessions during ECT course) (R. J. Porter et al., 2020),
57 frequency of sessions (maximum 2 to 3 sessions per week), duration of seizures, method
58 of determining the epileptogenic threshold (the titration methods is better tolerated than
59 the age-dose method), delivery of current (pulsed square-brief is better tolerated than
60 sinusoidal current), use of ultra-brief pulse width (0.3 to 0.5 msec) and electrode
61 positioning (better cognitive tolerance with right unilateral (RUL) electrode placement
62 than with bitemporal (BT) placement)(Mankad et al., 2010). Despite their widespread
63 use in medicine, still very little is known about anticholinergic treatments' effects on ECT
64 cognitive tolerance.

65

66 Anticholinergic treatments are among the most frequently prescribed treatments
67 in medicine, particularly in psychiatry (Nishtala et al., 2016). Anticholinergic treatments
68 - including antidepressant, antipsychotic or anxiolytic treatments - bind to muscarinic
69 receptors and block acetylcholine neurotransmission causing dysfunctions in the central
70 and peripheral nervous system (López-Álvarez et al., 2019). In view of their antagonism
71 on muscarinic M1 receptors, which are preferentially located in the prefrontal cortex and
72 the hippocampus (Sathienluckana et al., 2018), anticholinergic treatments can cause
73 attention, memory and executive functions disturbances (Campbell et al., 2009). Their
74 cognitive impacts depend on several factors such as advanced age, poly-medication, low

75 basic cognitive level and individual vulnerabilities such as pharmacokinetic and
76 pharmaco-dynamic variations (López-Álvarez et al., 2019). For example, older people are
77 more sensitive to anticholinergic treatments due to a depletion of anticholinergic neurons
78 or their receptors, reduced liver and kidney metabolism, and an increased permeability
79 of the blood-brain barrier (Pierce et al., 2019). Considering that ECT can transiently
80 increase the permeability of the blood-brain barrier as well as cerebral blood flow (Singh
81 & Kar, 2017), questioning the cognitive impact of anticholinergic treatments during ECT
82 courses is legitimate. Currently, there is little data available on treatment's anticholinergic
83 effect on ECT cognitive tolerance. Two studies have shown that the use of Atropine or
84 Glycopyrrate, two strongly anticholinergic molecules, was not associated with greater
85 memory disorders after ECT courses (Kelway et al., 1986), even in older people (Sommer
86 et al., 1989). However, these studies focused on small samples of patients (20 patients)
87 and neglected other anticholinergic treatments received during ECT.

88

89 Based on the hypothesis that anticholinergic treatments administered during ECT
90 courses are associated with poorer cognitive tolerance, this research aims to investigate
91 this association in a group of patients suffering from a unipolar or bipolar TRD treated by
92 ECT between 2017 and 2020. Our main goal was to assess the existence of a link between
93 variations of anticholinergic burden on one hand, and the sum of anticholinergic scores
94 on the other, with cognitive changes after ECT, regardless of changes in depression scores.
95 As secondary goal, we looked for an association between cognitive scores and changes in
96 depression scores.

97

98 **2 Methods**

99

100 *2.1. Patients*

101

102 We included 42 patients suffering from a treatment-resistant major depressive
103 episode (MDE) according to the criteria of the *Diagnostic and Statistical Manual of Mental*
104 *Disorders, 5th Edition* (DSM-5) (American Psychiatric Association, 2013) and treated by
105 ECT between 2017 and 2020 in a French reference center (Centre Hospitalier Le Vinatier,
106 Bron, France).

107

108 Inclusion criteria were: age ≥ 18 years; diagnosis of unipolar or bipolar TRD with a
109 total score on the Montgomery and Asberg Rating Scale (MADRS) ≥ 20 before ECT
110 (Montgomery & Asberg, 1979); indication to ECT (Milev et al., 2016) (in our study, we
111 included in-patients suffering from moderate to severe TRD, with or without psychotic
112 symptoms, or suffering from depression with a high risk of suicide, excluding catatonic
113 syndromes that were unable to complete clinical scales) ; patients hospitalized during
114 ECT to have access to a complete computerized traceability of their treatments; patients
115 able to fill in clinical scales.

116

117 Non-inclusion criteria were : patients who had invoked their right to oppose access
118 to their medical data; diagnosis of schizophrenia, schizoaffective disorder or manic state;
119 depressive or catatonic syndrome with an organic origin; lack of computerized
120 traceability of the treatments provided during ECT courses (patients hospitalized in other
121 establishments or patients with ECT courses carried out before the project to computerize
122 the patient file); patients with post-ECT clinical evaluation carried out more than 72 hours

123 after the last session of ECT course; patients unable to fill in clinical scales; patients unable
124 to give their consent for access to their medical data; ECT sessions in the last 6 months
125 before the start of the ECT course.

