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## The journal of ECT

## **Original study**

## Dynamics of depressive and psychomotor symptoms during electroconvulsive therapy in older depressive patients: A case series

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The authors report no conflicts of interest.

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### Abstract

**Objective.** Electroconvulsive therapy (ECT) is an effective treatment for patients suffering from a major depressive episode, especially older ones. Identification of specific responses within early ECT sessions remains an issue of debate, however. Hence, this pilot study prospectively examined the outcome in terms of depressive signs, symptom by symptom, throughout a course of ECT, concentrating particularly on psychomotor retardation symptoms. Methods. Nine patients were clinically evaluated several times during the ECT course, before the first session and then weekly (over 3 to 6 weeks, according to their evolution), by completing the Montgomery-Asberg Depression Rating Scale (MADRS), the Mini-Mental State Examination test, and the French Retardation Rating Scale for Depression (ERD) for assessing the severity of psychomotor retardation. Results. Non-parametric Friedman tests showed significant positive changes in mood disorders during ECT in older depressive patients (mean: -27.3% of initial MADRS total score). Fast improvement in ERD score was observed at  $t_1$  (i.e., after 3–4 ECT sessions), whereas a slightly delayed improvement in the MADRS scores was found at  $t_2$  (i.e., after 5–6 ECT sessions). Moreover, the scores for items linked to the motor component of psychomotor retardation (e.g., Gait, Postural control, Fatigability) were the first to significantly decrease during the first two weeks of the ECT course compared with the cognitive component. Conclusions. Interestingly, participants' concentration on daily functional activities, their interest and fatigability, and their reported state of sadness were the first to progress, representing possible precursor signs of positive patient outcomes following ECT.

Key words: Depression, ECT, Psychomotor Retardation, Older Adults, Course of symptoms

### **Original Study**

#### Introduction

Electroconvulsive therapy (ECT) is now well documented to be an effective treatment for 80 to 90% of patients suffering from a major depressive episode,<sup>1-3</sup> especially older patients (> 65 years)<sup>4-5</sup> and those suffering from depression associated with psychotic features, catatonia symptoms, or a high suicide risk.<sup>6-13</sup>

As a core symptom, psychomotor retardation (PMR) is a long-established component of depression including motor and cognitive impairments that can have significant clinical and therapeutic implications for treatment.<sup>14-16</sup> Hence, PMR has become considered as a predictive factor of response to ECT, as have psychotic symptoms, catatonia, and older age. Interestingly, all these factors seem to be associated with better clinical outcomes.<sup>17-32</sup> Although a few studies did not find any relationship between depressive symptoms, psychotic features, retardation, and agitation,<sup>33-34</sup> psychotic symptoms, or psychomotor retardation/agitation are most likely the best predictors of positive response.<sup>22,29,35-40</sup> For example, Bouckaert et al.<sup>41</sup> investigated longitudinal brain volume changes in older patients with severe late life depression treated with ECT. They observed a significant right hemispheric grey matter volume increase in the caudate nucleus, medial temporal lobe (including the hippocampus and amygdala), insula, and posterior superior temporal cortex. Furthermore, a correlation was shown between the increase of grey matter volume in the caudate nucleus region and positive changes in psychomotor function.<sup>41</sup> This finding should be considered in light of the observation that reduced caudate nucleus volume is one of key predictors (with age) of the psychomotor speed in patients with late life depression.<sup>42</sup> In the same vein, Bak et al.<sup>43</sup> observed an increased metabolic activity in the cerebral cortex and basal ganglia during the course of ECT, in correlation with psychomotor retardation, in a 55-year-old woman with treatment-resistant late onset depression. These conclusions were recently confirmed by functional neuroimaging data, which revealed the importance of the basal ganglia in the therapeutic effect of ECT on psychomotor functioning.<sup>44</sup> Similarly, Belge et al.<sup>45</sup> showed the association between an increase of within-posterior default mode network connectivity and an improvement of PMR in depression following ECT. They also demonstrated that this post-ECT improvement was related to the immunomodulatory properties of the treatment, particularly a decrease in IL-6 levels.<sup>46</sup>

