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LONG-TERM EFFICACY OF ELECTROCONVULSIVE THERAPY COMBINED WITH DIFFERENT ANTIPSYCHOTIC DRUGS IN PREVIOUSLY RESISTANT SHIZOPHRENIA

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SUMMARY

Background: *In treatment-resistant schizophrenia a combination of ECT with antipsychotics has been reported to have superior outcomes compared to other strategies, however the results were inconsistent. We investigated the long-term effects of the combination of unilateral, non-dominant hemisphere ECT with three antipsychotics.*

Subjects and methods: *The clinical study was a naturalistic, prospective, open-labeled, active-controlled study in adult outpatients of both genders suffering from treatment-resistant schizophrenia with a follow up of 2 years. The patients received sulpiride (n=17, 100-400mg/day, PO), risperidone (n=26, 2-8mg/day, PO) or olanzapine (n=27, 5-10mg/day, PO). Unilateral ECT was applied in 1 unit (0.5A, 0.8 mS) in six single applications, once a week and further according to the clinical need, in fortnight steps. Clinical efficacy was established using the PANSS and CGI psychometric scales.*

Results: *According to the results, the most effective treatment mode was olanzapine plus ECT, then risperidone plus ECT, while sulpiride plus ECT had lower clinical efficacy. Olanzapine plus ECT was significantly superior in all scale scores vs sulpiride plus ECT, as well as risperidone plus ECT except for PANSS-P (t=1.85, p>0.05). During the study, 38 of 70 patients were withdrawn due to treatment failure (n=21), side effects (n=6) and non-compliance (n=11).*

Conclusion: *The combination of novel antipsychotics and ECT can be used safely and effectively in treatment-resistant schizophrenia.*

Key words: *schizophrenia – ECT – antipsychotics - combination*

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INTRODUCTION

The results of ECT may sometimes be controversial but they are usually favourable in proper indications. It is an undisputable fact that ECT has good effects on many mental disorders (Lévy-Rueff et al. 2008, Lisanby 2007), but we are interested in schizophrenia because drug treatment is not fully effective (Lieberman et al. 2005). The ECT mechanism of action is multidimensional. At first, ECT has a primary focus on monoamine in the area of action on neurotransmitters and peptidergic substances. ECT stabilizes beta-adrenergic receptor systems in a pattern of down-regulation. Furthermore, it leads to an increased density of 5-HT2 receptors. All these neurotransmitter systems are also the targets of antipsychotic drugs, particularly the novel ones. As for the key neurotransmitter, dopamine (Yoshida et al. 1998), the results are rather controversial mostly indicating increased dopaminergic function after ECT. This is an underlying action for therapeutic effects in Parkinson's disease, but it does not help clarify the effect of ECT in patients with schizophrenia and other psychotic illnesses for which dopaminergic antagonism is presumed to be critical, at least in some brain regions. It important to mention that ECT increases mixed gabaergic activity and up-regulates adenosine receptors, and that it blocks anticonvulsant effects of opioid

antagonists (Borowicz et al. 2005). More recent preclinical research reports the connection between ECT and neuropeptides and growth factors. These are increased after a single ECT and after repeated ECT sessions, down-regulation has been observed. There is also an interest in finding find the connection between these observations and distinct neuroplasticity in the same brain regions e.g. the hippocampus due to ECT (Banerjee et al. 2005). Wide variations of other neurotransmitters, neuromodulators and neuropeptides (somatostatin, cholecystokinin, precursors of opiates, thyroid hormones), as well as second-messengers, transcription regulation and genetic expression factor substances in diverse brain areas have been also noted. The neurophysiologic approach presents one of the most important parameters of assessment of ECT efficacy. Increases in global cerebral blood flow and cerebral metabolic rate parallel the increase in blood-brain barrier permeability during generalized seizures, including the electrically-induced ones (Vangu et al. 2003). Patients responding to ECT have a post-ictal decrease in cerebral blood flow as well as a slow-wave EEG activity in some prefrontal regions which is not found in non-responders. These changes depend on the manner of the ECT application technique. For example, unilateral ECT (used in our study) causes a reduction of CBF in the anterior brain areas while bilateral ECT targets primarily the site near the prefrontal pole.

