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ARTICLE

Revising polypharmacy to a single antipsychotic regimen for patients with chronic schizophrenia

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Abstract

Antipsychotic polypharmacy has been empirically used and a recent trend in favour of that mode of therapy has been suggested for the treatment of schizophrenia. The clinical efficacy, however, still remains to be clarified. In order to critically evaluate the usefulness of such kind of psychopharmacotherapy, antipsychotic combination regimen (polypharmacy) was switched to a treatment with the single main antipsychotic (monotherapy) in cross-tapered fashion, while approximately maintaining the total amount, for patients with chronic schizophrenia. Patients had been treated with an average of three antipsychotics and maintained with the same antipsychotic polypharmacy regimen for more than 6 months before the entry. They were followed up with an antipsychotic monopharmacy and evaluated at 24 wk after completion of switching. Forty-seven patients were recruited for this study. Of 44 patients for whom evaluation was possible, 24 (54.5%) remained stable, while 10 (22.7%) showed improvement and the same number of patients ended in a deleterious status. Twenty-two patients were converted to antipsychotic monotherapy, while another 12 needed minimal dosing of low-potency agents. Overall, social functioning, evaluated by the Global Assessment of Functioning and the Clinical Global Impression, remained unchanged. Eighteen of 34 successful patients showed adverse effects of the main antipsychotic medication, which necessitated a significant dose reduction. Nine out of 10 deteriorating patients had been treated with a combination of low- and high-potency antipsychotics. It is suggested that many instances of antipsychotic polypharmacy is avoidable. The result is compatible with the current treatment recommendations, which dictate the use of a single antipsychotic agent.

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Introduction

It is a well-established fact that all antipsychotics on the market share the only one common pharmacological property of the dopamine D_2 receptor blockade in the central nervous system (Stahl, 2000). It thus might seem irrational to prescribe multiple antipsychotics, instead of increasing the dose of one, single antipsychotic medication.

However, while there might be little established evidence to make use of two or more antipsychotics concomitantly, and such treatment may seem like treating hypertension with calcium blockers alone, reduced adverse effects and clinical effectiveness of agents which act at various receptors, such as clozapine or olanzapine, are attributed in part to their action on multiple receptors in the central nervous system other than the classic D_2 occupancy. One such candidate is the serotonin 5-HT_{2A} receptor (Stahl, 2000). It may then be possible to assume that antipsychotic polypharmacy is yielding by acting on various receptors (Freudenreich and Goff, 2002).

Further, for those who are still suffering from devastating illness even after implementation of clozapine, which has been used as a last resort because of the life-threatening adverse effects of agranulocytosis, antipsychotic polypharmacy may be unavoidable, since there are some options (in other words, no consensus) for those difficult-to-treat patients (Buckley et al., 2001; Weiden et al., 1998). Standardized routine pharmacotherapies might not be suitable for schizophrenia,

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the aetiology of which still remains to be elucidated. It is well known that patients with schizophrenia may not be homogeneous (Ciompi, 1980; Davidson and McGlashan, 1997).

The principle of psychopharmacotherapy for schizophrenia, however, has been to treat patients with a single antipsychotic medication at the lowest possible dose (Miller et al., 1999; Taylor et al., 2001), although as is evident from various reports (Clark et al., 2002; Ito et al., 1999; Procyshyn et al., 2001; Williams et al., 1999), antipsychotic polypharmacy has been commonplace in real-world clinical settings. This kind of pharmacotherapy has been used for years with little established evidence for even theoretical combinations and is mostly empirical.

Although there are some reports to suggest that antipsychotic polypharmacy is useful for selected patients (Godlesky et al., 1989; Jones et al., 1968; Lerner et al., 2000), studies that systemically evaluate the effectiveness of antipsychotic polypharmacy for psychosis are scarce.

In order to critically evaluate the usefulness of that kind of treatment and to argue against its overutilization, we revised antipsychotic polypharmacy into a single antipsychotic regimen (monotherapy) for patients with chronic schizophrenia. The present report is unique in that while other studies assess the combination regimen after monotherapy fails (see Freudenreich and Goff, 2002, for a review; Shiloh et al., 1997), the course is the opposite; antipsychotic polypharmacy was revised to monotherapy. We know of only two unsystematic studies which evaluate it by such a procedure (Godlesky et al., 1989; Jones et al., 1968).

