

## SAFETY OF THE ELECTROCONVULSIVE THERAPY AND AMISULPRIDE COMBINATION

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### SUMMARY

**Background:** Electroconvulsive therapy is frequently considered when pharmacotherapy is ineffective. In such cases the combination of the two treatment modalities are commonly used. Amisulpiride, a second generation antipsychotic drug is used in the treatment of schizophrenia and psychotic depression. When amisulpiride is ineffective as a monotherapy, combination with ECT could be an option to enhance its efficacy. To the best of our knowledge, to date there have been no data about the safety of this combination.

**Subjects and methods:** Medical notes of all patients who were given ECT while on amisulpiride were selected from the archives of the Department of Psychiatry, Semmelweis University Medical School, Budapest, covering a 10-year period. A randomly selected matched control group was formed from patients who underwent ECT but were not taking amisulpiride. Patients in both groups also received a variety of psychotropic drugs other than amisulpiride. Side effects were compared between the two groups of patients.

**Results:** Twenty patients received amisulpiride with ECT. The most common side effects were headache, hypertension, tachycardia, nausea, dizziness, confusion, psychomotor agitation, sialorrhea, and prolonged seizure activity. All adverse effects resolved within 24 hours. No side effects of any kind were observed in 7 and 8 cases in the study and control groups, respectively.

**Conclusions:** This was the first study that examined the safety of amisulpiride-ECT combination in schizophrenia. Comparing the side-effects between the study and control groups, no significant differences were detected in terms of their types or frequency. The amisulpiride-ECT combination appears to be a safe treatment option.

**Key words:** electroconvulsive therapy – amisulpiride - side-effects - safety

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### INTRODUCTION

The main indications of electroconvulsive therapy (ECT) are affective disorders (mainly depression) and certain clinical features of schizophrenia (Gazdag et al. 2009a, Zervas et al. 2011, Moksnes & Ilner 2010, Gazdag et al. 2009b). ECT as monotherapy has been effective in the treatment of major depression (Bailine et al. 2010) and is recommended by most influential guidelines (American Psychiatric Association 2001, Royal College of Psychiatrists 2005) although in clinical practice combination of ECT with pharmacotherapy is quite common (Ravanić et al. 2009).

In all international recommendations published in the last ten years, second generation antipsychotics (SGA) are considered as first-line treatment in psychotic disorders, mainly due to their favorable safety profile (American Psychiatric Association 2004). Amisulpiride, a substituted benzamide, is a SGA with unique pharmacological properties and therapeutic profile. Due to its effect of "dual dopamine blockade", amisulpiride acts as an antipsychotic at high doses while it has a disinhibitory action at low doses which explains its effectiveness in both positive and negative symptoms of schizophrenia and as well as in depression (Wetzel et al.

1998, Danion et al. 1999, Smeraldi 1998, Lecrubier et al. 1998). Most common side effects of amisulpiride include sleep disturbance, anxiety, agitation (5-10%), drowsiness, constipation, nausea; vomiting and dry mouth (2%) can also appear (Green 2002). Prolongation of the QTc interval (Stöllberger et al. 2005) and bradycardia (Pedrosa et al. 2001) could also occur with amisulpiride, but these are rather rare.

The largest study reporting on the combined treatment of ECT and different classes of antipsychotic drugs included 455 patients (Nothdurfter et al. 2006). No difference in clinical efficacy was found between ECT monotherapy and the ECT-first generation antipsychotic (FGA) combinations. Furthermore, no clinically meaningful differences in side effects were found between ECT monotherapy and ECT-FGA or ECT-SGA combinations (Nothdurfter et al. 2006). As for the epileptogenic properties of the SGAs, olanzapine and clozapine lower seizure threshold, whereas quetiapine could increase it (Gazdag et al. 2004). A higher risk is associated with the clozapine-ECT combination in terms of development of spontaneous seizures (Pisani et al. 2002) and prolongation of seizure activity (Bloch et al. 1996, Masiar & Johns 1991), although the latter could be clinically insignificant (Cardwell & Nakai 1995).

In a sample of 15 patients with treatment-resistant schizophrenia, no adverse effects were observed with ECT-olanzapine or ECT-risperidone combinations; in only one case was asymptomatic ST elevation detected in the V3, V4 ECG leads after the second ECT session (Tang & Ungvari 2002). A few case reports attest to the safe administration of ECT together with ziprasidone (Masdrakis et al. 2010) or aripiprazol (Masdrakis et al. 2008).

To the best of our knowledge, there are no data about the safety of the ECT and amisulpride combination. Thus, the aim of this study was to assess the safety of this treatment option.

## SUBJECTS AND METHODS

This was a chart review of patients who received ECT at the Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, between 2000 and 2010. The medical notes of patients who were given ECT while on amisulpride – singly or in combination with other psychotropic drugs – were selected and analyzed. As amisulpride can only be used in the treatment of schizophrenia in Hungary, all patients had a diagnosis of schizophrenia which was established according to ICD-10 criteria. A randomly selected control group matched according to age, sex and diagnosis was formed comprising patients who underwent ECT at the same Department during the study period but did not receive amisulpride. Side effects and adverse events during the course of ECT that appeared in association with the combined treatment were analyzed and compared between the two groups.