Antipsychotic drugs are still the first therapeutic choice in schizophrenic patients. However, in highly treatment-resistant cases the combination of ECT and some antipsychotic drugs has been reported to have superior outcomes to other strategies (Chanpattana & Chakrabhand 2001). On the other hand, some studies reported beneficial effects in the first few weeks of treatment initiation probably due to response acceleration (Painuly & Chakrabarti 2006). The recent Cochrane Systematic Review confirmed that the combination of ECT and antipsychotics is an effective treatment mode for rapid and global symptoms improvement and in the cases of suboptimal response to medications (Tharyan & Adams 2005). There are still not many details about this treatment mode - the most optimal drug, its dose and dosing schedule, the type of ECT technique and ECT dosing regime as well as the long-term effects. The majority of the published reports were on conventional antipsychotic drugs and all the studies published in the last 25 years or so included no more than 1,500 patients (Braga & Petrides 2005). Among atypical antipsychotic medications, clozapine is most frequently combined with ECT with either unilateral or bilateral placement (Kho et al. 2004).

Taking unresolved issues into consideration, we investigated the long-term effects of the combination of unilateral, non-dominant hemisphere ECT with four antipsychotic drugs, one typical, two atypical and one of borderline pharmacological profile.

SUBJECTS AND METHODS

The clinical study was prospective, open-labeled, active-controlled. It studies outpatients suffering from schizophrenia and follow up was for 2 years. Inclusion criteria were: adult age from 18 years on, both genders, diagnosis of schizophrenia established by means of Structured Clinical Interview for DSM-IV (First et al. 1997), treatment resistance, presence of positive and negative symptoms and the absence of contraindications for ECT and/or the drugs under study. Exclusion criteria were: age younger than 18, pregnant and lactating women, significant mental and/or somatic co-morbidity and refusal of the patient or her or his legal representative to participate in the study. The study was conducted during the period from 2004-2006 at the Psychiatric Clinic of the Clinical and Hospital Centre Kragujevac.

The allocation of the patients in three study arms followed a pragmatic (naturalistic) design as it has been reported to be suitable for researching the combined clinical effects of ECT and drugs, including atypical antipsychotics (Ucok & Cakir 2006). This means that the treatment allocation of the study subjects was governed only by the usual clinical practice criteria, not by the subjects' study status. In other words, the decision for ECT was made by a physician who was responsible for the treatment according to the indications above. In addition, the drugs were used in regulatory approved indications and dose regimens. Participation in the study was completely voluntary, and informed consent was obtained. The physical condition of the patients were also evaluated with electrocardiogram, laboratory tests, and physical examinations before, during and after the ECT sessions. The

study procedures were considered and approved by the ethical board of the Psychiatry Clinic.

Three drugs were used as active treatment as mono-therapy. The first group of patients received sulpiride orally, in dose range of 100-400 mg, daily. The second group received risperidone orally, in dose range of 2-8 mg, daily. The third group received olanzapine orally, in dose range 5-10 mg, daily. Doses of all the drugs were adjusted according to the clinical response. Daily doses were administered in one or more (generally in 2-3) doses. Other medications were used according to the clinical need, but no other antipsychotics were used in the period of 12 weeks before ECT application and after it during the study course. Allowed concomitant medication included benzo-diazepines, selective hypnotics, and antimuscarinic adjuvant drugs. Compliance to prescribed medication during the follow-up period was assessed at each visit by interviewing the patient and his/her relatives. If due to the clinical status, there was a need for a change of the antipsychotic drug and/or addition of antidepressant medication, lithium or anticonvulsive drugs (carbamazepine, valproic acid or lamotrigine), the patient was excluded from further follow-up.

ECT was applied unilaterally, over the non-dominant hemisphere. We did not use general anesthesia, as in other countries where ECT use is low and underused (Ikeji et al. 1999, Motohashi et al. 2004, Chanpattana et al. 2005). In addition, we had long lasting positive experience with this technique, which had been reported not to result in tissue damage (Ohaeri et al. 1992). ECT was administered by using a Siemens Convulsator-2077S. An ECT dose was delivered through the currents consisting of brief-pulses with a frequency of 50 Hz, width of 1.5 milliseconds, and mean stimulus duration of 2.2 ± 0.5 S. Convulsions were monitored during the course by clinical obser-vation. Motor seizure durations varied between 22 and 35 seconds. During the acute phase every patient received one series of ECT lasting six weeks, with two single applications per week. During continuation or maintenance phase thera-peutic goals were achieved primarily by adjusting the dose of an antipsychotic drug. If the patent experienced any kind of relapse the ECT was re-applied at fortnight intervals, until the therapeutic effects were achieved or the patient was excluded after three consecutive, unsuccessful ECT applications.