There have been many practice guidelines or algorithms on the treatment of schizophrenia [APA, 1997; Expert Consensus Guideline Series (ECGS), 1999; Lehman et al., 1998; Miller et al., 1999; Taylor et al., 2001], none of which currently recommend antipsychotic polypharmacy. We, therefore, anticipated that although it is unavoidable for some difficult patients, most instances of antipsychotic polypharmacy are unnecessary and its routine application is not acceptable. Also, by examining demographic variables, the identification of patients was sought, for whom antipsychotic polypharmacy might be unavoidable.

Methods

Subjects

Patients with schizophrenia, according to ICD-10 classification (F20.x; WHO, 1992), were recruited. They had been followed up at the same psychiatric hospital and their psychotropic medication regimen had been kept constant for more than 6 months before entry into the study.

Patients with the following criteria were excluded: active somatic complications, mental retardation severe enough to interfere with the ability to give consent, a history of substance abuse including alcohol, neurological disorders, and significant head injury. Also, patients with overt fluctuations of symptomatology [operationally defined as fluctuations of the Global Assessment of Functioning (GAF) score of more than 10] during the 6 months before entry were excluded to clarify the effect of medication switching. Outpatients had been followed up at regular intervals and when applicable, blood concentration of the antipsychotic medication was obtained to monitor drug compliance.

Table 1. Relative potency of antipsychotic medications

Risperidone (*RIS*): *1*
Timiperone (*TMP*): *1.3**
Bromoperidol (*BPD*): *2*
Fluphenazine (*FPZ*): *2*
Haloperidol (*HPD*): *2*
Pimozide (*PMZ*): *4*
Nemonapride (*NMP*): *4.5**
Perphenazine (*PPZ*): *10*
Propericyazine (PCZ): 20
Mosapramine (MSP): 33*
Clocapramine (CCP): 40*
Zotepine (ZTP): 66
Oxypertine (OXP): 80*
Chlorpromazine (CPZ): 100
Levomepromazine (LPZ): 100
Thioridazine (TRZ): 100
Sulpiride (SLP): 200
Sultopride (STP): 200
CPZ 100 mg/d =HPD 2 mg/d =haloperidol decanoate (HP-D): 30 mg/4 wk =fluphenazine decanoate (F-D): 7.5 mg/2 wk =fluphenazine enanthete (F-E): 7.5 mg/2 wk

High-potency agents are those with a relative potency of less than 10 are depicted in *italic*.
* Available only in Japan.

Change of antipsychotic medications

The total daily chlorpromazine (CPZ) equivalent dose of antipsychotic medications was calculated for each subject (see Table 1) (Inagaki et al., 1999), and the main antipsychotic was determined. The dose of that

agent was gradually increased and the other(s) tapered off in ascending order of dosage. The change of antipsychotics was implemented in cross-tapered fashion, while approximately maintaining the total dose.

For example, if a patient had been treated with a daily dose of 10 mg haloperidol (HPD) (equivalent to 500 mg CPZ), 400 mg sulpiride (SLP) (200 mg) and 100 mg CPZ, the final target was set at 16 mg HPD, which has an equal potency of 800 mg CPZ. The basic rule was that CPZ, which accounts for the least relative potency, was switched first and HPD was increased by 2 mg. Then SLP was tapered off while increasing HPD by 4 mg. The entire process was performed with caution, and the rate for medication switching was left to the individual clinician to decide. However, as many symptoms can emerge as a result of discontinuation (Weiden et al., 1997) and risks following abrupt withdrawal of antipsychotics are reported (Viguera et al., 1997), the switch of medications was conducted gradually.

For those who were treated with depot antipsychotic, the dose was determined according to the equation shown in Table 1. When a patient had been treated with the same oral and depot agent, that patient was considered to have been treated with one medication. Here, high-potency antipsychotics were defined as having a potency of more than 10 mg CPZ per 1 mg of medication.

Doses as low as approx. 25 mg CPZ, or its equivalent, were allowed at night, as many patients had been using low-potency antipsychotics, such as CPZ and levomepromazine, as an aid to hypnotics; these doses are very unlikely to exert antipsychotic effect when used alone.