The statistical analysis was performed with the SPSS 11.5 Package (Statistical Package for Social Sciences, Chicago, IL, USA). Descriptive data are presented with means, confidence intervals and standard deviations. If the distribution of the variables was normal, data were compared with t-tests; in case of non-normal distribution (dose of clonazepam, number of sessions, number of restimulations) with Mann-Whitney U-tests.

The practice of consenting to ECT in Hungary conforms to international standards (Gazdag et al. in press).

## RESULTS

Before commencing the course of ECT, all patients received pharmacotherapy in adequate doses and for adequate length without noticeable improvement. ECT was administered with a Thymatron DGx device delivering constant-current, brief-pulse, bi-directional square-wave impulses with bilateral frontotemporal electrode placement for all patients. After premedication with atropine (0.5 mg iv.), propofol (1 mg/kg) and succinylcholine (0.5–1 mg/kg) were used for sleep induction and muscle relaxation, respectively. Seizure activity was monitored with EEG and EMG.

Over the 10-year period, 222 patients were treated with ECT; in 182 cases (82%) ECT was administered in combination with antipsychotic drugs. Twenty patients received amisulpride with ECT. The mean age of the study and control groups was  $43.2 \pm 15.1$  and  $43.3 \pm 15.2$  years, respectively; 10 patients (50%) were female in each group. The mean daily dose of amisulpride was  $745 \pm 258$  mg (range: 200–1200 mg). The mean daily dose of the most commonly used sedative drug, clonazepam was  $2.8 \pm 1.6$  mg (range: 2–6 mg) and  $2.0 \pm 0.0$  mg in the study and control groups, respectively ( $p=0.30$ ). Additional psychotropic drugs taken in the study group included clozapine (13 cases), clonazepam (6 cases), haloperidol and lithium 5 cases each, lamotrigine and alprazolam 2 cases each, and quetiapine, cisordinol, olanzapine, citalopram, sertraline, mirtazapine, paroxetine, reboxetine, sodium valproate and biperiden, 1 case each. In the control group the number of concomitant medications was clonazepam (12 cases), clozapine (8 cases), haloperidol (7 cases), lithium (6 cases), risperidone, sodium valproate and quetiapine 3 cases each, olanzapine, zuclopenthixol, alprazolam, bupropione, paroxetine, lamotrigine, mirtazapine and biperiden 1 case each.

ECT was administered twice a week. There was no significant difference regarding the number of sessions ( $p=0.41$ ), number of repeated stimulations ( $p=0.36$ ), seizure threshold ( $p=0.24$ ), and the mean seizure duration measured with EEG ( $p=0.19$ ) and EMG ( $p=0.07$ ) between the two groups. The mean stimulus doses in the study and control groups were 140.5 mC (CI: 54.6–204.9, SD: 43.5) and 159.9 mC (CI: 75.6–352.8, SD: 58.4), respectively. Seizure threshold was determined with dose titration.

**Table 1.** Frequency of the side-effects in the study and control groups

Side-effects	Amisulpride-ECT group	Control group
Headache	5	2
Hypertension	4	6
Tachycardia	1	4
Nausea	1	0
Dizziness	0	1
Confusion	2	1
Psychomotor agitation	1	2
Seizure prolongation	1	1
Sialorrhoea	1	0

The most common side effects were headache, hypertension, tachycardia, nausea, dizziness, confusion, psychomotor agitation, sialorrhoea, and prolonged seizure activity (Table 1). All were resolved within 24 hours. The number of side-effects is shown in Table 1. No side effects of any kind were observed in 7 and 8 cases in the study and control groups, respectively. No ECT course was interrupted or shortened because of

side effects. In the study group metamizole-Na was given for headache in 5 cases. In one case 1 mg of clonazepam was administered intravenously for prolonged seizure activity; the rest of the side effects were spontaneously resolved. In the control group metamizole-Na was given for headache in 2 cases and 25 mg of metoprolol for tachycardia on one occasion.

## DISCUSSION

The concomitant use of ECT and antipsychotic drugs raises the important questions of effectiveness and side effects. The majority of studies reported that the combined treatment was safe and effective although methodological shortcomings render this conclusion preliminary (Braga & Petrides 2005).

To the best of our knowledge, this was the first study that examined the safety of amisulpride-ECT combination. This treatment combination was well-tolerated in all 20 cases. Side-effects occurring during the combined ECT-amisulpride treatment were transient and mild. Comparing the side-effects between the study and control groups, no significant differences were detected in terms of their types or frequency. The amisulpride-ECT combination did not cause more or more severe side-effects even in high amisulpride doses. Cardiac and central nervous system side-effects should be paid particular attention (Sartorius et al. 2005) as they could appear more frequently with increasing age and could be more important in a larger sample.

The main limitations of this study include the retrospective design the relatively low number of cases, the concomitant treatment with other drugs, the relatively young age of patients and the lack of ECG monitoring.

## CONCLUSION

In conclusion, the amisulpride-ECT combination is safe; more accurately, adding amisulpride to other psychotropic drugs while administering ECT is safe in clinical practice.

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**Conflict of interest :** None to declare.

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