J. M. Criado[1]
A. Fernández[2]
T. Ortiz[2]

Long-term effects of electroconvulsive therapy on episodic memory

[1] Instituto R. Coullaut de Psiquiatría
[2] Psychiatry and Medical Psychology Department
Universidad Complutense
Madrid (Spain)

Introduction. Current guidelines consider electroconvulsive therapy (ECT) as a treatment of choice for some depressive disorders; however some psychiatrists are still reluctant toward using ECT as first choice treatment. This fact is probably due to its short-term deleterious effects on memory and cognition.

Objective. To investigate long-term effects of ECT on anterograde episodic memory.

Methods. Participants were assigned to three groups: 20 major depression patients receiving ECT treatment (group A), 28 major depression patients following only pharmacological therapy (group B) and 26 healthy controls (group C). Group A patients received three ECT sessions. Memory evaluation consisted of three tests: list of words, and logical memory I and II. Memory evaluation was performed before treatment (baseline) and six months post-treatment.

Results. Groups A and B performed at a similar level in baseline evaluation. Post-treatment evaluation indicated that ECT was associated with a significantly better clinical situation and improvement in all memory tests. There was also a very strong correlation between clinical improvement and memory performance.

Conclusions. According to our results, ECT was not associated with deleterious effects on anterograde episodic memory. ECT produced faster and significantly higher clinical improvement, as measured by means of Hamilton Depression Rating Scale, which also correlates with memory performance.

Key words:
Electroconvulsive therapy. Major depression. Episodic memory. Amnesia.

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Correspondence:
Tomás Ortiz Alonso
Departamento de Psiquiatría y Psicología Médica
Facultad de Medicina, pabellón 3
Universidad Complutense de Madrid
28040 Madrid (Spain)
E-mail: tortiz@med.ucm.es

Efectos a largo plazo sobre la memoria de la terapia electroconvulsiva sobre la memoria episódica

Introducción. Los criterios actuales consideran la terapia electroconvulsiva (TEC) como un tratamiento de elección para ciertos trastornos depresivos; sin embargo, algunos psiquiatras son aún reticentes a su utilización. Este hecho se debe probablemente a sus efectos deletéreos a corto plazo sobre la memoria y la cognición.

Objetivo. Evaluar los efectos a largo plazo de la TEC sobre la memoria anterógrada episódica.

Métodos. Tres grupos participaron en el estudio: 20 pacientes con depresión mayor tratados con TEC (grupo A), 28 pacientes con depresión mayor que se mantienen exclusivamente con el tratamiento farmacológico (grupo B) y 26 sujetos control (grupo C). Los pacientes del grupo A recibieron tres sesiones de TEC. Las pruebas para la evaluación de la memoria fueron: recuerdo de una lista de palabras y memoria lógica I y II. La evaluación de la memoria se realizó antes del inicio del tratamiento (línea de base) y 6 meses postratamiento.

Resultados. Los grupos A y B mostraron unos niveles de ejecución similares en línea de base. La evaluación postratamiento indicó que la TEC está asociada con una situación clínica significativamente mejor y puntuaciones superiores en todas las pruebas de memoria. Además existe una correlación muy fuerte entre la mejoría clínica y la ejecución en la pruebas de memoria.

Conclusiones. De acuerdo con nuestros resultados la TEC no está asociada con efectos deletéreos sobre la memoria anterógrada episódica. La TEC produjo una mejoría clínica más rápida y más importante, medida según la Escala de Hamilton para la Depresión, que además se correlaciona con la ejecución en las pruebas de memoria.

Palabras clave:
Terapia electroconvulsiva. Depresión mayor. Memoria episódica. Amnesia.

INTRODUCTION

According to the American Psychiatric Association guidelines, electroconvulsive therapy (ECT) is a very effective treat-