As we used dose equivalence as a rough guide, when adverse effects were a problem, dose reduction was allowed until the adverse effects subsided. However, doses were not reduced any further, because our concern was not to validate the relative potency of antipsychotics nor to seek dose reduction, but to demonstrate the feasibility of antipsychotic monopharmacy.

Patients were followed up for 24 wk, when the final evaluations were made, with the maintenance dose of antipsychotic monopharmacy. Other medications, including psychotropics such as antiparkinsonian drugs and benzodiazepines, were basically kept constant during the switching and the follow-up period.

Evaluation

At entry, at least weekly thereafter, and at the end of follow-up, patients were evaluated by the GAF (APA, 1994), the Clinical Global Impression (CGI): Severity of Illness (SOI) and Global Impression (GI) (Guy, 1976). Although no other formal ratings were applied, any changes on psychopathology as well as adverse effects of medications were noted. Judgement of GI was based both on social functioning of the subjects and adverse effects of medications. All patients were present at regular meetings and an evaluative consensus was reached on every patient.

The initial and the final number of antipsychotic(s), the dose, GAF and SOI were compared by the Wilcoxon Signed Rank test. To clarify the demographic differences between those who were successfully managed with antipsychotic monotherapy and those who were not, comparison of variables by the Mann–Whitney U test was made in terms of age, Duration of Illness (DOI), initial dose as well as the number of antipsychotics, SOI, weeks required for switching, GAF and total lifetime duration of admission. A p value of less than 0.05 was considered significant (two-tailed).

This study received ethical approval from all participating hospitals. After full description of the study, written informed consent was obtained from all participants.

Results

Forty-seven patients were recruited from nine Japanese institutions. There were 33 male and 27 inpatients. Table 2 shows initial demographic data of all patients. Their mean age, DOI, GAF, and SOI were 51.0 yr, 24.1 yr, 35.5 and 4.7 respectively.

The GAF score of 35.5 (31–40) means that there is some impairment in reality testing or communication (e.g. speech is at times illogical, obscure, or irrelevant) or there is a major impairment in several areas, such as work or school, family relations, judgement, thinking, or mood (e.g. a depressed man avoids friends, neglects family, and is unable to work; a child frequently bullies younger children, is defiant at home, and performs badly at school) (APA, 1994) and the SOI of 4.7 (5) indicates severe illness (Guy, 1976). A DOI of approx. 24 yr shows that participants had been suffering from chronic course of illness.

Table 3 shows the change of antipsychotic agents of all patients. As is seen, almost all patients had been treated with a combination of typical high-potency agents and typical low-potency antipsychotics. Forty-one patients (87.2%) had been treated concomitantly with antiparkinsonian drugs, 33 (70.2%) with hypnotics and seven (14.9%) with mood stabilizers, leaving only two patients who had been treated with antipsychotics alone.

Table 2. Demographic variables of patients before the entry

	27 in-patients	20 outpatients	All patients
Number of male and female patients	19 and 8	14 and 6	33 and 14
Diagnostic subtype	Paranoid 10, residual 11, hebephrenic 4, undifferentiated 0, catatonic 2, simple 0	Paranoid 9, residual 6, hebephrenic 1, undifferentiated 3, catatonic 0, simple 1	Paranoid 19, residual 17, hebephrenic 5, undifferentiated 3, catatonic 2, simple 1
Age (yr)[a]	57.0 (31–72)	42.9 (22–69)**	51.0 (22–72)
Duration of illness (yr)[a]	29.0 (15–49)	17.4 (3–50)*	24.1 (3–50)
Total duration of admission (yr)[a]	21.3 (3–47)	2.6 (0–21)***	13.3 (0–47)
Number of antipsychotics[a]	2.96 (2–5)	2.85 (2–4) ns	2.91 (2–5)
Global assessment of functioning[a]	27.7 (15–41)	46.0 (33–61)***	35.5 (15–61)
Severity of illness[a]	5.30 (3–7)	4.00 (3–6)***	4.74 (3–7)
Dose of antipsychotics (CPZ equiv., mg/d)[a]	1362 (151–6030)	769 (188–1975) ns	1109 (151–6030)

[a] Data are provided as mean and range.

* $p<0.01$, ** $p<0.001$, *** $p<0.0001$ by the Mann–Whitney U test.

