

Article

Polypharmacy in the management of patients with schizophrenia on risperidone in a tertiary-care hospital in Malaysia

SA Jacob B Pharm M Pharm PhD

Lecturer, Discipline of Pharmacy, Monash University Sunway Campus, Malaysia

MI Mohamed Ibrahim BPharm PhD

Associate Dean of Research and Graduate Studies Affairs, College of Pharmacy, Qatar University, Doha, Qatar

F Mohammed MBBS MPM Dip. Child Psychiatry

Head of Department of Psychiatry and Senior Consultant, Hospital Tengku Ampuan Rahimah, Klang Selangor, Malaysia

ABSTRACT

The present study was conducted primarily to determine the occurrence of polypharmacy in patients with schizophrenia on risperidone. The secondary aim was to ascertain the incidence of inappropriate prescribing with anticholinergics. A retrospective review of the medical records of all patients who were being followed up at the out-patient clinic of a tertiary-care hospital in Malaysia was conducted. Only patients who were being prescribed risperidone between 1 June 2008 and 31 December 2008 were included in the study. Demographic data such as patient's age, gender and race were obtained from the patient's medical records. In total, 113 patients met the selection criteria. Polypharmacy was found to occur in 34 patients (30.09%), with the majority (76.47%) being on two antipsychotics. In total, 27 patients

(34.18%) on monotherapy with risperidone were prescribed an anticholinergic on scheduled dosing, while 19 patients (24.05%) were prescribed it on an as-needed basis. Of the patients on polypharmacy, 26 (76.47%) were on scheduled dosing of anticholinergics, while three (8.82%) were taking the medication on an as-needed basis. Polypharmacy should be avoided, and the use of anticholinergics should be closely reviewed. By adopting more efficient prescribing practices, costs can be reduced and financial resources can instead be channelled towards more beneficial areas for the patients.

Keywords: anticholinergic, antipsychotic, polypharmacy, risperidone, schizophrenia

Introduction

Current treatment guidelines have consistently recommended antipsychotic monotherapy as the treatment of choice for the management of schizophrenia.^{1,2} Although antipsychotic polypharmacy has received little support in the literature and in

expert consensus guidelines, some authors suggest that antipsychotic polypharmacy can be used as a last resort after all of the monotherapy alternatives have been exhausted.² Despite these reservations, polypharmacy is widespread in the treatment of

schizophrenia, with an incidence in the range 13–68%.^{3–11} In a study conducted by Faries *et al*,¹² it was found that 66% of patients were on polypharmacy at the time of initiation. Of these, only 30% ceased polypharmacy within 60 days, while the rest continued on polypharmacy for prolonged periods of time.

Polypharmacy is defined here as the concomitant use of two or more antipsychotics,^{11,13} and it has been reported to increase the risk of non-adherence, drug–drug interactions, the incidence of hospitalisations, and patient morbidity and mortality. It also increases the risk of adverse events and the need for additional medications to treat them.^{5,7,14–16} Another particular problem with polypharmacy is the cost associated with its use, and several studies have shown a substantial increase in total treatment costs.^{5,7,11} In a study by Loosbrock *et al*,¹⁴ compared with monotherapy, polypharmacy was associated with an increase of \$888 in treatment costs ($P < 0.0001$) and an increase of \$4244 in total cost ($P < 0.0001$).

However, budget cuts in the allocation for psychiatry drugs have necessitated an evaluation of the prescribing practices in the psychiatry department. A pattern of inappropriate prescribing of anticholinergics has also been observed, whereby they are frequently prescribed with atypical antipsychotics despite the fact that it has been demonstrated that there is minimal to no risk of extrapyramidal side effects (EPS) with atypical compared with typical antipsychotics.^{3,17,18}

A drug use evaluation (DUE) of risperidone was conducted in a tertiary-care hospital in Malaysia. Risperidone was selected because the majority of patients in the outpatient psychiatric department are prescribed this drug, and in view of this we wanted to ensure that appropriate prescribing practices were adhered to. This paper presents some of the data obtained from the DUE.

Thus the aim of this study was to investigate the occurrence of polypharmacy in patients with schizophrenia on risperidone. A secondary aim was to determine the incidence of inappropriate prescribing with anticholinergics and to discuss the prescribing practices for atypical antipsychotics, specifically risperidone, as well as the use of anticholinergics with atypical antipsychotics.

Methodology

This was a retrospective review of the medical records of all patients who received risperidone at the outpatient clinic of the psychiatric department of a

tertiary-care hospital in Malaysia between 1 June 2008 and 31 December 2008. Patients who were prescribed risperidone for diseases other than schizophrenia were excluded from the study. Demographic data, concomitant medications and diagnosis were obtained from the medical records. Diagnosis of schizophrenia did not take into account the severity or phase of the disease (e.g. acute or chronic). With regard to anticholinergics, prescribing on an as-needed basis is defined as the prescription of anticholinergics to be taken only when EPS occur, whereas scheduled dosing is the prescription of anticholinergics to be taken on a daily basis.

Statistical analyses

Descriptive statistics were generated for patient demographics, diagnosis and concurrent medication, as well as for the incidence of polypharmacy and inappropriate prescribing of anticholinergics. All analyses were performed using Microsoft Excel and SPSS (version 11.1).