ment for severe depression[1]. ECT is a psychiatric therapeutic technique in which electrical current applied in the brain is used to achieve gran mal seizure. It represents the last exponent of shock treatments in Psychiatry and is one of the most controversial and polemical ones as some consider it the most effective treatment while others an anacronism full of repressive and punitive elements. In the 1979 survey conducted by Barcia and Martínez-Prado[2] among psychiatrists on electroshock, 13.2 % of those interviewed considered the method as repressive, 74.6 % believed it caused deterioration (irreversible in some cases) and 10 % thought it was a cruel treatment. Even though there are very solid data to support the safety and efficacy of ECT (see the magnificent review of Reisner[3]), we could wonder if the subjective perception of the technique has changed substantially, at least in certain professional groups of Psychiatry. Very recently, Van der Wurff et al.[4] conducted a survey on the opinions of Dutch psychiatrists on ECT. The authors indicate that this technique is of first choice for certain types of depressive disorder and that the stigma associated to it is due to the bad use made of it until the sixties. However, the results of their survey were discouraging. Only 4 % of the professionals would use ECT for depressive disorder as psychotic component, 2 % in case of high risk of suicide and 5 % in case of extreme physical postration. In conclusion, most of the Dutch psychiatrists surveyed were very reticent to use ECT as therapy of first, second, or third choice, even in patients with major drug-resistant depression.

If we are looking for an explanation for such a situation, it should be multifactorial. In fact, there are at least three factors that may be considered essential to understand reluctance to use ECT: *a)* limited knowledge on the antidepressive action mechanism of the technique and its effects on the neurostructural and neurofunctional levels; *b)* the possibility that ECT causes permanent brain damage, and *c)* cognitive type side effects, especially mnemic ones. In regards to action mechanisms, the data are very heterogeneous and include reduction in the number of 5-HT_2[5] and α2-adrenergics receptors[6,7], which would mean «normalization» of a previous state of hypersensitivity of these receptors in depressive patients. Equally, ECT has been associated with the appearance of hyperintensities that would affect both the gray and white matter and can be detected by magnetic resonance (MRI). This supposition is fundamentally based on retrospective studies. However, when the patients are investigated through prospective studies, it can be demonstrated that many of these lesions were already visible before initiating ECT and, in fact, would remain stable during the treatment (see Nobler et al.[8] for review). The neurofunctional studies are also contradictory. Nobler et al.[9] found a significant reduction in prefrontal metabolism after ECT while the most common finding is a regulation of hypofunctionality of certain structures observed in depressive patients[10]. Once again, the discrepancies between studies may be due not only to the different techniques used to measure cerebral functioning (PET versus SPECT, for example) but also to the design of the experiments. As it is made clear in the Blumenfeld et al.[11] study, the effect of an increase of blood flow in certain brain areas, such as the frontal cortex or cingulate, becomes clearer as it moves closer to the time when the ECT causes the seizure (ictal SPECT). In any vent, it seems that the long-term effects of ECT on brain metabolism could be negligible[12].

However, the factor that has contributed most to the black legend of ECT is its deleterious effect on memory. We have known for more than 60 years that the characteristics of amnesia associated to ECT are parallel to those of any other amnesia having an organic origin. This means difficulty to retain new material learned (anterograde amnesia) and for recall of past events (retrograde amnesia)[13,14]. Once again, studies on the extension of this deficit show a large variability of results. Fink[15] showed that memoristic capacity returned to normality a few weeks after the last ECT. Jackson[16] presented data that demonstrated how the scores on neuropsychological tests of memory had returned to baseline levels as soon as 10 days after the last ECT. Afterwards, Sackeim et al.[17] found that the acquisition of new information was normal 4 days after the last ECT, but this was not true for the differed recall of this information. In fact, it should not be forgotten that some patients maintain their complaints about memory years after completing ECT treatment and, in some cases, this problem prevents them from carrying out a «normal» daily life[3,18]. This situation gives rise to the need to evaluate objectively the possible memory problems that ECT may cause in the long term in patients with major depression. Thus, in the present study, we compare the performance of patients treated with ECT and patients exclusively treated with drug therapy in several tests that evaluate episodic memory. This comparison is done both at baseline and 6 months after treatment onset. The scores of the depressive patients are also compared with those of a control group. In this point, our hypothesis is that the patients who have followed ECT treatment will have similar levels of performance in memory tasks (without statistically significant difference) to those of the group that have exclusively followed drug therapy. In addition, the relationship between cognitive state of the patients and improvement of depression severity will be analyzed.

METHODS

Subjects

The patients who participated in the study were selected from a larger sample of patients diagnosed of major depression in the Instituto R. Coullaut de Psiquiatría. All the patients had had at least two months of drug treatment prior to the study onset. This therapy included the range of drugs commonly used in the treatment of major depression: tricyclic antidepressants, monoamine oxidase inhibitor (MAOI), selective serotonin reuptake inhibitors (SSRI), benzodiazepines, etc. The choice of the drug type was made according to the specific needs and characteristics of each patient. After

this minimum two month period, a subgroup of patients was referred to ECT if they met any of the following three strict criteria: *a)* demonstrated intolerance to the drug; *b)* persistent ideas of suicide, and *c)* no adequate response to the drug treatment. After this selection process, the clinical groups were formed as follows: group A formed by 20 patients with major depression treated with ECT and group B formed by 28 patients with major depression who are maintained exclusively with the above mentioned drug treatment. Furthermore, a third group, group C was included. It was formed by 26 control subjects, balanced in age, education level and gender (table 1).