Patients had been treated with an average of 2.9 antipsychotic medications and total dose had exceeded 1000 mg/d.

The result of switching is shown in Table 4. As can be seen, by changing antipsychotic polypharmacy to monotherapy, 24 patients (54.5%) remained stable, 10 (22.7%) got better, while 10 became worse. Overall, the GAF score stayed unchanged at 35.5 and the GI of 4.05 equated to no change.

For three patients, evaluation could not be drawn. One patient was lost to follow-up (but relapse has not been confirmed for months) and another was managed with monopharmacy but at a much higher dose than the baseline. One patient had been treated with sultopride and chlorpromazine. When he was first switched to sultopride, dystonia appeared and he was then successfully switched to chlorpromazine monotherapy.

As expected, the number of antipsychotics in the 34 successful (better plus stable) subjects significantly decreased from 3.0 to 1.4 ($p<0.0001$, $z=-5.120$) over an average period of 4.8 wk (median 4.0 wk, range 0–20 wk). The dose of medication was significantly reduced from 1171 to 952 mg ($p<0.0001$, $z=-4.292$), which resulted from dose reduction in 18 patients (of 34 successful instances, 52.9%) for whom adverse effects were a problem. In this group, 22 patients (50.0%) were maintained with antipsychotic monotherapy. Another 12 (27.3%) eventually needed minimal adjunctive dosing of low-potency antipsychotic medications.

The GAF score for the 10 patients who improved increased from 39.3 to 43.1, which was also significant ($p<0.01$, $z=-2.692$). One patient experienced a dramatic decrease in seizure frequency, which was judged to have been induced by antipsychotics. Others enjoyed a higher GAF score by switching to antipsychotic monotherapy.

Among the 10 patients who got worse, two manifested the obvious detriment of substuporous status. They were both subsequently treated with olanzapine with much improvement. Six patients showed increased irritability or aggression. Inadequate sedation was implicated for four of them with worsened extrapyramidal side-effects in the other two. Another initially did not show seizure activity, however, several attacks followed in approx. 24 wk. One patient died from infection, which was unrelated to medication switching.

Nine out of the 10 patients who deteriorated had been treated with a combination of low- and high-potency antipsychotics. Those who showed deleterious effects tended to do so 10.3 wk on the average (median 8.0 wk, range 1–24 wk) after the initiation of switching. Most of the patients who got worse were first managed by reinstitution of the former antipsychotic medications.

While 8 out of 27 in-patients deteriorated, only 2 out of 20 outpatients became worse, although the difference did not reach significance. However, as in-patients had longer DOI, were older, had longer duration of lifetime admission, were worse on GAF score, as well as SOI score at entry than outpatients, which all reached significance, they were analysed separately.

Among in-patients, those who got worse by converting to monotherapy had been admitted to hospital longer ($p<0.05$, $z=-2.337$). As for outpatients, no predictors were found between those who were