126

127 *2.2. Procedure*

128

129 We carried out a retrospective, single-center and analytical research based on the
130 analysis of computerized medical records of patients treated by ECT between 2017 and
131 2020. Based on a review of patient records, we included all patients who met our inclusion
132 and non-inclusion criteria. Access to medical record data allowed us to collect clinical
133 scales scores (MADRS and MoCA) routinely performed before and after ECT courses. In
134 the same way, we were able to access patients' socio-demographic and clinical data, as
135 well as treatments provided during ECT courses. Indeed, each daily treatment dispensed
136 in hospital is validated on computer by nurses. In this way, we had access to a precise
137 traceability of treatments received during ECT courses including the names of the
138 molecules and the daily dosages.

139

140 ECT sessions were administered twice weekly, using a MECTA spECTrum 5000Q
141 device (MECTA Corp, Tualatin, Oregon), coupled with electroencephalography (EEG)
142 monitoring. In France, the maximum charge that can be delivered during ECT stimulation
143 is 1152 millicoulomb (mC). Seizure threshold (ST) was individually determined during
144 the first ECT session, according to titration schedule. ECT was administered at 2 times the
145 ST for BT stimulation and at 6 times the ST for RUL stimulation. The pulse duration was
146 brief (1 ms) during BT stimulation and ultra-brief (0.3 ms) during RUL stimulation.
147 During ECT courses, the charge was doubled if there was no seizure, or increased by 50%

148 if the seizure was aborted (< 20 seconds). Anesthesia procedures were either Propofol
149 or Etomidate, combined with succinylcholine curarisation. The placement of electrodes in
150 the right unilateral (RUL) or bitemporal (BT) position was at the discretion of the
151 psychiatrists who performed ECT sessions.

152

153 *2.3. Clinical scales and evaluation*

154

155 Sociodemographic data collected were age and gender. Clinical data collected
156 included: unipolar or bipolar MDE, presence of a neurodegenerative disorder with brain
157 imaging data - including presence of age non-specific or pathological white matter lesions
158 (WML), as well as presence of cortical or hippocampal atrophy - ECT history, clinical scale
159 scores (MADRS and MoCA) before and after ECT courses.

160

161 ECT parameters collected were: number of ECT sessions; average charge in
162 millicoulomb (mC) excluding titration sessions without comital crisis; electrical duration
163 (EEG) of seizure (in seconds); placement of electrodes in RUL or BT. If the electrode
164 placement was changed from BT to RUL during the treatment, the main placement
165 determined the group to which the patient was assigned.

166

167 MDE was assessed by MADRS (Montgomery & Asberg, 1979). In our study, MADRS
168 was carried out before the ECT sessions and within 24-72 hours after the last session of
169 the ECT treatment. Δ MADRS corresponded to the difference between MADRS score after
170 and before ECT course. Response was defined as a MADRS reduction of $\geq 50\%$ after ECT
171 (Leucht et al., 2017). Remission was defined by a MADRS score < 10 after ECT (Hawley
172 et al., 2002)(Thase et al., 2016).

173

174 The Montreal Cognitive Assessment (MoCA, version 7.1) (Nasreddine et al., 2005) is
175 a scale assessing seven cognitive domains: visuospatial and executive abilities (5 points);
176 naming (3 points); delayed recall (5 points); attention (6 points); language (3 points);
177 abstraction (2 points); orientation (6 points). Total score (range 0 to 30) reflects the
178 global cognitive performance. A score of ≥ 26 or higher is considered normal. In our study,
179 the MoCA was carried out before ECT and within 24-72 hours after the last ECT course
180 session.

181

182 The Anticholinergic Impregnation Scale (AIS) (Briet et al., 2017) was used to calculate
183 the anticholinergic burden of treatments received during ECT courses. AIS is a
184 classification of the anticholinergic effects of 128 drugs and is based on an analysis of
185 7278 prescriptions collected from 34 French psychiatric institutions. AIS has the
186 advantage of being adapted to our study population and considers treatments frequently
187 prescribed in France, such as Cyamemazine or Tropatepine, which are absent in other
188 existing Anglo-Saxon classifications. In AIS, treatments are classified into three categories:
189 1 point for treatments with limited anticholinergic effects demonstrated in vivo or
190 moderate anticholinergic effects; 2 points for treatments with significant anticholinergic
191 effects at high doses; 3 points for treatments with major anticholinergic effects. However,
192 some treatments commonly prescribed in psychiatry are missing in AIS. In order to limit
193 treatments without anticholinergic score, we used the Anticholinergic Cognitive Burden
194 Scale (ACB) (Boustani et al., 2008) updated in 2012 (Campanelli, 2012) to complete
195 treatments not referenced in the AIS. Following treatments were scored using the ACB: 1
196 point for Venlafaxine and Aripiprazole. In our study, we analyzed the cumulative AIS
197 (AIScum), which corresponds to the sum of the anticholinergic scores of each molecule

198 received during ECT course, and the Δ AIS, which corresponds to the difference between
199 AIS score at the beginning and at the end of ECT course. All treatments administered
200 during ECT courses were listed apart from: Atropine, which was included in the study's
201 explanatory variables, local treatments; treatments that were given only once during ECT
202 course; treatments with no known anticholinergic effect according the AIS and the ACB.