Clinical efficacy was assessed using well-established psychometric instruments (Timotijevic & Paunovic 1992) including: General Well-Being Scale-GWB (Fazio 1977, Norman et al. 2000), Positive and Negative Syndrome Scale-PANSS (Kay et al. 1987), and Clinical Global Impression Scale-CGI (Guy 1976). Assessment of the general status (GWB) was scored by a psychiatrist from 0 (the worst) to 110 (the best). The PANSS scale scores were used to assess positive symptoms (PANSS-P), scored from 7 (the best) to 49 (the worst), negative symptoms (PANSS-N) scored from 7 to 49 and general psychopathology (PANSS-G) scored from 16 to 112. The CGI scale was used to score: a) severity of illness (SI) which defined the severity of illness, from 1 (normal) to 7 (the most extremely ill), b) global improvement (GI), from 1 (very much improved) to 7 (very much worse) c) therapeutic effect (TE) from 1 (unchanged or worse) to 4 (vast improvement), and d) adverse effects (AE), from 1 (none) to 4 (outweigh therapeutic effect). Efficacy index (EI) was calculated by dividing the mean TE score with the mean AE score (EI=TE/AE). The scale scores were calculated at baseline, after 6, 12, 52 and 104 weeks. However, after the acute treatment phase, the patients were routinely followed every 6-8 weeks. All measures were collected by two trained raters. The safety of the treatment was evaluated by recording and assessing every adverse clinical event, particularly hematology reactions. The patients were withdrawn from the study when: no satisfactory clinical response was detected, serious adverse effects appeared or at the patient's own will.

The study data were tested by the methods of descriptive statistics and hypothesis testing (Altman 1991) using SPSS software version 8.0. The difference in scores between treatment groups was evaluated by t-test. Hypothesis testing was done by per-protocol analysis, by a two-sided procedure where the level of statistical significance was established at $p \leq 0.05$.

RESULTS

The main demographic and clinical properties of the patients were presented in Table 1. In

general, no heterogeneity among the treatment groups was found (p>0.05) and the groups were fully comparable according to the main clinical and demographic properties, at baseline.

Table 1. Demographic and clinical properties of the study population

Variable	Sulpiride group	Risperidone group	Olanzapine group
Number of subjects	17	26	27
Mean age at disease onset (range)	28.09 (19-38)	26.20 (20-33)	24.52 (19-32)
Mean age at study onset (range)	38.52 (21-56)	33.30 (29-53)	33.60 (24-55)
Gender (f/m)	10/7	12/14	10/17
Dominant negative symptoms	11	11	11
Dominant positive symptoms	6	15	16
ECT applications per year (n)*	2.5 (2-7)	1.9 (1-5)	1.2 (1-4)
Withdrawn (n)	10	14	14
Mean daily doses, mg (range)	294.52 (100-400)	6.23 (2-8)	6.82 (5-10)

*continuation and maintenance phase

According to the results of the psychometric instruments, the most effective treatment mode was olanzapine plus ECT, then risperidone plus ECT, while sulpiride plus ECT showed lower clinical efficacy. The results of psychometric scores at the rating visits are presented in the tables 2 to 4 (table 2 for sulpiride, table 3 for risperidone, table 4 for olanzapine). The comparison of olanzapine with sulpiride showed greater efficacy of the former and statistical significance in the difference of all psychometric scores (figure 1 and 2). The t-test values of differences for mean absolute changes of psychometric scores between olanzapine (n=13) group and sulpiride group (n=7) at the final visit (from baseline to 104th week) for GWB, PANSS-P, PANSS-N, PANSS-G, and CGI-SI as well as CGI-GI and CGI-EI (from 6th week) were 2.91 (p<0.01), 2.87 (p<0.01), 2.52 (p<0.05), 2.27 (p<0.05), 2.85 (p<0.01), 3.24 (p<0.01), and 3.11 (p<0.01), respectively. The comparison of olanzapine with risperidone showed greater efficacy of the former and statistical significance in the difference of all psychometric scores, except for PANSS-P. The t-test values for the same scales (13 and 12 patients) were 2.23 (p<0.05), 1.85 (p>0.05), 2.27 (p<0.05), 2.11 (p<0.05), 2.07 (p<0.05), 3.14 (p<0.01) and 2.83 (p<0.01).