Table 3. Change of antipsychotic medications

10 better patients				
HPD 40→78.5 *HP-D 200 mg/4 wk* *FPZ 12→0* *F-E 75 mg/2wk→0* *ZTP 300→0* *LPZ 350→0* *CPZ 25→0*	BPD 30→39.5 SLP 500→0 FPZ 3→0 PMZ 3→0	NMP 30→50 SLP 600→0 PMZ 5→0	HPD 6→8 HP-D 150 mg/4 wk PPZ 8→0	RIS 6→8.5 FPZ 3→0 CPZ 75→0 LPZ 50→25
BPD 12→15 PMZ 5→0 LPZ 50→0	*CPZ 100→650* *HPD 6→0* *LPZ 250→0*	*FPZ 4→9* *PPZ 24→0* *LPZ 50→25* *VegetaminA 2→2T*	*RIS 3→5* *LPZ 125→0*	BPD 3→5 CPZ 87.5→0 TRZ 30→0
24 stable patients				
BPD 50→100 *HPD 40→0* *STP 1800→0* *ZTP 300→0* *VegetaminA 3→2T*	*BPD 36→45* *HPD 9→0* *LPZ 100→0* *VegetaminA 1→0T*	*BPD 24→37* *RIS 4→0* *CPZ 250→0*	BPD 33→37 SLP 400→0	*RIS 6→16* *HP-D 200 mg/4wk→0* *STP 600→0*
HPD 27→29.5 CPZ 125→0	*RIS 12→13* *LPZ 100→0*	HPD 18→22 ZTP 150→0 VegetaminA 1→1T	*TMP 6→14.6* *ZTP 300→0* *STP 400→0*	*HPD 12→20* *SLP 800→0* *LPZ 25→25*
HPD 18→19 *LPZ 90→25*	*HPD 15→19* *CPZ 200→0* *LPZ 25→25*	BPD 9→18 HPD 9→0 LPZ 25→25	BPD 9→17 SLP 800→0 CPZ 25→0	MSP 150→250 BPD 6→0 CPZ 25→0
ZTP 375→475 *LPZ 150→0*	*FPZ 4→9* *LPZ 250→25* *PPZ 16→0* *VegetaminA 2→2T*	HP-D 50→100 mg/4 wk CCP 75→0 LPZ 25→0 CPZ 25→25	BPD 6→8 PPZ 8→0	BPD 3→6 CPZ 100→0 LPZ 75→25
PPZ 6→24 BPD 3→0 TRZ 75→0 LPZ 10→10	*ZTP 150→175* *LPZ 25→0*	HP-D 20 mg/4 wk HPD 0→3 MSP 50→0	*CCP 30→60* *ZTP 30→0* *TRZ 30→0*	
10 worse patients				
HPD 27→45 *PMZ 18→10* *CPZ 400→0* *LPZ 300→0*	*HPD 30→36* *PCZ 60→0*	*HPD 24→27* *ZTP 100→0* *LPZ 50→0*	*RIS 6→9.25* *TRZ 300→0* *CPZ 25→0*	*HPD 12→16* *LPZ 200→0*
HPD 6→12 *LPZ 300→0*	HPD 6→7.5 SLP 150→0	*TRZ 100→350* *HPD 3→0* *LPZ 100→0*	*LPZ 250→325* *PPP 150→0*	HPD 2→3 ZTP 50→0 TRZ 25→25
Other 3 patients[a]				
CPZ 150→0→350 *STP 400→700→0*	*BPD 36→75* *STP 600→0* *CPZ 200→0* *PCZ 20→0*	HPD 3→3.75 ZTP 25→0		

The main antipsychotics are underlined.
VegetaminA is composed of 25 mg CPZ, 40 mg phenobarbital and 12.5 mg promethazine.
In-patients are shown in *italic.*
See Table 1 for abbreviations of antipsychotic medications.
[a] Evaluation could not be made.

Table 4. Results of switching antipsychotic polypharmacy to monotherapy

	In-patients	Outpatients	All patients
Number of patients who got better/remained stable/got worse	4/13/8 evaluation could not be made for two patients	6/11/2 evaluation could not be made for one patient	10/24/10 evaluation could not be made for three patients
Global assessment of functioning[a]	27.8 (20–41) – 27.0 (10–41) ns	45.7 (33–61) – 47.2 (33–65)*	35.5 (20–61) – 35.5 (10–65) ns
Severity of illness[a]	5.32 (4–6) – 5.36 (4–7) ns	4.05 (3–6) – 3.95 (3–5) ns	4.77 (3–6) – 4.75 (3–7) ns
Global impression[a]	4.24 (2–7)	3.79 (3–5) ns[b]	4.05 (2–7)
Number of antipsychotics for successful patients[a]	3.12 (2–5) – 1.47 (1–3)***	2.94 (2–4) – 1.35 (1–2)***	3.03 (2–5) – 1.41 (1–3)****
Dose of antipsychotics for successful patients[a]	1484 (151–6030) – 1062 (150–4041)**	858 (233–1975) – 742 (67–1800)**	1171 (151–6030) – 952 (67–4041)****

Successful patients = those who got better plus remained stable (17 in-patients and 17 outpatients).
Overall, GAF score stayed unchanged at 35.5 and GI equalled 4, indicating no change. The number, the dose of antipsychotics were significantly reduced in the successful 34 patients.
[a] Data are provided as mean and range.
[b] Not significant by the Mann–Whitney *U* test.
* $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$ by the Wilcoxon signed rank test.

successful in switching and those who were not, although caution should be exercised because there were only two outpatients who showed deterioration, which might preclude any meaningful statistics. Overall, those patients whose clinical condition could not be maintained with antipsychotic monotherapy had a longer history of lifetime admission ($p<0.01$, $z=-2.587$) and had initially exhibited a lower GAF score ($p<0.05$, $z=-2.093$) than those patients who could (Table 5).