203

204 *2.4. Ethics*

205

206 All patients signed an informed consent to received ECT, and were informed orally
207 and in writing about the use of the data for research. Data were collected in strict
208 confidentiality with respect for medical secrecy. The database was approved and
209 registered (record number MR-003-2017-002) by the French national commission for
210 information technology, data processing and civil liberties. In accordance with law n°78-
211 17 of 6 January 1978 amended in 2004 relating to information technology, files and
212 freedoms, patients could exercise their right to refuse or withdraw their consent at any
213 time, without justification and without any consequence on their medical follow-up. In the
214 absence of opposition from the patient, it was considered that the patient was not
215 opposed to the use of this data for research.

216

217 *2.5. Statistical analysis*

218

219 Our study was based on a retrospective files review including all patients meeting
220 our inclusion and non-inclusion criteria with available data. Therefore, we did not
221 calculate the number of subjects required. Qualitative variables were expressed in

222 number and percentages, continuous variables in means and standard deviations.
223 Regarding treatments administered, results are expressed in minimum, maximum and
224 mean daily doses. Scales changes before and after ECT were analyzed using the Student t-
225 test for paired data. In a first step, to analyze the association between anticholinergic
226 burden and MoCA performances, we performed a univariate analysis, including socio-
227 demographic and clinical variables already identified in the literature as potential
228 variables that can influence ECT cognitive tolerance. In a second time, we performed a
229 logistic regression by adjusting our results on Δ MADRS which is our main confounding
230 factor considering that depression improvement is a powerful factor of cognitive
231 functions improvement during ECT. Results are expressed as an odd ratio with 95%
232 confidence intervals and p-values. Associations between Δ MADRS and MoCA scores
233 changes were analyzed by linear regression. The significance threshold was set at 5%. The
234 statistical analyses were carried out using R software version 4.0.1.

235

236 **3. Results**

237

238 Out of 136 patient records analyzed, 42 patients were included in our study. Socio-
239 demographic and clinical characteristics of our sample are summarized in Table 1. Our
240 results showed a significant reduction in MADRS after ECT courses ($t = 15.803$, $df = 41$,
241 $p < 0.0001$). The response rate was estimated at 85.71% and the remission rate at
242 45.24%. There was no significant reduction in the total MoCA score after ECT treatment
243 ($t = -1.323$, $df = 41$, $p = 0.193$). Changes in total MADRS and MoCA scores before and after
244 ECT courses are summarized in Figure 1. MoCA sub-scores analysis showed a significant
245 increase in visuospatial and executive functions ($t = -2.033$, $df = 41$, $p = 0.049$),
246 attentional functions ($t = -2.238$, $df = 41$, $p = 0.031$), but a significant reduction in delayed

247 recall ($t = 2.088$, $df = 41$, $p = 0.043$). Variations in MOCA sub-scores are summarized in
248 Table 2 with a graphical representation in Figure 2.

249

250 Sixteen patients (38.10%) had a reduction in the total MoCA score. Delayed recall
251 sub-score was the most frequently reduced in 18 patients (42.86%), more frequent than
252 reduction in visuospatial / executive ($n=12$, 28.57%), attention ($n=7$, 16.67%), language
253 ($n=8$, 19.05%), abstraction ($n=9$, 21.43%) and orientation ($n=9$, 21.42%) scores. No
254 reduction in naming scores was shown ($n=0$).

255

256 Anticholinergic mean scores remained stable before and after ECT courses without
257 significant reduction ($t = 0.848$, $df = 41$, $p = 0.401$). Moreover, 64.29% of patients before
258 ECT courses, and 66.67% after ECT courses, had a total anticholinergic score > 3 . In our
259 sample, the mean cumulative anticholinergic score (AIScum) during ECT courses was
260 5.33 ± 2.89 (mean \pm standard deviation). After ECT courses, 12 patients (28.57%) had a
261 reduction in their anticholinergic scores (-6.75 ± 2.20), 22 patients (52.38%) had stable
262 anticholinergic scores compared to the beginning of ECT, and 8 patients (19.05%) had an
263 increase in their anticholinergic scores ($+2.25 \pm 2.00$) (see Supplementary Material 1). A
264 total of 21 patients (50%) received at least one treatment with an important
265 anticholinergic score (AIS = 3) during ECT courses. Treatment's details administered to
266 patients during ECT courses are summarized in Table 3. The three most frequently given
267 treatments were Lorazepam (47.62%), Venlafaxine (35.71%) and Cyamemazine
268 (26.19%). It is important to specify that the 31 molecules listed with an anticholinergic
269 value in our study represented only 38% of the 82 treatments received by the patients.

