Short Communication

Alterations in the Prescription of Psychotropic Drugs After Electroconvulsive Therapy Immediately in Patients with Schizophrenia

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Keywords

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Abstract

Introduction: Electroconvulsive therapy (ECT) and antipsychotic polypharmacy (APP) have been utilized frequently for patients with schizophrenia, particularly for treatment-resistant cases in clinical practice. The prevalence of APP and high-dose antipsychotics is high in Japan, although they are associated with an increased risk for various adverse effects. The aims of this study were to evaluate the prescription patterns of antipsychotics and other psychotropic drugs before and after ECT in patients with schizophrenia.

Methods: This was a retrospective clinical chart review of 49inpatients with schizophrenia hospitalized at St. Marianna University School of Medicine Hospital in Japan. We reviewed the types of medication (antipsychotics, antiparkinsonian drugs, and benzodiazepines) and compared their dose before and after modified ECT (m-ECT).

Results: The mean dose of antipsychotics significantly decreased after m-ECT (risperidone equivalent; 11.0 ± 7.0 to 9.0 ± 3.7 mg/day; P=0.008). The mean number of antipsychotics significantly decreased from 2.1 ± 1.2 to 1.6 ± 0.6 (P=0.002). In addition, the mean dose of antiparkinsonian drugs significantly decreased after m-ECT (biperiden equivalent; 3.1 ± 1.7 to 1.8 ± 2.4 mg/day; P=0.007), although there were no significant changes in the mean dose of benzodiazepines.

Discussion: There was a significant decrease in the dose and number of antipsychotic drugs and in the dose of antiparkinsonian drugs after m-ECT. The results suggest that m-ECT may be a useful treatment option to optimize high-dose antipsychotics and antiparkinsonian drugs as well as APP in patients with schizophrenia.

INTRODUCTION

Schizophrenia for many patients is a lifelong mental disorder characterized by positive, negative, cognitive, and affective symptoms [1]. Current treatment of schizophrenia is mainly based on pharmacotherapy of antipsychotic drugs [2]. However, one fifth to one third of patients with schizophrenia experience persistent psychotic symptoms despite adequate trials of antipsychotic monotherapy [3,4]. This group of patients is defined as "treatment-resistant schizophrenia (TRS)", although its exact definition is controversial [5]. The use of combinations of 2 or more antipsychotics (antipsychotic polypharmacy; APP) has become an increasingly common treatment approach for patients with TRS [6].

Electroconvulsive therapy (ECT) has also been used for the treatment of schizophrenia since the 1930sand the efficacy of ECT for schizophrenia has been shown repeatedly [7]. The evidence-

based treatment guidelines for schizophrenia [6,8-11] generally recommend ECT as a third-line treatment option and APP only after clozapine or ECT has failed [12]. Currently, modified-ECT (m-ECT), specifically ECT with short acting anesthetic and muscle relaxant [13], combined with antipsychotic treatment may be considered a treatment option for certain cases of schizophrenia such as people with catatonic features [9,14] or TRS [6,15,16].

In a systematic review of 147 studies published between the 1970s and 2009, Gallego et al. [17,18], reported that a median APP prevalence rate was 19.6% and the highest prevalence was observed in Asia (32%) [17,18]. In East Asia, the prevalence of APP in inpatients with schizophrenia was highest in Japan (78.6%) [19]. In addition, excessive dosing of antipsychotics (e.g., risperidone equivalent doses of \geq 10mg) is highly prevalent in Japan [20-22]. Although the reasons for a higher APP rate in Japan are unclear, high-dose antipsychotics and APP are well known to be associated with an increased risk for various adverse effects

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[18,23].

In daily clinical practice, we often experience that excessive antipsychotic dosing and APP can be optimized after repeated m-ECT in patients with TRS. However, there is no clear evidence to show such effectiveness of ECT. Thus, the aims of this study were to evaluate the prescription patterns of antipsychotic drugs and other psychotropic drugs before and after m-ECT in patients with schizophrenia.

METHODS

This was a retrospective clinical chart review of all patients hospitalized at St. Marianna University School of Medicine Hospital in Japan. It was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the St. Marianna University School of Medicine Bioethics Committee.

We searched patients with schizophrenia who were treated with antipsychotics and adjunctivem-ECT in our hospital between April 2008 and March 2014. Eligible subjects were inpatients with a clinical diagnosis of schizophrenia and related psychoses according to criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) [24].