During the study, 38 of 70 patients were withdrawn due to treatment failure (n=21), side effects (n=6) and non-compliance (n=11). There were no unexpected adverse effects either from the drug or ECT treatment arm, including serious adverse events. Most of adverse effects were of mild to moderate intensity and therefore well tolerated by the patients who completed the study, e.g. extrapyramidal reactions, autonomic and metabolic disturbances. These adverse effects were managed according to usual clinical practice by dose titration or inclusion of adjuvant drugs (e.g. anticholinergic drugs in the case of extrapyramidal reactions) as needed.

During the initial study phase (about six weeks) all the patients were compliant. If, later in the study, patients did not follow the treatment directions for at least a month, they were excluded due to non-compliance.

Table 2. The psychometric scores in sulpiride plus ECT group

Weeks	GWB	PANSS-P	PANSS-N	PANSS-G	SI	GI	EI
0 (17)*	29.99±8.70	33.45±9.70	23.22±6.50	55.88±14.28	4.93±1.23	-	-
6 (17)*	49.12±12.28	24.68±6.91	13.33±3.47	32.29±8.20	3.28±0.72	2.85±0.60	0.87±0.25
12 (14)*	51.1±13.29	20.77±4.98	12.57±2.77	27.52±7.66	3.17±0.73	2.77±0.61	1.50±0.38
52 (11)*	50.15±13.54	20.68±5.17	11.11±2.67	24.83±5.46	3.12±0.78	2.89±0.78	1.71±0.41
104 (7)*	50.86±11.19	21±5.67	11.99±2.40	25.13±6.03	3.27±0.65	2.88±0.58	1.66±0.38

*(number of patients); the values represent the mean (± standard deviation); GWB-assessment of general status, PANSS-P-positive symptoms, PANSS-N-negative symptoms, PANSS-G-general psychopathology, SI-severity of illness, GI-global improvement, EI-Efficacy index

Table 3. The psychometric scores in risperidone plus ECT group

Weeks	GWB	PANSS-P	PANSS-N	PANSS-G	SI	GI	EI
0 (26)*	29.94±8.08	34.17±9.67	23.37±6.78	55.78±15.62	4.95±1.39	-	-
6 (26)*	57.44±13.79	18.78±4.88	12.72±3.53	30.78±9.23	3.06±0.84	2.91±0.79	0.96±0.27
12 (20)*	59.14±15.56	15.78±3.91	11.91±2.76	22.99±5.92	3.00±0.71	2.68±0.70	1.83±0.48
52 (17)*	59.44±16.05	15.64±3.42	11.38±2.88	21.84±5.90	2.98±0.67	2.62±0.60	2.21±0.53
104 (12)*	62.22±12.42	15.55±3.31	10.29±2.80	20.81±5.85	2.95±0.62	2.6±0.55	2.41±0.46

*(number of patients); the values represent the mean (± standard deviation); GWB-assessment of general status, PANSS-P-positive symptoms, PANSS-N-negative symptoms, PANSS-G-general psychopathology, SI-severity of illness, GI-global improvement, EI-Efficacy index

Table 4. The psychometric scores in olanzapine plus ECT group

Weeks	GWB	PANSS-P	PANSS-N	PANSS-G	SI	GI	EI
0 (26)*	29.22±8.27	33.09±9.60	24.17±7.25	56.11±16.27	4.92±1.23	-	-
6 (26)*	56.9±14.23	19.02±5.71	12.18±3.41	30.85±7.01	2.82±0.79	2.80±0.73	0.94±0.25
12 (20)*	63.41±14.15	15±3.85	9.93±2.45	20.69±5.79	2.78±0.75	2.40±0.60	2.10±0.50
52 (17)*	64.32±17.04	14.66±3.84	9.22±2.21	19.88±4.57	2.74±0.63	2.29±0.55	2.66±0.53
104 (13)*	65.55±13.95	14.23±3.52	9.2±1.84	19.23±5.19	2.70±0.57	2.01±0.46	2.94±0.59

*(number of patients); the values represent the mean (± standard deviation); GWB-assessment of general status, PANSS-P-positive symptoms, PANSS-N-negative symptoms, PANSS-G-general psychopathology, SI-severity of illness, GI-global improvement, EI-Efficacy index