There were five patients (10.6%) treated with risperidone (the only marketed atypical antipsychotic in Japan when this study was begun in 1999), four of whom were successfully managed by monotherapy. It means that this study dealt mostly with polypharmacy of typical agents. A low-potency antipsychotic had been the main medication in only eight patients (17.0%). It is known that low-potency agents are used at lower doses compared to high-potency ones (Baldessarini et al., 1984), partly implying the difficulty of applying them as a monotherapy for patients with schizophrenia owing to adverse events.

Discussion

To our knowledge, this is one of the few studies that evaluate the effectiveness of antipsychotic polypharmacy. We assessed its usefulness by converting polypharmacy to monotherapy. However, there are shortcomings which should be noted. Most of all, limited assessment of patients, especially with respect to adverse effects, may have prevented appreciation of the results. However, although no formal ratings other than GAF and CGI were performed, at least in three patients, worsening of side-effects were the reasons for failure (extrapyramidal symptoms in two and seizure in one) and decreased sedation owing to the cessation of low-potency agents were implicated in four. For two patients, substuporous status ensued, implying unavoidable polypharmacy for them.

In addition, the design of this study was a naturalistic one. There may be the additional possibility that non-specific treatment circumstances such as longer contact with patients could bring about a better outcome. We tried to eliminate this possibility, however, by applying very simple measures instead of elaborating PANSS and so forth. Our main concern was whether we could revise polypharmacy in a daily clinical setting.

There are some other limitations. First, in order to evaluate the superiority or inferiority of antipsychotic polypharmacy over monopharmacy, we had to follow patients from the very start of treatment and compare

Table 5. Comparison between those who were successful and unsuccessful in dose reduction

	Group	In-patients		Outpatients		All patients	
Age (yr)	Successful	56.2 (31–72)	ns	42.9 (22–69)	ns	49.6 (22–72)	ns
	Unsuccessful	57.8 (41–72)		43.5 (36–51)		54.9 (36–72)	
Duration of illness (years)	Successful	27.3 (15–49)	ns	17.3 (3–50)	ns	22.3 (3–50)	ns
	Unsuccessful	30.8 (20–41)		19.0 (10–28)		28.4 (10–41)	
Initial number of antipsychotics	Successful	3.12 (2–5)	ns	2.94 (2–4)	ns	3.03 (2–5)	ns
	Unsuccessful	2.63 (2–4)		2.50 (2–3)		2.60 (2–4)	
Initial amount of antipsychotics (CPZ eq., mg/d)	Successful	1484 (151–6030)	ns	858 (233–1975)	ns	1171 (151–6030)	ns
	Unsuccessful	1088 (325–2500)		301 (226–375)		930 (226–2500)	
Initial severity of illness	Successful	5.24 (4–6)	ns	4.00 (3–6)	ns	4.62 (3–6)	ns
	Unsuccessful	5.50 (4–6)		4.50 (4–5)		5.30 (4–6)	
Time required for switching (wk)	Successful	6.6 (0–20)	ns	3.0 (0–12)	ns	4.8 (0–20)	ns
	Unsuccessful	5.9 (5–12)		0.0		4.7 (0–12)	
Initial Global assessment of functioning	Successful	28.5 (20–41)	ns	46.6 (33–61)	ns	37.6 (20–61)	*
	Unsuccessful	26.3 (20–34)		38.5 (37–40)		28.7 (20–40)	
Duration of total lifetime admission (yr)	Successful	17.6 (3–47)	*	2.8 (0–21)	ns	10.2 (0–47)	**
	Unsuccessful	26.1 (19–37)		2.0 (1–3)		21.3 (1–37)	

Data are provided as mean and range.
* $p < 0.05$, ** $p < 0.01$ by the Mann–Whitney U test.
Those who got worse by switching had been admitted to the hospital significantly longer and had a lower baseline GAF score.

the results between the two. What is implicated is, at best, the evidence that many instances of antipsychotic polypharmacy were unnecessary. It might be that because GAF and GI were stationary in total, both pharmacotherapeutic approaches are comparable in efficacy, it is then reasonable to select monotherapy to monitor clinical effectiveness and side-effects, which is completely compatible with the recommendations in the treatment guidelines for psychoses (Miller et al., 1999; Taylor et al., 2001).