Psychomotor retardation can also be considered in a longitudinal perspective during ECT (rapidity and dynamics). Nonetheless, research examining the course of depressive symptoms during ECT is relatively scarce. Browning and Cowen (1986) focused on depressive symptoms over time (apparent sadness, reduced appetite, psychomotor retardation, etc.) throughout the course of ECT.<sup>47</sup> Their key results showed that PMR and reduced appetite in ten patients with major depressive disorders were the earliest depressive features to improve during a course of ECT; only three ECT sessions were required to produce a 50% reduction in pre-treatment rating score of PMR. In this respect, Husain et al. (2004) focused on the speed of response and remission rates in a cohort of 253 depressed patients who received a course of acute-phase ECT.<sup>48</sup> Over half had an initial first response by ECT treatment #3, while 34% of patients achieved remission at or before ECT #6, and 65% achieved remission at or before ECT #10. Likewise, associations were found between a fast response and younger age,<sup>49-50</sup> psychotic features,<sup>1,30</sup> and high baseline depression severity.<sup>51</sup> In addition, a rapid response was associated with an ECT schedule of three treatments a week <sup>52</sup> and a high seizure energy index.<sup>51</sup> This is consistent with van Diermen et al.<sup>53</sup>, who showed a significant reduction in psychomotor disturbance during the first week that was clearly associated with higher ECT effectiveness.

In a large sample consisting of 156 consecutive in-patients receiving ECT for severely unipolar depressive disorder, Cinar et al. (2010) identified five different classes of trajectories (improvement rates) of depressive symptoms, i.e., fast improvement (39 patients), intermediate improvement (47 patients), slow improvement (30 patients), slow improvement with delayed onset (18 patients), and finally a trajectory with no improvement (20 patients).<sup>54</sup> The course of depressive symptoms

at the end of treatment for the trajectories of intermediate improvement, slow improvement, and slow improvement with delayed onset was still improving and did not reach a plateau. The different courses of depressive symptoms during ECT probably contribute to the mixed results found by prediction studies of ECT outcome. <sup>21,55-60</sup> The issue of the identification of specific responses within early ECT sessions ECT sessions is still a matter of debate.<sup>48</sup>

However, such studies did not systematically report specific data on psychomotor retardation, duration of illness, age of first depressive episode, or vegetative symptoms, all of which might be related to ECT outcome.<sup>54</sup> Finally, it is worth considering that differences may occur between the time course of improvement in clinical observations and patients' self-reports, especially for mood, interest, energy, and concentration.<sup>61-62</sup> This is a key point for treatment decisions guided by clinical response.

Considering the diagnostic, prognostic, and therapeutic relevance of PMR in older depressed patients,<sup>37,63-67</sup> a finer analysis of the clinical feature dynamics would further strengthen ECT strategy choices, such as the total number of ECT treatment administrated to each patient. Hence, we performed a pilot study to prospectively examine the outcome in terms of depressive signs, symptom by symptom, throughout an ECT course, in eleven patients suffering a major depressive episode, concentrating particularly on psychomotor retardation symptoms. Based on recent studies we conducted,<sup>64,67</sup> the earliest positive changes were expected in the "*Fatigability*" and "*Concentration*" items on the PMR ratings scale.

#### Methods

#### Participants

Eleven older patients with a major depressive episode (MDE) (mean age:  $67.4 \pm 9.3$  years, range 53–81; 6 women and 5 men) were included in this naturalistic observational study in the Nantes University Hospital (France). They had all been referred to the Addictology and Liaison Psychiatry Department to receive bitemporal ECT. All patients provided a signed consent form for

participation. Inclusion criteria were that subjects had to be: aged over 50; diagnosed with MDE according to DSM-V; and had failed to respond to at least one previous adequate course of an antidepressant or had a score of more than 20/60 on the Montgomery–Asberg Depression Rating Scale (MADRS), a criterion of severity.<sup>68</sup> Exclusion criteria were evolutive neurological disorders, dementia, and any anesthetic contraindication.