270

271 Concerning the main objective of our study, univariate analyses did not show an
272 association between socio-demographic and clinical variables (age, over 65, gender, type
273 of unipolar or bipolar depression, severity of depression, baseline cognitive level, initial
274 anticholinergic scores, dementia, WML, cortical atrophy, hippocampal atrophy, history of
275 ECT, electrode placement, change in electrode placement BT > RUL, number of ECT
276 sessions, mean charge, seizure duration, atropine use) with cognitive score changes.
277 Results of the logistic regression between cumulative AIS on the one hand, and Δ AIS on
278 the other hand, with MoCA scores reduction adjusted on Δ MADRS are respectively
279 summarized in tables 4 and 5 and did not show any significant association ($p > 0.1$).

280

281 Concerning the impact of ECT on cognitive performance through the improvement
282 of depression scores, we performed a linear regression analysis to look for an association
283 between MoCA and MADRS scores changes before and after ECT courses. Results found a
284 significant inverse association between Δ MADRS and variation in the attention sub-score
285 (Coefficient: -2.617, Standard Error: 1.288, t: -2.032, $p = 0.049$). Our analyses did not
286 show any other association, either with the evolution of visuo-executive (Coefficient:
287 0.006, Standard Error: 0.025, t: 0.253, $p = 0.802$), naming (Coefficient: -2.636, Standard
288 Error: 3.754, t: -0.702, $p = 0.487$), language (Coefficient: 3.204, Standard Error: 1.740, t:
289 1.842, $p = 0.073$), abstraction (Coefficient: 3.529, Standard Error: 2.122, t: 1.663, $p =$
290 0.104), delayed recall (Coefficient: 0.494, Standard Error: 0.875, t: 0.564, $p = 0.576$) or
291 orientation (Coefficient: 1.088, Standard Error: 1.458, t: 0.746, $p = 0.460$) scores.

292

293 **3 Discussion**

294

295 To our knowledge, this is the first study evaluating the potential impact of
296 anticholinergic treatments on the cognitive tolerance of ECT courses under naturalistic
297 conditions. All patients included in our study had brain imaging prior to ECT in order to
298 exclude any organic cause of cognitive impairment other than incipient or installed
299 degenerative processes. We used the Anticholinergic Impregnation Scale (AIS) (Briet et
300 al., 2017) to calculate the anticholinergic burden of treatments received during ECT
301 courses. Contrary to other known anticholinergic scales, the scale we used was an
302 anticholinergic burden scale which we deemed adapted to our study population, and
303 which took into account commonly prescribed treatments in France. Our study is part of
304 a research effort to optimize cognitive tolerance of ECT. A lot of research is currently being
305 carried out on the optimization of electrode placement, for example with LART
306 placements (Left Anterior Right Temporal) (Steward et al., 2020), new techniques such
307 as FEAST (Focal Electrically-Administered Seizure Therapy) (Sahlem et al., 2020) or MST
308 (Magnetic Seizure Therapy) (Zhang et al., 2020). Concerning medications, studies also
309 focus on the impact of specific treatments on the cognitive tolerance of ECT, but not
310 necessarily the impact of their specific anticholinergic profile. It was recently brought to
311 light that Lithium concomitant use increases the risk of confusion by 11.7 and increase by
312 5 the risk of cognitive impairments (Patel et al., 2020), requiring a suspension or a
313 decrease of the posology during ECT courses. Regarding the most frequently prescribed
314 treatments in our sample, one area of interest for European psychiatrists could be the
315 prescription of Cyamemazine (AIS score = 3) during ECT courses. Indeed, its strong
316 anticholinergic effect may raise questions about its cognitive impact during ECT, with
317 cognitive risks that could be similar to those of tricyclics (Janjua et al., 2020). The
318 importance of sedative or anxiolytic treatments prescribed in our study - such as
319 Cyamemazine (26%) or Lorazepam (48%) - also underlines the importance of anxiety

320 management during ECT courses to improve patient's comfort and ECT compliance,
321 especially in women or patients with psychotic depression (Obbels, Vansteelandt,
322 Verwijk, et al., 2020). Empirically, and accurately, Lorazepam had been prescribed to
323 manage patient anxiety. Catatonic patients not responding to Lorazepam who warranted
324 ECT were not included in our work because they were unable to complete the clinical
325 scales.