We reviewed clinical charts of patients. Information about pharmacological regimen, diagnosis, and demographic data such as sex and age was obtained from each patient's medical records. Among psychotropic drugs administered, we selected antipsychotics, antiparkinsonian drugs, and benzodiazepines, since antiparkinsonian drugs and benzodiazepines are often used in combination with antipsychotics [25]. The type and the dose of each psychotropic agent were recorded on the day of hospital admission and discharge. Daily doses of antipsychotics, antiparkinsonian drugs, and benzodiazepines were converted to equivalent daily doses of risperidone, biperiden, and lorazepam, respectively according to the literature [26]. We compared the number of antipsychotics and the dose of these psychotropic agents before and after m-ECT.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Japan Inc., Tokyo, Japan). All variables were tested for distribution normality using the Shapiro-Wilks normality test or Chi square test for goodness of fit. Differences in mean values before and after m-ECT were compared using paired t-tests and/or the chi-square test based on normal distribution of the data. All statistical tests were two-tailed, and a *P* value less than 0.05 was considered significant.

RESULTS

Patients' demographic and clinical characteristics

The study population included 49 patients. Patients' demographic and clinical characteristics before m-ECT are shown in Table (1).The mean age was 46.9 ± 15.8 years old and 24.5% were males. Thirty seven (75.5%) patients had schizophrenia. A total of 63.3% received APP. The mean daily dose of antipsychotics before m-ECT was 11.0 ± 7.0 mg/

Table 1: Baseline	demographic	and	clinica	characteristics	before
m-ECT.					
Gender (male/fema	le)		1	2 / 37	

Genuer (male/lemale)	12/3/			
Age ^a (years)		46.9 (15.8)		
Diagnosis:	Schizophrenia	3	7	
Schizoaffective disorder		12		
Antipsychotics:	monotherapy	18	(36.7%)	
	two	16	(32.7%)	
	three	10	(20.4%)	
four or more		5 (10.2%)		
Antipsychotic drug dose ^{a,b} (m	11.0 (7.0)			
Biperiden dose ^a (mg/day)	3.1 (1.7)			
Benzodiazepine dose ^{a,c} (mg/	2.1 (1.5)			
Abbreviations: SD: standard	deviation			
^a Values represent mean (S.D.).				
^b Risperidone equivalent dose.				
^c Lorazepam equivalent dose				

day (risperidone equivalent, range: 0.75-35.80 mg/day). The antipsychotic class distribution included second-generation antipsychotic (SGA) monotherapy (34.7%), first-generation antipsychotic (FGA) + SGA (32.7%), SGA+SGA (28.6%), FGA+FGA (2%), and FGA monotherapy (2.0%). Individual SGAs included risperidone (38.3%), olanzapine (27.7%), quetiapine (21.3%), zotepine (21.3%), aripiprazole (19.1%), blonanserin (19.1%), perospirone (6.4%), and paliperidone (6.4%). Individual FGAs included levomepromazine (38.9%), haloperidol (33.3%), nemonapride (22.2%), chlorpromazine (16.7%), bromperidol (11.1%), sulpiride (11.1%), pimozide (11.1%), fluphenazine (9.1%), andpropericiazine (9.1%). All patients had been hospitalized for at least 1 week before m-ECT was started.

Changes in the prescription of psychotropic drugs after m-ECT

The mean number of m-ECT was 9.5 (range, 1-30). All patients received with bilateral electrode placement and the initial stimulus dose was chosen with a formula-based method that considered age, and the energy level of treatment was titrated based on clinical response.

The mean daily dose of antipsychotics significantly decreased after m-ECT (P=0.008; from 11.0 ± 7.0 to 9.0 ± 3.7 mg/day) (Figure 1).The mean number of antipsychotics significantly decreased from 2.1 ± 1.2 to 1.6 ± 0.6 (P=0.002). Particularly, excessive APP (four or more antipsychotics) was not seen after m-ECT (from 10.6% to 0%; Figure 2). Furthermore, the mean daily dose of antiparkinsonian drugs significantly decreased after m-ECT (P=0.007; from 3.1 ± 1.7 to 1.8 ± 2.4 mg/day; (Figure 3). However, there were no significant changes in the mean dose of benzodiazepines after m-ECT (anxiolytics: P =0.53; from 1.6 ± 1.1 to 1.4 ± 1.3 mg/day, hypnotics: P =0.71; from 2.4 ± 1.4 to 2.5 ± 1.1 mg/day; (Figure 4).

DISCUSSION

To the best of our knowledge, this is the first study that examined alterations in the prescription of psychotropic drugs before and after ECT in patients with schizophrenia. The mean dose of antipsychotics and antiparkinsonian drugs as well as



Figure 1 Changes in the dose of antipsychotics before and after m-ECT. Changes in the dose of antipsychotics before and after m-ECT.