#### Protocol

The patients were clinically evaluated several times during the ECT course, before the first ECT session and then weekly (during 3 to 6 weeks, according to the evolution of patients). This was done using the three following scales, completed by the same trained rater: the MADRS (/60); the Mini-Mental State Examination test (/30), used to assess the cognitive state of patients;<sup>69</sup> and the French Retardation Rating Scale for Depression (ERD: /60) <sup>70</sup>, a validated 15-item rating instrument to assess the severity of psychomotor retardation in depressed populations. Briefly, this scale has been validated with the specific objectives of clinical and quantitative evaluation of psychomotor retardation in depressive states. This rating scale consists of 14 specific items (+ 1 general item about "General appreciation of retardation"): 6 concern motor retardation (among which 3 first items are for movement retardation – gait, balance, and movements of neck // head -, and the 3 others are for verbal retardation - language and verbal flow, modulation of the voice and brevity of responses) and 8 ideational retardation (variety of spontaneous themes, richness of associations to topics proposed by the examiner, subjective experience of ruminations, fatigability, interest in habitual activities, patient's perception of time, memory, concentration...)<sup>71</sup>.

The ECT sessions were administered twice or three time weekly, using a MECTA spECTrum 5000Q device (MECTA Corp, Tualatin, Oregon), coupled with electroencephalography (EEG) monitoring. The electrode placement was in bitemporal position. Seizure threshold was individually determined during the first ECT session, according to titration schedule. During ECT

courses, the charge was adapted to individual seizure threshold. Anesthesia procedures were either propofol or etomidate, combined with succinylcholine curarisation. It is important to note that no change in medication occurred during ECT treatment.

#### Data analysis

All statistics were performed with N = 9 (mean age:  $66 \pm 9.1$  years). Considering the small number of participants, the non-parametric Friedman test for dependent samples was used to assess the changes in depression (MADRS score), cognitive state (MMSE score) and PMR (ERD score) as a function of time course:  $t_0$  (inclusion before the first ECT session; n = 9),  $t_1$  (after about  $3 \pm 0.9$  ECT sessions; n = 9),  $t_2$  (after about  $5.2 \pm 0.8$  ECT sessions; n = 9), and  $t_3$  (after about  $7 \pm 1.4$  ECT sessions; n = 8). The number of ECT sessions and the number of days between the assessments are indicated in Table 1. In cases with a main effect of time course, we used Wilcoxon signed-ranks tests for pairwise comparisons with a P value of < 0.05. Note that the Kendall's W coefficient was reported as the Friedman test effect size. Kendall's W uses the Cohen's interpretation guidelines of 0.1 - < 0.3 (small effect, 0.3 - < 0.5 (moderate effect) and >= 0.5 (large effect).<sup>72</sup>

#### Results

Among the eleven patients initially included in the study, note that two male patients were not included in the data analyses. The causes of dropout were death (suicide) and remission before starting the ECT. The total number of sessions for each patient was between 4 and 13, depending on the speed of the clinical efficacy, the tolerance, and the patient's willingness to complete the treatment. Table 1 summarizes all the patients' characteristics and descriptive results.

\*\*\* Please INSERT TABLE 1 here \*\*\*

The statistical analyses revealed a main effect of time course for the overall MADRS scores (W = 0.68) and the ERD scores (W = 0.62). Overall, we observed a positive change in depression, with a strong decreasing trend in MADRS scores between  $t_0$  and  $t_1$  (p =.08), between  $t_1$  and  $t_2$  (p =.01), and between  $t_2$  and  $t_3$  (p = .06). For the psychomotor retardation, the ERD scores decreased significantly at  $t_1$  (p = .03) (see Table 2 for descriptive data). No change in MMSE scores was found (p = .95; score at  $t_0$ : 21.6 ± 3.7).

# \*\*\* Please INSERT TABLE 2 here \*\*\*

To get more insight into the dynamics of depressive symptoms and PMR during the ECT course, we reran the analyses considering each item of the rating scales separately [10 items for MADRS (each on a 7-point scale; 0–6); 15 items for ERD (each on a 5-point scale; 0–4)].

*MADRS ratings*. The repeated measures Friedman tests revealed a main effect of time course for all the items (all W values: [0.31 - 0.54]), except item 6 "*Concentration difficulties*". Note that the post-hoc comparisons only showed a significant difference between  $t_0$  and  $t_1$  for item 2 "*Reported sadness*" (p =.04), between  $t_1$  and  $t_2$  for item 1 "*Apparent sadness*" (p =.04) and item 3 "*Inner tension*" (p =.04), and between  $t_2$  and  $t_3$  for item 7 "*Lassitude*" (p =.02).