326

327 Unlike psychiatry, geriatrics has long been studying issues of anticholinergic
328 treatments in view of their impact on morbidity and mortality in the elderly. In this
329 specific population, anticholinergic treatments are indeed associated with increased risks
330 of falls, confusion, loss of autonomy, cognitive disorders, institutional mortality, increased
331 risk of hospitalization with longer hospitalization periods and increased risks of
332 emergence or acceleration of dementia processes (López-Álvarez et al., 2019). In view of
333 these elements, it is recommended to regularly evaluate the anticholinergic treatments
334 with a reduction as much as possible (Pierce et al., 2019). Despite these
335 recommendations, 20% of patients in specialized geriatric units receive highly
336 anticholinergic treatments because of the need for therapeutic effectiveness
337 (Pfistermeister et al., 2017), which requires the clinician to regularly and rigorously
338 assess the benefit/risk balance. Considering that highly anticholinergic treatments are
339 associated with a risk of cognitive decline and mortality in the elderly (Fox et al., 2011),
340 it would seem necessary to apply the same rules of caution in patients suffering from
341 mental disorders, especially if they are elderly and/or with a low basic cognitive level and
342 need to be treated with ECT. Interestingly, 50% of the patients included in our study,
343 including 45% of elderly people, were taking at least one strongly anticholinergic
344 treatment (AIS score = 3).

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However, contrary to our initial hypothesis, our results did not show any association between increased anticholinergic burden and decreased performance in MoCA, the latter being effective in detecting cognitive impairment in patients treated with ECT (Moirand et al., 2018). The lack of association between anticholinergic scores and cognitive performance in our study is probably largely due to the measurement of anticholinergic burden by anticholinergic scales which have some limitations. Indeed, the gold standard for measuring anticholinergic effects of treatments is by the anticholinergic activity of the serum (in vivo *Serum Anticholinergic Activity, SAA*) (L. Tune, 1980). However, this technique is not routinely performed, which explains why clinicians would rather use anticholinergic scales, them being both quicker and easier to use. Although anticholinergic scales are simple to use, their limitations could explain the negative results of our study. Indeed, these scales do not take into account the following elements (Sathienluckana et al., 2018)(Bishara et al., 2017)(Fox et al., 2011)(Ruxton et al., 2015)(Zarowitz, 2006) : (i) pharmacological interactions, in particular the combination of several anticholinergic treatments is considered simply cumulatively without taking into account potential specific anticholinergic interactions; (ii) duration of prescription; (iii) co-morbidities, for example diabetes increases the permeability of the blood-brain barrier for some treatments; (iv) the homogeneity of anticholinergic values, without dose weighting, whereas our study shows significant variations in the daily doses of the treatments administered; (v) the failure to take into account renal and hepatic functions; (vi) the failure to take into account the affinity of molecules for anticholinergic receptors; (vii) the presence of unrecorded treatments, which may lead to an underestimation of anticholinergic scores. This last point is clearly established in our study, where despite the complement of ACB to the missing values of AIS, 62% (n=51) of treatments remained

370 without anticholinergic value. The treatments not listed included molecules commonly
371 prescribed in MDD such as Mianserine, Lamotrigine, Escitalopram or Vortioxetine but
372 also other treatments such as Pregabalin, Zopiclone or Lormetazepam. By way of
373 comparison, it is estimated that there are more than 600 molecules that have
374 anticholinergic activities in vitro (L. E. Tune & Egeli, 1999), a figure well above the number
375 of molecules listed in existing anticholinergic scales. In our study, we therefore combined
376 the ACB scores with the AIS to calculate the anticholinergic scores. This association
377 between anticholinergic scales has already been carried out in other studies to limit
378 missing values (Kable et al., 2019) and seems all the more justified as AIS draws heavily
379 on ACB to define its anticholinergic scores (Briet et al., 2017). In order to enable clinicians
380 to simply and effectively evaluate a patient's anticholinergic score, it seems necessary to
381 benefit from scales with the most exhaustive treatment lists possible. In addition,
382 anticholinergic scales should clearly indicate whether or not the molecules have a known
383 anticholinergic effect. At this time, it is unclear whether a missing treatment on an
384 anticholinergic scale corresponds to an unrecorded treatment or to a treatment without
385 anticholinergic activity. We therefore feel it would be appropriate to insert a score of "0"
386 in the AIS, which would make it possible in practice to clearly define the treatments
387 evaluated without anticholinergic activity. In addition to the limitations attributable to
388 the anticholinergic scales, our negative results can also be explained by the limited size of
389 our sample, with a retrospective study on file limited to available data.