The mean dose of antipsychotics significantly decreased after m-ECT (risperidone equivalent; 11.0 ± 7.0 to 9.0 ± 3.7 mg/day, *P=0.008).



Figure 2 Changes in the number of antipsychotics before and after m-ECT. Changes in the number of antipsychotics before and after m-ECT. The mean number of antipsychotics significantly decreased from 2.1 ± 1.2 to 1.6 ± 0.6 (P=0.002).



m-ECT. Changes in the dose of antiparkinsonian drugs before and after m-ECT. The mean dose of antiparkinsonian drugs significantly decreased after m-ECT (biperiden equivalent; 3.1 ± 1.7 to 1.8 ± 2.4 mg/day, * P=0.007).

the mean number of antipsychotics significantly decreased after m-ECT. The results suggest that ECT may be a useful treatment option to optimize high-dose antipsychotics and antiparkinsonian drugs as well as APP in patients with schizophrenia.

All patients in this study were admitted to our hospital for the treatment of persistent psychotic symptoms despite adequate trials of antipsychotic monotherapy. We found that a



Figure 4 Changes in the dose of benzodiazepines before and after m-ECT. Changes in the dose of benzodiazepines before and after m-ECT. There were no significant changes in the mean dose of benzodiazepines (anxiolytics and hypnotics) after m-ECT.

total of 63.3% received APP and the mean dose of antipsychotics was excessively high before m-ECT. Indeed, the extremely high dosages of antipsychotics (e.g., risperidone equivalent doses of >30mg) were prescribed for some of the participants. Similarly, Kristensen et al., [12], reported that 72.2% of inpatients with TRS received APP who were ultimately treated with ECT in Denmark. Excessive dosing of antipsychotics and APP have been associated with increased side effect burden, including extra pyramidal symptoms (EPS), peripheral anticholinergic side effects, hyper prolactinemia, sexual dysfunction, hypersalivation, sedation/ somnolence, cognitive impairment, and diabetes [20,23], and greater financial costs [27]. Undoubtedly, caution should be paid on the use of extreme dosing in order to avoid such side effects and more serious adverse events (e.g., sudden death).

At present, there is no convincing evidence that APP is a more effective treatment approach than antipsychotic monotherapy in schizophrenia [28]. However, switching from APP to monotherapy may present considerable clinical challenges [29]. Some studies indicated that a subgroup of patients may exacerbate or discontinue antipsychotic treatment when switching from APP to monotherapy [29,30]. Thus, our results suggest that ECT may provide a possible chance of reducing excessive antipsychotic dosing and APP without worsening symptoms in patients with schizophrenia, particularly for treatment-refractory cases.

The precise reason why ECT could reduce antipsychotic dosing and number is unclear. It has been reported that long-term treatment with antipsychotics can induce dopamine D₂ receptor up-regulation, so-called dopamine super sensitivity, in patients with schizophrenia [31]. Although the mechanism of actions of ECT remains poorly understood, particularly with respect to antipsychotic effects [32,33], Cooper et al. [34], hypothesized that ECT can increase presynaptic dopamine release and induce postsynaptic D₂ receptor down-regulation, which ultimately results in improvement of psychotic symptoms. Taken together, it is possible that ECT ameliorates postsynaptic D₂ receptor super sensitivity induced by chronic treatment with antipsychotics. In fact, reduction of the dose of antiparkinsonian drugs was observed after ECT, suggesting the improvement of EPS after ECT. To confirm our hypothesis, further longitudinal studies using positron emission tomography are warranted to evaluate the D₂ receptor density during the course of ECT in patients with schizophrenia.

There are several limitations in this study. First, this research is a retrospective chart review and we did not evaluate changes in psychiatric symptoms, adverse events, or functioning before and after m-ECT. Second, the sample size was small and this study contained heterogeneous characteristics of patients on different treatments. It is thus unclear whether the present results are potentially generalizable to patients with schizophrenia in the real-world settings. Third, a control (sham-ECT) group was not set in this study. Thus, the changes in the prescription of psychotropic drugs observed after ECT may be attributed to other confounding factors, such as duration of untreated psychosis or remission after drug treatment itself, in addition to an ECT effect. Our results will require replication in a larger cohort and a prospective study.

Despite these limitations, this study provides the first evidence that ECT may be a treatment option that clinicians should consider to improve APP and/or antipsychotic excessive dosing. Further studies are needed to search optimal strategies of reducing antipsychotics during ECT.

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