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Optimization of psychopharmacotherapy for schizophrenia in a male, locked, non-acute unit serving for persistently ill patients over one year

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ABSTRACT

We describe real-world psychopharmacological treatment in a Japanese, male, closed psychiatric unit where clozapie was still unavailable. Fifty-five persistently-ill patients with schizophrenia (ICD-10), mean ± S.D. age: 57.5 ± 13.0 y.o., duration of illness and admissions: 30.9 ± 15.2 years and 20.7 ± 14.5 years, respectively) treated longitudinally were evaluated. The rule was to treat with a simplest possible psychotropic regimen without polypharmacy. Compared to the baseline, the number and dose of antipsychotics were reduced from 1.9 to 1.1 and 1012 mg/day to 607 mg/day, respectively. The number of total psychotropics was minimized from 4.7 to 2.1, with a simplified once or twice daily dosing. Overall, the CGI-Severity and FACT-Sz (global functioning) improved slightly from 5.8 to 5.5 and 28.7 to 32.6, respectively. Of note, no patients got worse in comparison with the baseline clinical presentation. Forty-four patients were successfully treated with a single antipsychotic; only seven needed two antipsychotics simultaneously while 36 had been treated with antipsychotic polypharmacy at baseline. Benzodiazepines (mostly lorazepam) and antiparkinsonian drugs were prescribed in 28 and only two, respectively. Nineteen needed adjunctive valproate (average blood levels: 99.3 ± 21.8 μg/mL) and nine used lithium (0.61 ± 0.26 mEq/L). Optimization of psychopharmacotherapy is still possible for difficult-to-treat patients and, while augmentation of an antipsychotic with mood stabilizers is frequently needed, antipsychotic polypharmacy should be exceptional.

1. Introduction

Antipsychotic polypharmacy (or using two or more antipsychotics concurrently) has been frequently utilized for patients with schizophrenia although evidence in favor of such mode of treatment is still scarce and equivocal at best (Correll et al., 2009; Dold and Leucht, 2014). Nevertheless, in the real-world, many patients remain refractory to treatment with a single antipsychotic agent and are indeed treated with other psychotropic medications such as benzodiazepines and mood stabilizers (Procyshyn et al., 2010; Tor et al., 2011; Xiang et al., 2012b) despite limited evidence-base (Basan et al., 2004; Leucht et al., 2007; Gillies et al., 2013).

Clozapine is an option for patients with treatment-resistant schizophrenia (TRS), which has usually been defined as a failure to respond to two different antipsychotics for sufficient period of time at sufficient doses (Kane et al., 1988; Suzuki et al., 2012), and is usually positioned as the third choice medication in the treatment algorithm (Moore et al., 2007). However, clozapine use in reality is not without challenges; use of clozapine is known to be delayed substantially on many occasions and a number of patients indeed refuse or stop the medication for a variety of reasons (Howes et al., 2012; Davis et al., 2014). Evidence is still scarce for those who are persistently sick but cannot take clozapine. In this context, more data are sorely needed for those who are difficult-to-treat with currently available psychotropic agents.

We previously reported on a possibility of psychopharmacological optimization even for those with schizophrenia who deemed challenging to treat in the absence of clozapine in a series of

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publications (Suzuki et al., 2003, 2004a, 2004b, 2005, 2007, 2008a, 2009) and thought replication of our prior experiences in a real-world clinical setting is important. Therefore the purpose of this paper was to shed light on optimal psychopharmacological treatment in a Japanese closed unit serving for persistently and severely ill, male psychiatric patients over 1 year where clozapine was still unavailable.

2. Methods

This is a retrospective study in which naturalistic treatment in a single ward for 1 year was reviewed. The study was approved by the institutional review board of Inokashira Hospital in Tokyo, Japan, which has a total of 659 beds exclusively for psychiatric patients. The unit investigated herein has 62 beds and is a male, locked, and non-acute one serving for persistently and severely ill patients in serious needs (note that many of acutely ill but responsive patients are discharged directly from acute wards). Psychopharmacotherapy of patients with schizophrenia who gave informed consent and who were treated for more than 3 consecutive months in the unit during the fiscal year (F.Y.) 2013 (April 2013 through March 2014) was critically evaluated. Those treated for 3 months or less were excluded as they were transferred to other units for administrative reasons or discharged prematurely, all without attaining clinical stability in a reasonable manner for this sort of patients.

Psychopharmacological treatment represented a case-by-case judgment without any restrictions imposed in order to reflect the best interests for clients; however, every effort was made to simplify medication regimens with newer antipsychotics (Suzuki et al., 2004a) and avoid irrational polypharmacy (Suzuki et al., 2004b) as well as high-dose therapy (Suzuki et al., 2003), while at the same time offering a safe treatment environment for all patients as well as for treatment staff. Clozapine was unavailable in the unit at the time of the investigation; in light of past (albeit limited) evidence and experiences, a choice upon non-response usually included antipsychotic switching (Suzuki et al., 2007) as well as antipsychotic augmentation with mood stabilizers (Suzuki et al., 2009) or, very exceptionally combination of antipsychotics (Suzuki et al., 2008a). Simplification of medication regimens was also performed, aiming for a single night dosage where possible (Suzuki et al., 2005). All antipsychotic medications were dosed within the licensed range.