*ERD ratings.* A main effect of time course was found for item 1 "*Gait*" (W = 0.34), item 2 "*Movement* [slowness and paucity of trunk movements]" (W = 0.29), item 3 "*Mimetic* [slowness and paucity of head-neck movements]" (W = 0.40), item 7 "*Ideational initiative*" (W = 0.37), item 9 "*Ruminations*" (W = 0.43), item 10 "*Fatigability*" (W = 0.54), item 11 "*Interest*" (W = 0.47), item 12 "*Time perception*" (W = 0.43), and item 14 "*Concentration*" (W = 0.44).

Interestingly, the pairwise comparisons showed significant improvements at  $t_1$  compared with scores at  $t_0$  for item 10 "*Fatigability*" (p = 0.03), item 11 "*Interest*" (p = 0.03), and item 14

"*Concentration*" (p = 0.04). At  $t_2$ , positive changes were found for item 1 "*Gait*" (p = 0.03), item 2 "*Movement*" (p = 0.04), item 3 "*Mimetic*" (p = 0.03), item 9 "*Ruminations*" (p = 0.01), item 10 "*Fatigability*" (p = 0.02), and item 11 "*Interest*" (p = 0.03) (Figure 1).

\*\*\* Please INSERT FIGURE 1 here \*\*\*

#### Discussion

In this pilot study, significant positive changes in mood disorders were found over the course of ECT in older patients with a major depressive episode (mean: -27.3% of initial MADRS total score). Considering a positive response to the treatment as a decrease of at least 50% between baseline MADRS total score and MADRS total score at the end point (i.e., after about 7 ± 1.4 ECT sessions), four patients out of 9 were identified as full responders [mean initial MADRS score: 37.5  $\pm$  7.8 vs. end MADRS score: 8.2  $\pm$  5], and four other patients as partial responders  $\geq$ 25% improvement from baseline MADRS. This finding confirms that ECT is an effective treatment for depression. The main original findings were obtained from examining the dynamics of all the depressive and PMR symptoms (which improved by 63% and 37.1% on average for the full and partial responders, respectively) throughout the course of ECT. Interestingly, fast improvement in the ERD total score was observed at  $t_1$  (i.e., 3–4 ECT sessions),<sup>53</sup> whereas a slightly delayed improvement in the MADRS total scores was seen at  $t_2$  (i.e., 5–6 ECT sessions). Furthermore, the scores of items linked to the motor component of PMR (Gait, Movement, Mimetic, Fatigability) were the first to significantly decrease during the two first weeks of the ECT course compared with the cognitive component of PMR. The implications of these results will be discussed in more detail below.

Though rare, some studies have investigated the course of depressive symptoms and psychomotor retardation in patients with MDE receiving ECT. In agreement with previous findings,<sup>41,53</sup> our results confirm that psychomotor retardation symptoms improved quickly, but at

different rates depending on the given items of ERD scale. Indeed, the positive changes in depressive symptoms (a decreasing trend in overall MADRS scores) were associated with an improvement of psychomotor retardation by the end of the first week of ECT therapy (-24.8% of baseline ERD scores). Other analyses may support certain conclusions - although still highly debated in the literature - on the basis of the 3-factor model of the MADRS, mainly used to assess clinical features of (non)-responders to neurostimulation treatments.<sup>73-74</sup> The "dysphoria" factor 1 (including reported sadness, pessimistic thoughts, and suicidal thoughts) and the "retardation" factor 2 (including apparent sadness, concentration difficulties, lassitude, and inability to feel) showed notable improvement from the first week (-26.7% and -20%, respectively; p < 0.001), with the most positive changes in reported sadness, apparent sadness and lassitude.

All these results seem consistent with our previous work showing the positive impact of repetitive transcranial magnetic stimulation (rTMS) in patients with major depressive disorders involving depression-related cognitive-motor functioning, sadness, and fatigability. Specifically, we showed that posture-cognitive dual tasking performance is a solid hallmark of depression-related psychomotor retardation.<sup>64-65</sup> In addition, the balance impairment at baseline in depressed patients is likely a sound moderator of positive outcomes after an rTMS intervention.<sup>64</sup> Finally, as they are closely linked, the balance performance and sadness/fatigue states have been found to provide reliable hallmarks of depression-related psychomotor functioning (see<sup>67</sup> for details). As an extension, an important finding of the current study is that the motor component of psychomotor retardation (as opposed to the cognitive/ideational component)<sup>14</sup> is the most sensitive and the first to improve in patients receiving ECT for a major depressive episode.