390

391 Finally, we can discuss the kinetics of cognitive performance evaluation in our
392 study. Indeed, the MoCA was carried out between 24 and 72 hours after the last session
393 of the ECT course. Our study therefore focused on the short-term cognitive effects of ECT,
394 distanced from acute effects such as confusion (R. Porter et al., 2008). In line with this, the

395 confusion scores in our work did not show a significant reduction. However, measuring
396 the quality of awakening through the reorientation time could be a more sensitive marker
397 of cognitive tolerance in the immediate post-ECT period, but also in the medium term, as
398 this reorientation time could be predictive of subsequent impairment of autobiographical
399 retrograde memory (Martin et al., 2018). While our study is based on objective cognitive
400 assessments, studying the impact of treatments on subjective memory complaints also
401 remains an interesting field of exploration. Beyond MoCA, new scales such as ECCA
402 (ElectroConvulsive Cognitive Assessment) are emerging to integrate these dimensions in
403 ECT evaluations (Hermida et al., 2020). Our results are consistent with the literature
404 showing memory impacts after ECT, with a significant reduction in recall scores, but
405 conversely a significant improvement in executive and attention scores, the latter being
406 inversely correlated with the MADRS evolution (Vann Jones & McCollum, 2019). In
407 addition, ECT could potentially limit the onset and speed of progression of major
408 neurocognitive disorders which are two to three times more common in mood disorders
409 than in the general population (Glass et al., 2017)(Obbels, Vansteelandt, Bouckaert, et al.,
410 2020). In the light of these elements, ECT should be considered as a pro-cognitive
411 treatment in medium and long-term depression, especially in the elderly subject
412 benefiting from maintenance ECT (Hermida et al., 2018).

413

414 **4 Conclusion**

415

416 Anticholinergic scores were not associated with more pejorative cognitive
417 development. However, further investigation is needed to affirm or refute this first study's
418 results. In any case, the potential impact of anticholinergic burden on ECT cognitive

419 tolerance needs to be better monitored and adapted by psychiatrists for patients with a
420 fragile somatic and cognitive profiles. For future research, progress must be made to
421 optimize the measurement of the anticholinergic burden (exhaustiveness, dosages,
422 plasma or cerebral correlates etc.) but also to systematically measure complementary
423 cognitive dimensions of ECT such as the time of reorientation on waking, autobiographical
424 memory and subjective memory.

425

426 **Conflicts of interest**

427 The authors declare that they have no conflict of interest.

428

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431

432 **Abbreviations:**

433 ACB: Anticholinergic Burden Scale, AIS: Anticholinergic Impregnation Scale, BT:
434 Bitemporal, DSM: Diagnostic and Statistical Manual of Mental Disorders, ECCA:
435 Electroconvulsive Cognitive Assessment, ECT: Electroconvulsive Therapy, EEG:
436 Electroencephalography, ET: Epileptogenic Threshold, FEAST: Focal Electrically-
437 Administered Seizure Therapy, LART: Left Anterior Right Temporal, MADRS:
438 Montgomery and Asberg Depression Rating Scale, mC: millicoulomb, MDD: Major
439 Depressive Disorder, MDE: Major Depressive Episode, MoCA: Montreal and Cognitive
440 Assessment, MST: Magnetic Seizure Therapy, RUL: Right Unilateral, SAA: Serum
441 Anticholinergic Activity, ST: Seizure Threshold, TRD: Treatment-Resistant Depression,
442 WML: White Matter Lesion.

443

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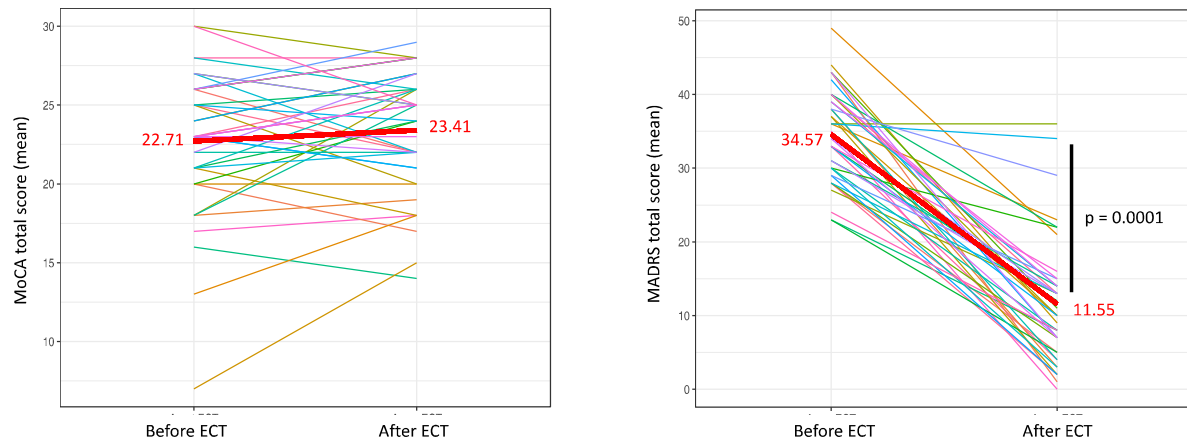


Figure 1: Changes in mean total MoCA (on the left) and MADRS (on the right) scores before and after ECT courses for each patient and for the entire sample (thick red line) (n=42). P-values was calculated using Student's t-test for paired data.