Enrolment criteria for Groups A and B were the following:

- Age between 30 and 60 years.
- Mini Cognitive Examination Test (MCE), with 28 points or more.
- Absence of neurological disorders.
- Hamilton Depression Rating Scale (HDRS) (35 points or more).

Enrolment criteria for group C were:

- Age between 30 and 60 years.
- Mini Cognitive Examination Test (MCE), with 28 points or more.
- Absence of neurological disorders
- Hamilton Depression Rating Scale (HDRS) (6 points or more)

Neurological examination included eye fundus, intraocular pressure and EEG (electroencephalogram).

Procedure

All the participants underwent the following tests, that make up the fundamental dependent endpoints of the present study: an assessment of the seriousness of the depressive state with the HDRS, word list recall test included in the ADAS-Cog scale, logical memory I test (WMS-R) conducted according to the usual procedure described in the Wechsler clinical scale of memory manual[19] and the logical memory II test (WMS-R), also conducted according to the usual procedure described in the Wechsler clinical scale of memory manual[19]. Once the baseline assessment was conducted, the group A patients were subjected to the first ECT session. Previously, these patients had complied with the protocol established for this therapeutic method: neurological examination, cardiologic examination, complete biochemistry study (including cholinesterase) and psychopathological examination with precise indication by the psychiatrist of the need for ECT. Finally, the patient's informed consent was obtained, as established and regulated by the General Health Law, establishing the insistence of the physician in the understandability and that it is both verbal and written in a clear and precise way for the patient and family members.

Table 1 Description of the sample

	N	Mean	SD
Age ECT depression	20	47.40	13.32
Non-ECT depression	28	50.14	14.67
Control	26	44.08	10.70
ECT Hamilton depression	20	45.15	7.79
Non-ECT depression	28	43.29	11.14
Control	26	3.115	1.37

Group A patients only received three ECT sessions and these were conducted in the period of one week. The ECT was conducted with a TYMATHRON BGX system of sinus pulse. In all the patient, pentotal was used as anesthesia, succinylcholine as muscle relaxant and atropine to prevent prolonged bradycardias, associated to the strong parasympathic stimulation of the tonic phase of ECT. The electrodes to produce seizure were placed in the bilateral position (bifrontal-temporal), using short pulse sinusoidal current. The criterion used to decide if the seizure caused by ECT was adequate was that the clonic phase lasted for a minimum of 22 seconds. At the end of six months of receiving ECT, the neuropsychological re-test test and a re-assessment of the seriousness of the depressive state with the HDRS scale were re-applied. During this time period, group A patients were maintained on drug treatment, with maintenance dose.

A similar procedure was followed with group B. In this case, the patients continued with their drug therapy after baseline assessment. At six months, a re-evaluation of the neuropsychology and seriousness of the depressive state was done. During these six months, the patients obtained significant clinical improvement and thus, when re-evaluated, many of the cases were taking maintenance doses. Finally, group C members were evaluated at baseline and after six months. This period was observed to assure the reliability of the re-test measures and avoid the learning effect.

RESULTS

Statistical analyses

As we briefly indicated in the Introduction, the fundamental purpose of this study is to verify the long-term changes attributable to treatment type in episodic memory tests. These are learning of the word list included in the ADAS-Cog test and the logical memory I and II sub-tests in-

cluded in the Wechsler clinical scale of memory. We also have attempted to assess the long-term differences regarding seriousness of the depressive state, evaluated by the HDRS scale and attributable to treatment type. The results of the HDRS and ADAS tests were analyzed by both ANOVA 3×2 (diagnostic and pre-post treatment) for repeated measures. The logical memory test included in the Wechsler Scale was analyzed by an ANOVA 3×2×2 (diagnostic×pre-post treatment×memory type [logical I vs logical II]). Significant interaction was analyzed by a posteriori comparisons of mean pairs, following the Bonferroni test. Finally, correlation between the improvement of depressive state index and performance of the patients in the episodic memory tests was evaluated.