This motor component, encompassing all the motor function disturbances, can be reasonably associated with items #1 (Gait), #2 (Movement: slowness and paucity of trunk movements), #3 (Mimetic: slowness and paucity of neck/head movements) and #10 (Fatigability) on the ERD scale. All the scores of aforementioned items decreased continuously throughout the ECT course, but already showed significant improvement after just one or two weeks. It is worth noting that reduced

fatigability and higher mobility were accompanied by parallel improvements in Concentration (item # 14) and Interest (in habitual activities) (item # 11). This likely marked more efficient (less cognitively demanding) daily motor activities.<sup>64,67</sup> In contrast, no (or more delayed) change was shown for the items more closely related to the cognitive/ideational component of PMR, such as the items #4 (Language: verbal flow), #5 (Volume: intensity and modulation of speech), #6 (Brevity of responses), #7 (Variety: ideational initiation), #8 (Richness: ideational fluidity) #9 (Ruminations), #12 (Time perception), and #13 (Memory) (see Figure 1). Because of the small size of our pilot sample, these findings need to be considered with caution. Nonetheless, we support the idea that psychomotor retardation is the aspect most sensitive to ECT, especially its motor component. This confirms the critical importance of assessing this symptom for both fundamental and clinical purposes. Undeniably, mood, cognitive, and movement disorders co-occur frequently in clinical psychiatry. For example, a slower gait speed at baseline predicts depressive symptoms.<sup>75</sup> Hence, psychomotor retardation appears to be more than a symptom, but rather the core of the depression,<sup>71</sup> and a probable consistent predictor of positive outcomes in patients with major depressive episode after a repetitive transcranial magnetic stimulation or ECT intervention.<sup>37,63-64</sup> There is a potential for bias here as the motor retardation is reversed before mood and cognitive disturbances.<sup>75</sup> In this respect, the issue of comprehensive quantification of PMR, which is easy to envisage in clinical settings, is of prime importance.14,63-67

From the clinical point of view, the current findings raise the issue of suicide risk in ECT-treated patients. Slater and Roth<sup>75</sup> already reported the imperative need to focus attention on the increased risk of suicide when ECT-treated patients recover motor activity (which typically increases their action capabilities) before their mood disorders are significantly improved. At least the first two weeks of an ECT course appear crucial in this regard, which is to say the minimal period of time necessary to observe the significant decrease in MADRS scores. Considering the different courses of depressive symptoms during ECT,<sup>54</sup> increased vigilance is required throughout ECT intervention because of positive changes in psychomotor retardation. The

psychomotor retardation is likely a precursor sign of delayed positive outcomes, but also, paradoxically, a risk factor for suicide. On the one hand, warnings have been made about the increased risk of suicide when ECT-treated patients recover motor activity before their depressed mood is alleviated.<sup>76</sup> On the other hand, some studies have shown a rapid reduction in expressed suicidal intent in patients treated with ECT.<sup>77</sup> In any case, suicide risk should be constantly assessed at all stages of treatment.

We acknowledge some limitations of the study that should be considered when interpreting our results. Despite the abundant literature,<sup>2,78</sup> it is difficult to make a robust conclusion about the possible effectiveness of ECT intervention in treating depression and the associated psychomotor retardation impairments since a comparative control group is lacking. In addition, it is well known that there exists a natural course to depression in the acute phase. The current positive effects of ECT intervention observed on PMR and mood disorders need to be described and interpreted with caution. Any intervention or even the natural course of the illness that improves depression severity may change psychomotor responses. For example, a two-month walking program allowed patients with major depressive disorder to improve, first and foremost, their postural balance, especially for the most cognitively demanding conditions.<sup>79</sup>

Another limitation is that the sample size (n = 9) is too small, which reduces the study's power and increases the margin of error. The current results need to be interpreted with caution. Additionally, some missing data in the medical file, such as the missing reason to stop ECT, may have impact on the outcomes. Lastly, another limitation, due to the naturalistic conditions, could be linked with the adaptation of the charge fixed by the psychiatrist responsible of the session. It may have impacted the efficacy of the seizure, and consequently the clinical effects of the session.