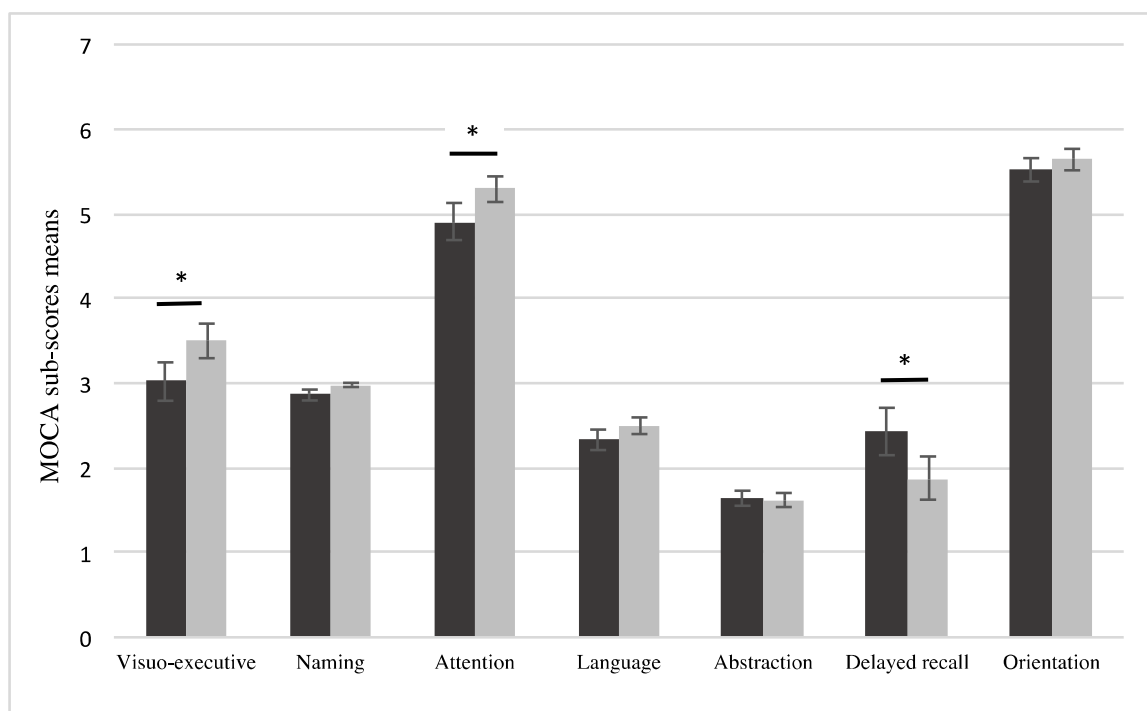


Figure 2: MoCA sub-scores before (in black) and after (in grey) courses of ECT (n=42). Data are mean \pm 1 standard error. (*) indicates a significant difference using the Student's t-test for paired data with a p-value < 0.05

Table 1: Sociodemographic and clinical characteristics of the study sample (n=42)

	Before ECT	After ECT
Sociodemographical data :		
Age (in years)	60.19 ± 14.09	-
≥ 65 years old	19 (45.24 %)	-
Sex (male)	19 (45.24 %)	-
Clinical data :		
Unipolar depression	25 (59.52 %)	-
Bipolar depression	17 (40.48 %)	-
Dementia	3 (7.14 %)	-
MADRS total score	34.57 ± 6.19	11.55 ± 8.39
MADRS - 50 % (response)	-	36 (85.71 %)
MADRS total score < 10 (remission)	-	19 (45.24 %)
MoCA total score	22.71 ± 4.46	23.41 ± 3.77
MoCA total score < 26	30 (71.43 %)	28 (66.67 %)
AIS total score	4.45 ± 2.29	4.19 ± 2.20
AIS total score > 3	27 (64.29 %)	28 (66.67 %)
Cumulated AIS		5.33 ± 2.89
Imagery data :		
Age non-specific WML	4 (9.52 %)	-
Pathological WML	11 (26.19 %)	-
Cortical atrophy	11 (26.19 %)	-
Hippocampal atrophy	2 (4.76 %)	-
ECT data :		
Number of sessions	-	15.07 ± 4.02
Charge (in millicoulomb)	-	363.95 ± 167.36
EEG duration of seizures (in second)	-	36.84 ± 14.60
Electrode placement in RUL	-	13 (30.95 %)
Electrode placement in BT	-	29 (69.05 %)
BT > RUL change	-	14 (33.33 %)
Atropine injection 0.5 mg (> 1 time)	-	7 (16.67 %)

Date are mean ± standard deviation or effective (%). Abbreviations: MADRS: Montgomery and Asberg Rating Scale, MoCA: Montreal Cognitive Assessment, AIS: Anticholinergic Impregnation Scale, WML: White Matter Lesions, RUL: Right Unilateral, BT: Bitemporal, ECT: Electroconvulsive Therapy.