All the statistical analyses were done with the SPSS for Windows version 8.0.

HDRS scale

This scale is an indicator of the patients' depressive state and we found that all the factors involved and their interaction were significant: diagnosis ($F_{2,71}$ = 215.290; p < 0.0001), pre-post treatment ($F_{1,71}$ = 67.868; p < 0.001) and pre-post treatment×diagnosis ($F_{2,71}$ = 19.259; p < 0.001). In the first place, as was to be expected, this indicates that the scores are always lower in group C compared with the two disease groups (p < v0.05), there being no differences between these. In turn, there is a significant reduction of the scale scores in the disease groups if we focus on the post-treatment measurement. In this case, we can establish that this reduction depends statistically on the treatment characteristics: reduction of the scores is much greater in group A than in group B, thus establishing a positive differential effect (p < 0.05) for ECT treatment (fig. 1).

Word recall (ADAS-Cog)

Once again, the tendency is maintained so that the principal effects of diagnosis ($F_{2,71}$ = 23; p < 0.001), pre-post treatment ($F_{1,71}$ = 7.378; p < 0.001) factors and their interaction ($F_{2,71}$ = 3.78; p < 0.05) are significant. These data make it clear that memory performance of group C is better than that of the disease groups (p < 0.05) both before and after treatment. However, there is a treatment dependant improvement in performance, which is seen clearly in Group A (p < 0.05). Figure 2 shows how post-treatment performance is significantly greater in group A if we compare it with group B (fig. 2).

Logical memory

This endpoint has special characteristics that complicate its description. In the first place, we verify the primary effect of the diagnosis endpoints ($F_{2,71}$ = 81.355; p < 0.001)

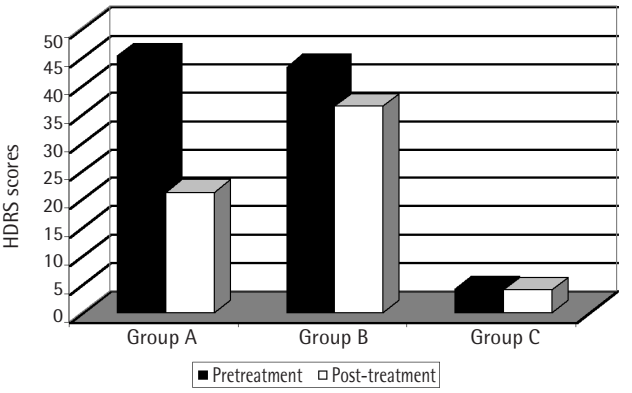

Figure 1 *HDRS score.*

and memory type ($F_{1,71}$ = 81,355; p < 0.001), and their interaction ($F_{2,71}$ = 8,708; p < 0.01). This first level of evidence indicates that group C obtains general scores that are always greater but also that while groups A and B forget part of the information in logical memory II (especially group A), the control group practically maintains it intact (p < 0.01). Thus, there is a greater forgetting rate in the disease groups in which group A stands out. On the other hand, we find the significant effect of the pre-post treatment interaction with diagnosis ($F_{2,71}$ = 8,163; p < 0.01). In this case, we verify that there is a differential effect of the treatment in the disease groups. Group A obtains significantly greater scores after treatment while there is a decrease in them in group B that indicates worse performance in the task (p < 0.05). That is, group A improves its cognitive state significantly thanks to the treatment that clearly exceeds that of group B in the post-treatment measurement. This superiority is not explained only in terms of absolute amount of material remembered but also in a decrease in forgetting rate, that is, group A patients forget more information before ECT treatment, but this situation is completelyreversed after it. The effect is more intuitively represented if we compare figures 3 and 4.

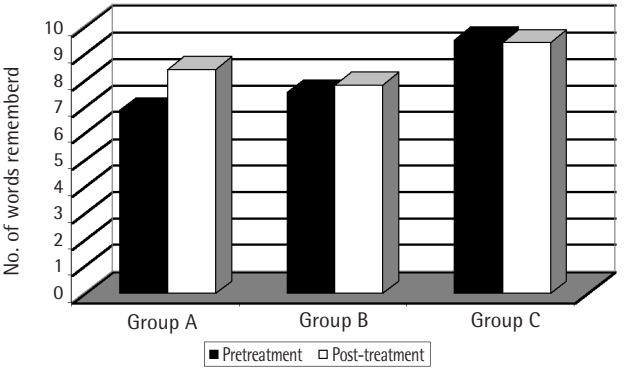

Figure 2 *Word recall before and after treatment.*

Correlation between improvement of depressive state and performance in episodic memory