Secondly, the main antipsychotic medication, as well as the dose, was different among patients. The dose of antipsychotics deserves another consideration. Mean initial dose of antipsychotics had exceeded 1000 mg/d, the dose of which is often cited as one of a criterion of treatment-resistant schizophrenia (Kane et al., 1988). As the applicability of monotherapy was our main concern, the final dose of medication (952 mg/d) is still higher than the optimal dose of approx. 300–600 mg/d in the maintenance phase, suggested by Baldessarini et al. (1988) and Lehman et al. (1998). Recommended dosing, however, is not always followed in the real-world clinical settings (Leslie and Rosenheck, 2001). According to their report, 36.3% of patients were treated outside this range and 13.0% were treated with higher doses than recommended.

Our group also assessed the feasibility of antipsychotic dose reduction, the results of which are generally in line with encouraging previous reports (Carpenter et al., 1999; Inderbitzin et al., 1994; Smith, 1994; Volavka et al., 2000). In that study, in 36 out of 41 patients (87.8%), most of whom (80.5%) were receiving a daily dose of more than 1000 mg of antipsychotics, dose reduction was successful. The GAF score and CGI improved significantly and 23 subjects (56.1%) were judged to be better (Suzuki et al., 2003). If the dose were reduced more, the results could be more favorable.

One might argue that this is another dose reduction study, because the final dose was significantly reduced. Among 34 successful instances, 18 (52.9%) showed adverse effects due to the main antipsychotic medication during or after switching, which necessitated reduction of the dose, although this was not our main concern in the study. With regard to the fact that most patients had been treated with a combination of low- and high-potency drugs, with the former used relatively at lower doses, the result may to some extent imply anticholinergic effects that low-potency agents intrinsically possess (Stahl, 2000).

It is therefore suggested, that when making use of dose equivalence, flexibility is important in determining the maintenance dose. Especially when the total

dose is high, CPZ equivalence should not be relied upon in a blind manner. For example, worsening of extrapyramidal side-effects can be anticipated when low-potency antipsychotics are switched to high-potency ones. While sharing the common property of central D_2 blockade, some differences do exist among antipsychotic medications. Familiarity with the characteristics of the individual antipsychotic agents thus seems crucial.

Thirdly, availability of atypical antipsychotics was low in Japan, especially when the only approved one was risperidone at the initiation of the study in 1999. We could not, therefore, compare the results between switching to the main typical antipsychotic and to other new atypical agents. Suggested theoretical combinations of novel antipsychotics, such as clozapine plus risperidone (Freudenreich and Goff, 2002), could not be studied either. However, although expanding evidence suggests that atypical antipsychotics are efficacious (Kupfer and Sartorius, 2002), the role of conventional antipsychotics does exist, especially for patients with chronic schizophrenia. According to the report from Sernyak et al. (2003), typical agents may be no less effective on a mass level.

It is of much interest that risperidone is often used as an add-on medication without a subsequent trial for monotherapy in Japan (Inagaki et al., 2001), indicating many Japanese doctors prefer to use multiple antipsychotics concurrently. But it is this easy tendency that ultimately leads to unjustified polypharmacy (Stahl, 1999b). Although there is a report supporting the recent trend of antipsychotic polypharmacy (Clark et al., 2002), this practice seems to be especially true in Japan (Inagaki et al., 2001; Ito et al., 1999), partly because clozapine, which is used as a last resort for treatment-resistant patients (Kane et al., 1988), is still unavailable.

A survey in Japan revealed the average number of antipsychotics for patients with schizophrenia in 1993 was 2.6 and the percentage of patients treated with a single antipsychotic was only 10.4% (Yamauchi et al., 1998). A more recent survey indicated that the rate of polypharmacy was more than 90% (Ito et al., 1999) or 84.9% (Inagaki et al., 2001). This fact is definitely in contrast with what is reported from foreign countries, showing a much lower rate of polypharmacy (4.6% by McCombs et al., 1999; 28.5% by Williams et al., 1999; 6.8% by Leslie and Rosenheck, 2001; 27.5% by Procyshyn et al., 2001; 24.3% by Clark et al., 2002; 7.4% by Leslie and Rosenheck, 2002).