Further investigation in a larger population, in a double-blind, sham-controlled trial protocol is now needed to confirm the positive effects of ECT intervention on psychomotor retardation, and to explore the predictive value of quantitative motor features (e.g., postural instability, gait velocity under dual-task) regarding response to ECT in depressed patients. Lastly, in the same vein, to track patient progression quickly and easily in clinical settings, patients could respond to two items assessing mood ('I feel continuously sad') and fatigability ('Everything I'm doing is very demanding') on a 10-cm visual analogue scale<sup>67</sup>. These could potentially serve as relevant hallmarks of depression-related mood and psychomotor functioning, but require further confirmation on a larger population.

#### Conclusion

Regardless of the different dynamics of depressive symptoms during ECT,<sup>54</sup> we identified the first positive responses within early ECT sessions, demonstrated by the time course of specific improvement in psychomotor retardation, especially for motor performance (gait and postural control). Interestingly, the first aspects to progress were patients' concentration related to daily , ar. ve patient ( activities, their interest and fatigability, and their reported sadness state, which are all, therefore, possible precursor signs of positive patient outcomes after ECT.

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#### **Conflict of interest**

The authors report no conflicts of interest.

#### **Ethical standards**

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

It should also be noted that in this study, no change in our current clinical practice or randomization were performed. As it was an observational study, according to the French legislation (articles L.1121-1 paragraph 1 and R1121-2, Public Health Code), no approval of the ethics committee was needed for the use of data in an epidemiologic study.

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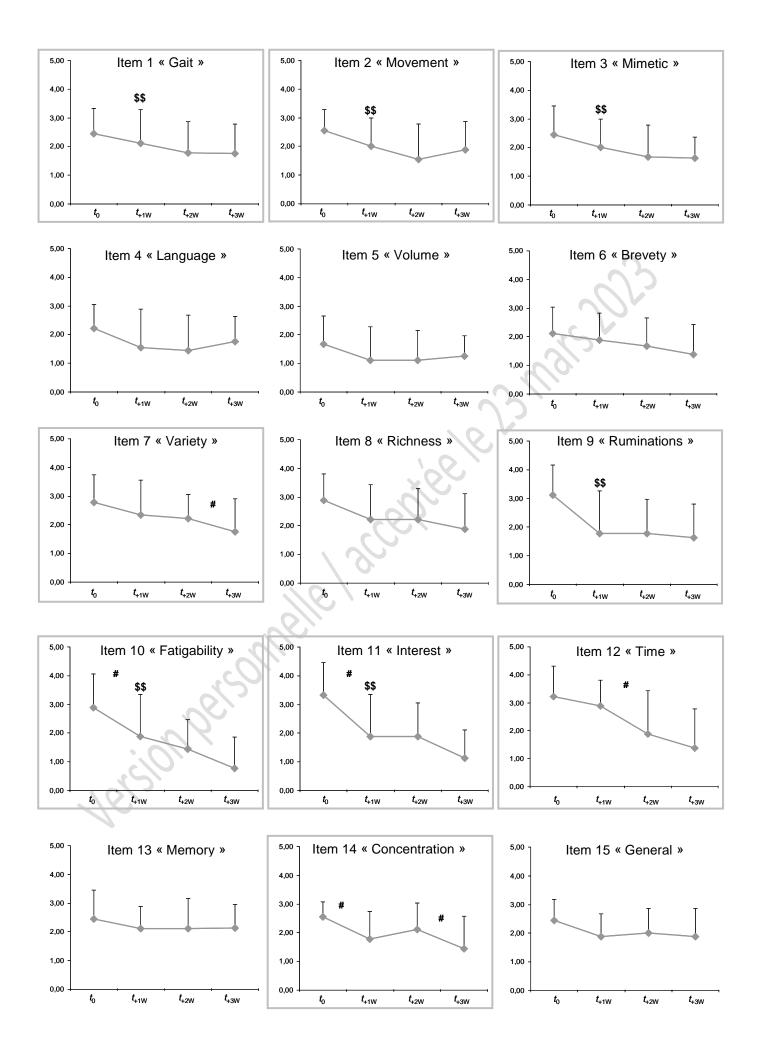
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19

## **FIGURE CAPTIONS**

**Figure 1**: Evolution of scores of each item on the ERD rating scale as a function of time [ $t_0$ ,  $t_1$  (after about 3–4 ECT sessions),  $t_2$  (after about 5–6 ECT sessions), and  $t_3$  (after about 7-8 ECT sessions)].