To complete the data analyses, we performed a study on the relationship between improvement of depressive state and performance in the memory tests of the patients included in groups A and B. In the first place, we created a new endpoint to estimate mathematically the improvement percentage. This endpoint, «improvement index» allows us to estimate the relative variations between pre and post treatment measurements of HDRS in percentages with the following formula:

$$\text{Improvement index} = (\text{pre-treatment HDRS} - \text{post-treatment HDRS}/\text{pre-treatment HDRS}) \times 100$$

In the same way that higher scores will mean a greater grade of improvement of the depressive state, «zero» scores will indicate absence of changes and negative scores, a deterioration of the depressive state. Once calculated, the endpoint «improvement index» is correlated with all the neuropsychological endpoints of the study: recall of a word list, logical memory I and logical memory II, all of them in their pre- and post-treatment measurements. This gives rise to the calculation of 6 correlation coefficients. To avoid the effect of the spreading of the error due to multiple comparisons, the Bonferroni method of correction of significance was used. That is, only those correlations with a $< 0.05/6$ and thus a < 0.008 will be considered significant.

The results show that «improvement index» only has a strongly significant correlation with the scores of post-treatment logical memory I ($r = 0.593$; $p < 0.0001$) and post-treatment logical memory II ($r = 0.630$; $p < 0.0001$). There is also weak correlation with post-treatment recall of word list (ADAS-Cog), however this tendency is not significant. In conclusion, we see that improvement of the depressive symptoms is clearly associated with better memory performance after treatment. Given that, as we have seen previously, it is group A that has a clearer improvement, it is not surprising that it is also this group that has the highest scores on the tests.

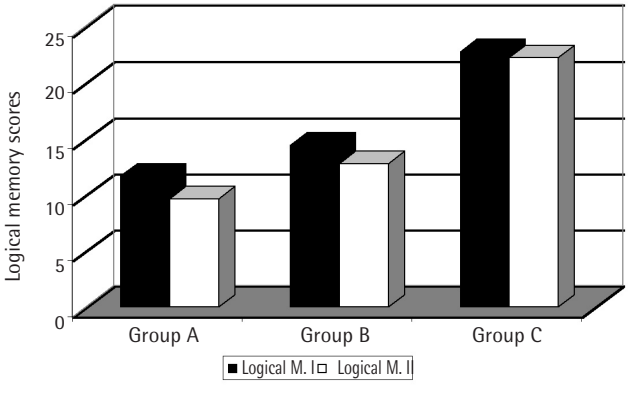

Figure 3 *Logical memory score before ECT treatment.*

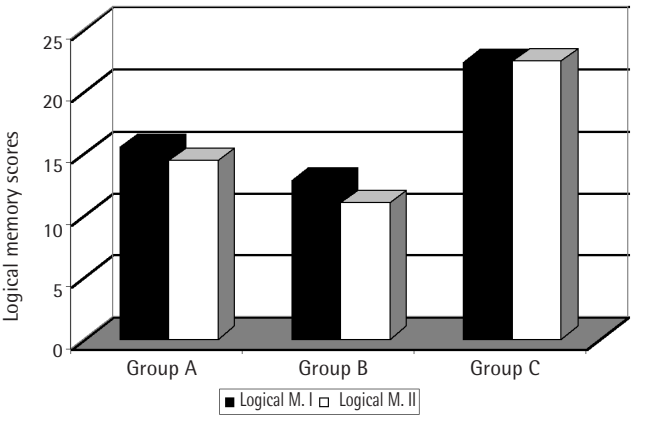

Figure 4 *Logical memory scores post-treatment.*

CONCLUSIONS

The results of the study allow for three fundamental conclusions. In the first place, it seems to be demonstrated that ECT, combined with maintenance drug treatment, produces much greater improvement of the depressive symptoms than purely drug treatment. Closely linked to this finding, we found that patients receiving ECT have higher values in the memory tests after treatment if we compare them with group B. This means that our initial hypothesis, that proposed the non-existence of differences attributable to the treatment between the depressive patient groups, has not been confirmed. In addition, we could verify that the performance levels in the memory tests conducted after treatment, especially in the case of the Logical Memory test, are closely related with improvement of depressive symptoms. Thus, it is understandable that those patients who have achieved a more important improvement (group A) obtain, on the average, higher scores in the memory tests than the group B patients. However, it is clear that there are other factors that may have an influence on the mnemic performance of the patients and should be discussed.