Table 2: MoCA sub-scores comparisons before and after ECT courses (n=42)

	Before ECT	After ECT	Stat	df	p-values
Visuo-executive (/5)	3.02 ± 1.47	3.50 ± 1.33	t = - 2.033	41	0.049
Naming (/3)	2.86 ± 0.42	2.98 ± 0.15	t = - 1.952	41	0.058
Attention (/6)	4.91 ± 1.43	5.29 ± 0.97	t = - 2.238	41	0.031
Language (/3)	2.33 ± 0.79	2.50 ± 0.63	t = - 1.311	41	0.197
Abstraction (/2)	1.64 ± 0.58	1.62 ± 0.54	t = 0.227	41	0.822
Delayed recall (/5)	2.43 ± 1.81	1.88 ± 1.66	t = 2.088	41	0.043
Orientation (/6)	5.52 ± 0.89	5.64 ± 0.82	t = - 0.759	41	0.452

Data are mean ± standard deviation with comparisons using the Student's t-test for paired data.

Table 3: Treatments administered to patients during ECT cures (n=42)

Molecul	n	%	Min	Max	Mean	SD	AIS
Lorazepam	20	47.62	0	20	2.98	2.47	1
Venlafaxine	15	35.71	0	262,5	134.49	78.03	1*
Cyamemazine	11	26.19	0	325	44.35	35.37	3
Clomipramine	10	23.81	0	225	84.40	46.57	3
Quetiapine	9	21.43	0	1200	383.96	225.06	2
Mirtazapine	8	19.05	0	60	24.53	11.44	1
Oxazepam	8	19.05	0	150	34.67	19.25	1
Olanzapine	8	19.05	0	15	8.66	3.92	2
Lithium	7	16.67	0	1400	655.02	277.87	1
Loxapine	7	16.67	0	400	67.27	55.28	2
Aripiprazole	6	14.29	0	20	9.75	4.31	1*
Diazepam	6	14.29	0	60	15.61	6.51	1
Alimemazine	3	7.14	0	20	13.28	3.80	1
Fluoxetine	3	7.14	0	40	21.70	6.00	1
Pramipexol	3	7.14	0	3.15	1.12	0.36	1
Alprazolam	2	4.76	0	0.50	0.20	0.04	1
Amitriptiline	2	4.76	0	150	114.69	32.29	3
Levodopa	2	4.76	125	400	361.70	78.10	1
Tramadol	2	4.76	0	100	14.55	3.47	1
Atenolol	1	2.38	0	50	44.35	-	1
Baclofen	1	2.38	0	40	34.89	-	1
Cetirizine	1	2.38	0	5	1.28	-	2
Chlortalidone	1	2.38	0	12.5	11.09	-	1
Citalopram	1	2.38	0	40	21.61	-	1
Clorazepate	1	2.38	30	40	38.33	-	1
Duloxetine	1	2.38	0	90	38.91	-	1
Hydroxyzine	1	2.38	0	50	8.14	-	3
Levomepromazine	1	2.38	0	250	101.02	-	2
Risperidone	1	2.38	0	3	1.63	-	1
Sodium valpromide	1	2.38	0	1200	620.34	-	1
Trihexyphenidyle	1	2.38	0	2	0.98	-	3

Date are number and %, Min : minimum daily dose, Max : maximum daily dose, Mean : mean daily dose received during ECT cures in milligrams/days, SD : standard deviation, AIS : Anticholinergic Impregnation Scale (* indicates a anticholinergic score according to the Anticholinergic Cognitive Burden scale).

Table 4: Association between cumulated AIS and reduction in MoCA scores with results adjusted for Δ MADRS using logistic regression

	Adjusted			
	OR	95% CI lower	95% CI upper	p-values
MoCA total score	1.038	0.984	1.095	0.175
Visuo-executive	0.981	0.934	1.029	0.430
Attention	1.005	0.965	1.047	0.800
Language	0.989	0.947	1.032	0.601
Abstraction	0.973	0.932	1.015	0.208
Delayed recall	0.972	0.922	1.025	0.295
Orientation	1.000	0.961	1.042	0.983

Table 5: Association between Δ AIS and reduction in MoCA scores with results adjusted for Δ MADRS using logistic regression

	Adjusted			
	OR	95% CI lower	95% CI upper	p-values
MoCA total score	1.015	0.939	1.098	0.706
Visuo-executive	0.997	0.930	1.069	0.936
Attention	0.991	0.935	1.051	0.771
Language	1.020	0.960	1.085	0.522
Abstraction	1.011	0.950	1.076	0.727
Delayed recall	0.982	0.910	1.061	0.653
Orientation	0.968	0.914	1.025	0.270