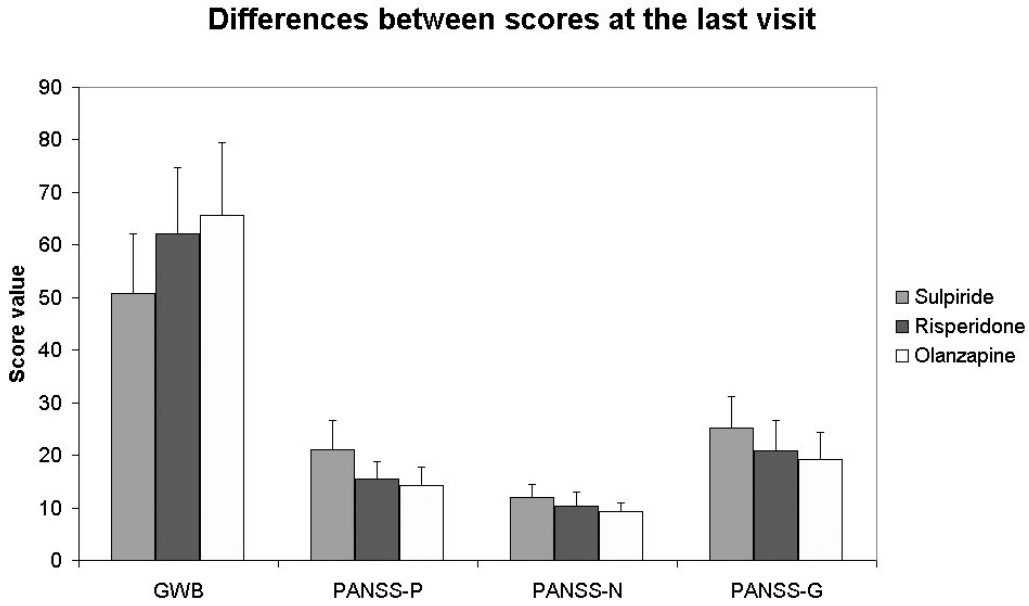

Figure 1. Differences between treatment group in final scores of General Well-Being Scale (GWB) and Positive and Negative Syndrome Scale (PANSS) for positive symptoms (PANSS-P), negative symptoms (PANSS-N) and general psychopathology (PANSS-G). Vertical bars represent standard deviations.

DISCUSSION

The results of our study suggest that, besides clozapine, other atypicals, such as risperidone and olanzapine, might be beneficial in treatment resistant schizophrenia in combination with ECT applications. Furthermore, these drugs are very safe in usual clinical practice, which is very important both for the patients and the clinicians. Olanzapine and risperidone are also more effective than the older drug, sulpiride. The patients recovered more rapidly in terms of the following clinical modalities: reduction of general psychopathology, positive symptom, and negative symptom amelioration. Although sulpiride was effective in some patients, in a substantial number of subjects it was not tolerated due to the side effects profile.