T.S. (an experienced full-time staff psychiatrist at Inokashira Hospital) was in charge of the entire management of the ward for this period of time and treated and evaluated all patients. Clinical evaluation was routinely performed with the Clinical Global Impression (CGI) (Guy, 1976) and Functional Assessment for Comprehensive Treatment of Schizophrenia (FACT-Sz) (Suzuki et al., 2008b). Adverse events were not assessed systematically but recorded in the medical chart in a real-world manner. Bloodwork and other safety profiles were monitored on a routine basis. All assessments were performed by the first author with a significant and periodic input from nursing staff at the ward or caregivers, as is likely to happen in a psychiatric hospital.

Collected information included demographic variables (note that the exact admission duration/number was not unequivocally clear for those with long, extremely complicated history on rare occasions) and psychopharmacologic details. Pre-post comparisons (March 2013 or the time of admission to the ward versus March 2014 or the time of discharge from the ward after 3 consecutive months of treatment) were made in terms of the number and the dose of antipsychotics (in chlorpromazine equivalents (Inagaki and Inada, 2008)), the total number of psychotropics as well as the CGI and FACT-Sz scores, using Wilcoxon Signed Rank Test. A p-value of <0.05 was considered statistically significant (two-tailed). Demographic variables of those who were successfully withdrawn from antipsychotic treatment versus those who could not were compared with Mann–Whitney's U-Test. Finally, pre-post comparison was performed with Fisher's Exact Test in terms of the proportion of patients treated with each characteristic.

3. Results

A total of 83 male patients were treated in the unit in the F.Y. 2013; 16 were not treated for more than 3 consecutive months in the unit, seven had other primary diagnoses (bipolar disorder: five cases; alcohol-related disorders: two cases), and five (schizophrenia: three cases; mental retardation two cases) failed to provide informed consent, leaving 55 patients with chronic schizophrenia to be studied in this report. The mean ± standard deviation (S.D.) age of the patients was 57.5 ± 13.0 y.o. with the duration of illness of 30.9 ± 15.2 years. The approximate number and duration of admissions were 6.1 ± 5.2 times and 20.7 ± 14.5 years, respectively. This means a significant chronicity of the sample in that they had spent, on the average, two-thirds of their time hospitalized since the onset.

Table 1 summarizes pre-post (baseline versus endpoint) comparative data. The severity of the sample may also be inferred from the baseline CGI-Severity score of 5.8, indicating severe to marked illness (Guy, 1976). The FACT-Sz score at baseline was 28.7, indicating extreme impairments where admission is clearly indicated. In detail, patients cannot do almost anything on their own. Living alone is just impossible. They function very little in every aspect (even when admitted and extensively assisted) and the life is always dysfunctional or dyscontrolled with problems and difficulties. Social functioning is essentially absent. At least some key symptoms are likely to be rated worse than severe. Inpatient treatment is surely necessary (Suzuki et al., 2008b).

As is seen in Table 1, post-treatment data were all favorable with smaller standard deviations compared with pre-treatment values. Compared to the baseline, the number and daily dose of antipsychotics was reduced from 1.9 to 1.1 and 1012 mg to 607 mg, respectively, representing a 40.0% decrease in the amount of antipsychotics on the average. The number of total psychotropics was also significantly minimized from 4.7 to 2.1, with a simplified once or twice daily dosing. Overall, the CGI-Severity and FACT-Sz improved slightly from 5.8 to 5.5 and 28.7 to 32.6, respectively. Likewise, the CGI-Improvement indicated no change for 34 patients (61.8%), minimally better for 17 patients (30.9%), much better for three patients (5.5%), very much better for one patient (1.8%); of note is the fact that no patients got worse in comparison with the baseline clinical presentation. Thus the mean ± S.D. score in the CGI-Improvement was 3.5 ± 0.7 on the whole sample.

The majority of patients ($n=36$, 65.5%) had been treated with antipsychotic polypharmacy at baseline; 18 were treated with monotherapy of a newer antipsychotic agent and another with bromperidol. Only four patients were treated exclusively with older antipsychotics. However, 44 (80.0%) patients were successfully treated with a single antipsychotic in the end and antipsychotics were olanzapine for 19 cases, risperidone for 18 cases, aripiprazole, fluphenazine (oral and depot), long-acting paliperidone, perphenzaine, perospirone (a serotonin–dopamine antagonist available in some Asian countries), quetiapine and zotepine for one case each, respectively. Only seven patients (12.7%) needed antipsychotic combination and antipsychotic treatment was discontinued in four patients (7.3%, see below).

At baseline, 25 patients (45.5%) had been treated with antipsychotics at a total amount higher than 1000 mg/day. At endpoint, there were a total of eight patients (14.5%) who were treated with the doses exceeding 1000 mg/day; they were seven patients treated with two antipsychotics (olanzapne plus risperidone, $n=5$; olanzapine plus

Table 1
Changes in variables.

	Baseline	Endpoint	p-Value [a]
CGI—severity	5.8 ± 0.7	5.5 ± 0.6	< 0.05
FACT-Sz	28.7 ± 7.6	32.6 ± 7.2	< 0.01
APs number	1.9 ± 0.8	1.1 ± 0.4	< 0.001
APs dose (CPZ equivalent)	1012 ± 644	607 ± 377	< 0.001
Total psychotropics number	4.7 ± 2.1	2.1 ± 1.0	< 0.001
Doses divided (times/day)	2.8 ± 0.7	1.5 ± 0.6	< 0.001

Data are mean (± S.D.).
Abbreviations: APs, antipsychotics; CGI, Clinical Global Impression; CPZ, chlorpromazine; FACT-Sz, Functional Assessment for Comprehensive Treatment of Schizophrenia.
[a] by Wilcoxon Signed Rank Test.