Finally, psychotropic polypharmacy is also common in the treatment of schizophrenia. This is not the exception for the subjects investigated. All but two were treated with concomitant psychotropic medication(s), for example benzodiazepines, mood stabilizers, and antiparkinsonian drugs.

Theoretically, a combination of medications having different pharmacological properties may sound reasonable, but much remain unproven. An example may be co-administration of an antipsychotic drug plus benzodiazepines in case of agitation, insomnia etc., which may be popular in western countries (Clark et al., 2002; ECGS, 1999). The efficacy, however, should be weighed against a combination of low- and high-potency antipsychotics, especially in view of the fact that this mode of therapy was necessary for the more debilitated patients in our sample.

In summary, even when novel antipsychotics are not available, routine application of polypharmacy with conventional antipsychotics can be avoided. The results are important on pharmacotherapy for schizophrenia, with respect to the reality that even though atypical antipsychotics are getting more and more popular (ECGS, 1999; Kupfer and Sartorius, 2002; Miller et al., 1999; Taylor et al., 2001) typical antipsychotics are still often utilized in daily clinical practice (Leslie and Rosenheck, 2002; McCombs et al., 1999; Sernyak et al., 2003; Williams et al., 1999).

In this study, in 22 out of 44 patients (50.0%) with chronic schizophrenia, treatment with antipsychotic polypharmacy was successfully converted to monotherapy. If minimal dosing of low-potency agents, which is very unlikely to work alone, but instead as just an aid to hypnotics was allowed, 34 (77.3%) were successful in switching, although this mode of therapy is not a genuine monotherapy, of course. In other words, however, 10 patients deteriorated after switching to monotherapy. They were over-represented by in-patients, had worse initial GAF and had a history of longer admission. A necessity of polypharmacy for more difficult patients is a possibility.

While overall results were not impressive, because there were no differences on GAF and CGI before and after switching, they have some clinical implications, taking into account the current trend in favour of antipsychotic polypharmacy (Clark et al., 2002). Our patients had originally exhibited a very low GAF score of 36 and had been treated with a daily dose of more than 1000 mg on average, which indicates that our patients were not very easy to treat. Even for them, the goal of monotherapy was attainable. This reminds us of the basic rule of pharcacotherapy for schizophrenia; that is to treat patients with a single antipsychotic agent (Miller et al., 1999; Taylor et al., 2001).

Variability of patients' responses to antipsychotic agents is quite striking. Algorithms or guidelines might

not be suitable for a difficult illness such as schizophrenia, which may be heterogeneous (Davidson and McGlashan, 1997). This has been true even before the advent of atypical antipsychotics (Ciompi, 1980). One example against them may be an individualized therapy such as taking comorbidities into account (ECGS, 1999) or determination of cytochrome P450 polymorphisms (Chou et al., 2000). Tailoring our approaches upon new proceedings will be a natural course.

Some guide is necessary when indicating any form of medications in the field of medicine, however, the recommendations currently advocate monotherapy at the lowest possible dose. Optimization of the medication regimen is necessary before resorting to polypharmacy (Freudenreich and Goff, 2002; Stahl, 1999b).

The conclusion is simple. At least some instances of antipsychotic polypharmacy are unnecessary for patients with chronic schizophrenia. It should not be overused and should be the exception, to be used when other therapeutic approaches have failed (Stahl, 1999b).

Rational examples of polypharmacy do exist, such as treatment for tuberculosis or hypertension, but polypharmacy of that kind is based on a theoretical background. Some theoretical combinations of antipsychotics have been suggested for the treatment of schizophrenia (Freudenreich and Goff, 2002), however, they still leave much to be proved.

There is even a report to suggest that antipsychotic polypharmacy is associated with higher mortality (Waddington et al., 1998). Until firm evidence of this currently unsupported practice is established, antipsychotic polypharmacy remains a dirty little secret (Stahl, 1999a).

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Statement of Interest

None.

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