The grey frame indicates a main effect of time course (Friedman test).



Patient / Sex		Number of previous depressive episodes	Number of suicide attempts	Current MD / All life diagnosis	Psychiatric Medications (at the beginning of the ECT) (name and dose per day)	Total number of ECT sessions	between <i>t</i> <sub>0</sub> - <i>t</i> <sub>+1w</sub>		between t <sub>+1W</sub> - t <sub>+2w</sub>		between <i>t</i> <sub>+2W</sub> - <i>t</i> <sub>+3w</sub>	
	Age (years)						n ECT sessions	Number of days	<i>n</i> ECT sessions	Number of days	<i>n</i> ECT sessions	Number of days
1/ Female	53	2	2	Chronic and resistant MDE / MDD	Clomipramine 125 mg Zopiclone 7,5 mg Cyamemazine 30 mg	10	4	9	2	7	2	7
2/ Male	62	0	0	First resistant MDE	Venlafaxine 150 mg Mirtazapine 37,5 mg Cyamemazine 12,5 mg Meprobamate 800 mg	8	3	12	3	12	1	10
3/ Female	71	15	0	MDE / MDD	Venlafaxine 175 mg Divalproate 1500 mg Clorazepate 10 mg Meprobamate 200 mg	6	3	9	2	7	1	8
4/ Male*	81	2	0	MDE with psychotic symptoms / MDD	Cyamemazine 30 mg Hydroxyzine 50 mg	0						
5/ Female	79	1	0	MDE (relapse) / MDD	Venlafaxine 300 mg Olanzapine 20 mg Zopiclone 7,5 mg Loxapine 75 mg	13	2	7	2	6	2	7
6/ Female	61	2	0	MDE / BD	Venlafaxine 150 mg Olanzapine 10 mg Alprazolam 0,75 mg Zolpidem 7,5 mg	4	2	8	2	6		
7/ Female	76	1	0	MDE with psychotic symptoms / MDD	Venlafaxine 375 mg Olanzapine 20 mg Cyamemazine 90 mg Zolpidem 7,5 mg	13	3	9	2	7	3	6
8/ Male	58	2	0	MDE with psychotic symptoms <del>/</del> MDD	Mirtazapine 7,5 mg Oxazepam 50 mg	9	4	9	2	7	2	7
9/ Male*	69	NK	0	MDE / BD	Valpromide 1800 mg							

2

**<u>Table 1</u>**. Patients' baseline clinical and treatment characteristics.

					Mirtzapine 30 mg Venlafaxine 225 mg Clonazepam 1 mg	13						
10/ Female	74	NK	1	MDE / BD	Milnacipran 150 mg		2	6	3	7	3	7
11/ Male	60	NK	1	Chronic MDE / MDD	Venlafaxine 225 mg Hydroxyzine 75 mg Zopiclone 7,5 mg Alprazolam 2 mg	13	4	15	2	7	2	7
Mean ± SD	66 ± 9.1						3 ± 0.9	9.3 ± 2.7	2.1 ± 0.6	7.3 ± 1.8	$2\pm0.7$	7.4 ± 1.2

sive Disorder; MDE: Major Depressive Epist

Patient	MADRS score (/60)				ERD score (/60)				20L-
	to	<i>t</i> +1w	<i>t</i> +2w	<i>t</i> +3w	t <sub>0</sub>	<i>t</i> +1w	<i>t</i> +2w	<i>t</i> +3w	alspr
1	20	14	10	14	18	18	14	12	alo.
2	44	38	36	28	49	37	41	32	5
3	42	7	10	3	33	10	14	9	
5	39	38	31	28	41	38	36	35	
6	29	9	5		26	15	14		
7	41	55	43	29	41	49	43	24	
8	46	18	15	12	49	23	17	9	
10	43	46	38	33	38	32	29	37	
11	33	20	11	13	35	26	15	17	
Mean (Standard Deviation)	37.4 (8.5)	27.2 (17.3)	22.1 (14.7)	20 (10.8)	36.7 (10.1)	27.6 (12.5)	24.8 (12.5)	21.9 (11.7)	
		10	500	X					