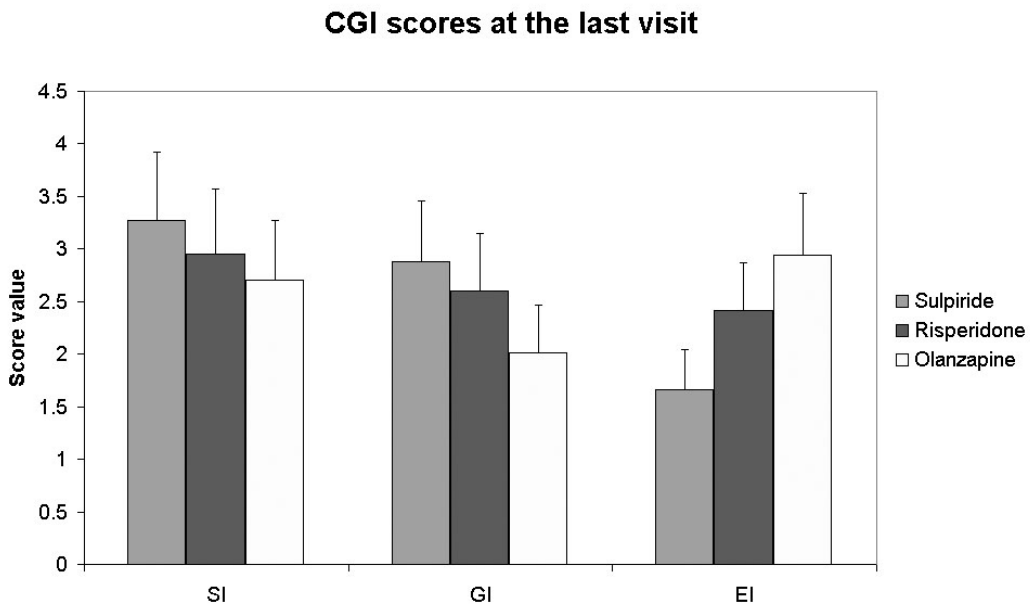

Figure 2. Differences between treatment group in final scores of Clinical Global Impression Scale-(CGI) for severity of illness (SI), global improvement (GI) and efficacy index (EI). Vertical bars represent standard deviations.

To the best of our knowledge, studies which compared older and novel antipsychotics in combinations with ECT in treatment resistant schizophrenia are rare. In a prospective trial that included thirty patients, a half of them received ECT sessions while the others were in the control group. Although there was a tendency for ECT to reduce positive and negative symptoms, the rate of improvement did not reach statistically significant levels. The addition of risperidone or olanzapine to ECT sessions had marginal augmentation efficacy (Tang & Ungvari 2003). However, these results can not be directly compared to our study results. We had a larger study sample and much longer follow-up (2 months vs 2 years). In another study, ten aggressive schizophrenic patients received very intensive ECT therapy (five sessions during a week) in combination with risperidone. The results of the study showed that this combination was very effective in both groups of aggressive schizophrenic patients either with predominantly positive or negative symptoms (Hirose et al. 2001). These results confirmed our conclusion, although there were some differences in design concerning inclusion of patients with different clinical characteristics, very intensive ECT courses and much shorter follow-up.

In a case report, a combined use of ECT and olanzapine was effective in the treatment of a young man with chronic and refractory catatonic stupor. In this patient, experiencing all characteristics of schizophrenic resistance, electroconvulsive treatment together with olanzapine dramatically improved social functions (Tan et al. 2006). In the meta-analysis of eleven studies and 4 controlled trials with about 750 patients in total, it was shown that the combination of antipsychotics and ECT achieved clinically meaningful results after 4-5 weeks (Painuly & Chakrabarti 2006). This is very similar to our results. Our patients significantly improved in all psychometric modalities after 6 weeks treatment.

Catatonic treatment resistance patients responded to a combination of ECT and neuroleptic drugs in the long term treatment phase of 48 weeks but relapse rate was very high, 63.6% at 1 year **(**Suzuki et al. 2004**)**, which is much more than in our study. However, these differences could be the result of a smaller sample, older age (in the middle of fifth decade) and specificity of catatonic schizophrenia, not present in our study.

Besides clinical effectiveness, the combination of antipsychotics and ECT was very safe in our patients. Some authors reported accidental serious adverse events, such as ventricular arrhythmias (Greene et al. 2000) and non-convulsive generalized epileptic status (Srzich & Turbott 2000). Most adverse effects in our study were of

mild to moderate intensity with predominance of extrapyramidal reactions, autonomic and metabolic disturbances. We had no serious adverse events probably because of carefully titrated doses of antipsychotic drugs and ECT doses.

In most of the studies conducted so far, typical antipsychotics were used and ECT was applied bitemporally (Braga & Petrides 2005). However, in our study, we used two additional atypical, unipolar placements and the electrical doses were lower. Clozapine was dominant among atypical antipsychotics, but we also gained some experience in application of other novel medicines, like olanzapine and risperidone. Despite the differences, our conclusions coincide with those obtained in earlier studies, in the sense that this combination presents a safe and efficacious treatment for patients with schizophrenia. In addition, the combined treatment also improves the long-term outcomes as confirmed by others (Chanpattana & Andrade 2006).

CONCLUSION

Our results showed that the combination of antipsychotics and ECT could be used safely and effectively in the treatment of resistant schizophrenia. Novel atypical drugs might be more convenient than older neuroleptic drugs. However, before their introduction into routine clinical protocols, our findings should be confirmed by further studies – randomized, with larger samples, double blind designs and variation of ECT techniques and drug doses.

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