As we briefly mentioned in the Introduction, ECT is a safe and effective treatment for major depression, especially in cases that are treatment resistant or that have a psychotic component[20,21]. This has been demonstrated both in those studies that compare effectiveness of real ECT versus fictitious ECT (placebo)[22,23] and in studies that compare ECT effectiveness versus drug treatment. The second line of investigation is especially relevant here since our results coincide with many studies of this type. For example, the United Kingdom group for the review of ECT recently conducted a meta-analysis[24] in which they analyzed 18 studies that compared ECT efficacy versus drug treatment. The results of the analysis showed that ECT was more effective than drug ther-

apy. This could be quantitatively translated into differences of 5.2 points on the HDRS scale. ECT treatment has also been associated with a faster therapeutic response (which has lead to considering this technique as a prevention of suicide attempts), although relapses are also more frequent[3]. However, there are not too many data supporting improvement of mnenic performance after ECT treatment. Prudic et al.[25] observed subjective improvement of memory in their patients after ECT treatment, an improvement that correlated with the grade of relief of depressive symptoms. These results coincide with those presented herein, although in our case, improvement has been measured by objective memory tests. Depression is a disease in which it is especially difficult to differentiate the cognitive disorders produced by the treatment from those caused by the disorder itself. The classical studies of Stenberg[26] objectively demonstrate that depression causes memory alterations, but also that improvement of the clinical state due to antidepressive treatment would produce a significant increase in performance. More recently, Deuschle et al.[27] concluded that the positive clinical response to antidepressants was associated with improvement of declarative memory, although this was produced slowly. Considering the similarity between these results and those obtained in our study, can we venture the existence of a common action mechanism of ECT and pharmacotherapy that associates clinical improvement and mnemic improvement? In fact, a very recent investigation with primates of Strome et al.[5] demonstrates that ECT down-regulates 5-HT_2 receptors, that follows a pattern identical to those observations already made by the clinicians on their patients: the effect appears with only a few treatments (even with only the first), which would be translated into a very rapid improvement of the mood state. However, after the completion of the sessions, the situation of the 5-HT_2 receptors also returns to their initial condition very rapidly. Thus, if maintenance treatment is not prescribed, relapse is almost unavoidable. According to these authors, the results of their study would speak about a general action mechanism of the antidepressant treatments, that would be the regulation of the 5-HT_2 receptors.

However, the limitations of the study do not allow us to state that the long term differences in episodic memory found in the two patient groups are due exclusively to ECT treatment. An additional factor that should be considered is that the maintenance treatment is not identical in both groups. As we have seen, the clinical state of the group A patients is significantly greater and this improvement occurs more rapidly than in the group B. This means lower doses of maintenance drugs or even the withdrawal of some of them. This fact is important both in the case of antidepressants and especially in the case of benzodiazepines. It is known that antidepressants may affect cognitive function and that this affectation is more likely as the patients' age increases. If we analyze this effect in greater detail, it seems that MAOI and SSRI produce fewer alterations while those having greater anticholinergic potential (amitriptyline, nortriptyline, maprotiline, etc.) would be associated with attention and concentration difficulties and memory disorders[28]. The harmful effect on memory is even better known in the case of the benzodiazepines[29-31]. These have a potential dose-dependent amnesic effect that would affect, to a larger degree, the tasks required for long-term recovery of new information learned, leaving the capacity to form short-term memories relatively intact. We could thus hypothesize that the lower performance of group B would not only be due to a slower clinical improvement but also to the possible adverse effect of drugs that affect mnemic performance. In any case, the possibility of avoiding long term drug treatments at relatively high doses would be another positive aspect of ECT that we should take into account.

In conclusion, we can state that ECT treatment followed by maintenance drug treatment does not cause negative affects on episodic memory and even that the rapid and significant clinical improvement of the patients is associated with better cognitive performance, at least if we compare it with patients who are treated exclusively with drugs. However, this study has only considered the capacity of the patients to form new memories (anterograde memory), but not the capacity of them to recover past events (retrograde memory). The fundamental complaint of some patients after following ECT treatment is that certain autobiographical events of their past have been «erased», which affects their daily life. Given the difficulty to evaluate objectively this type of memory, specific studies that evaluate this problem and that certify definitively the harmlessness of ECT treatment should be conducted.

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