Results

In total, 113 patients met the selection criteria, and the majority (86.7%) of these patients were under 60 years of age. Depression was the most common concomitant disease, while others included dementia, post-traumatic stress disorder, anxiety and obsessive-compulsive disorder (observed in one patient each). Fluvoxamine was the most commonly prescribed antidepressant, while diazepam (50.0%) was the most commonly prescribed anxiolytic. Other drugs included zolpidem (22.7%), alprazolam (13.6%), lorazepam (9.1%), carbamazepine (1.8%) and prothiaden (1.8%). Patients were on a mean dose (\pm SD) of 2.60 ± 1.67 mg of risperidone per day (see Table 1).

Polypharmacy was seen in 34 patients (30.09%) and of these, 26 patients (76.47%) were prescribed two antipsychotics and 8 patients (23.53%) were prescribed three antipsychotics. No patients were prescribed two atypical antipsychotics concurrently. All patients on flupenthixol decanoate (Fluanxol[®]) were prescribed a dose of 10 mg/month, while all patients on zuclopenthixol decanoate (Clopixol[®]) were on a dose of 200 mg/month. Patients on fluphenazine decanoate (Modecate[®]) were on an average dose of 26.6 mg/month (see Table 2). In none of the patients who were prescribed two or more antipsychotics that included a depot preparation

Table 1 Demographics and patient characteristics

Characteristics	Number of patients (%)
Mean age (\pm SD) (years)	39.25 \pm 15.91 (19–85)
<i>Gender</i>	
Female	57 (50.44%)
Male	56 (49.56%)
<i>Race</i>	
Malay	57 (50.44%)
Chinese	27 (23.89%)
Indian	29 (25.66%)
<i>Concomitant diagnosis</i>	
Depression	18 (15.93%)
Bipolar mood disorder	4 (3.54)
Mental retardation	4 (3.54)
Epilepsy	2 (1.77)
<i>Concurrent medication</i>	
Benzhexol (Artane [®])	75 (66.47)
Anxiolytics	22 (19.47)
Fluphenazine decanoate (Modecate [®])	16 (14.16)
Fluvoxamine	13 (11.50)
Chlorpromazine	13 (11.50)
Fluoxetine	6 (5.31)
Valproic acid	6 (5.31)
Flupenthixol decanoate (Fluanxol [®])	6 (5.31)
Zuclopenthixol decanoate (Clopixol [®])	3 (2.65)
Sulpiride	2 (1.77)

were there any reports of non-adherence in the patients' medical records.

Of the 75 patients who were prescribed benzhexol, 53 patients (70.67%) were on scheduled dosing, while 22 patients (29.33%) were prescribed the drug on an as-needed basis. In total, 19 patients (24.05%) who were on monotherapy with risperidone were prescribed benzhexol on an as-needed basis, while 27 patients (34.18%) were on scheduled dosing. Table 2 shows the concurrent prescription of benzhexol with combinations of antipsychotics where 26 patients (76.47%) were on scheduled dosing, while three (8.82%) were prescribed the drug on an as-needed basis.

Discussion

Polypharmacy

Polypharmacy was observed in approximately 30% of the patients in our study. This figure was much higher than those observed in studies conducted in Spain (13.9%), the UK (c. 10%) and the USA (10.1%).^{19–21} However, when compared with Asian countries, our results were found to be fairly similar to those observed in Korea (35.5%), China (25.2%) and Taiwan (22.2%), but very much lower than those reported in Japan and Singapore, where polypharmacy was observed in more than 70% of patients.²² Besides treatment settings, the differences in results between countries might suggest the influence of other factors, such as the effect of culture and local prescribing traditions.²²

However, with regard to the number of antipsychotics prescribed to patients on polypharmacy our study findings were similar to those of other studies where most patients were prescribed two antipsychotics, followed by three or more antipsychotics concurrently.^{3,19} Although this finding is encouraging, it still does not discount the fact that polypharmacy is associated with increased risks to patients. In a study by Centorrino *et al*,²³ the duration of hospitalisation was 1.5 times longer in the polypharmacy group compared with the monotherapy group. In another study by Centorrino *et al*, the risk of adverse effects was 56% higher with antipsychotic polypharmacy.²⁴ Other problems associated with polypharmacy are that it makes the recognition and management of adverse events more difficult, it complicates dose titration, and it confounds clinicians' ability to determine which drug is of benefit and which is not.^{3,11}

Current guidelines recommend monotherapy as the treatment of choice.¹ This is based on the compelling and extensive body of evidence supporting monotherapy with atypical antipsychotics.^{7,9} Monotherapy allows better monitoring of the patient's response to an adequate trial of each medication, thus preventing the use of complex medication regimens, reducing the risk of adverse events, and making it easier to identify and manage future symptom exacerbations.^{7,12} Indeed the rule of thumb to be adopted is 'start slow, go slow, but use enough.'²⁵

Thus far there is little evidence to suggest that several antipsychotics are better than one when equivalent doses are used. According to the Texas Medication Algorithm Project (TMAP) schizophrenia algorithms, combination therapy (atypical and typical antipsychotics) is only recommended for patients who have responded poorly to stages 1 to 5.² In a

Table 2 The frequencies of antipsychotics and anticholinergic prescribed concurrently

Antipsychotics	Number of patients on polypharmacy (%) (n = 34)	Number of patients on scheduled dosing of anticholinergic	Number of patients prescribed anticholinergic on as-needed basis
Risperidone + fluphenazine decanoate (Modecate [®])	11 (32.35)	8	0
Risperidone + chlorpromazine	5 (14.71)	5	0
Chlorpromazine + risperidone + fluphenazine decanoate (Modecate [®])	5 (14.71)	3	2
Risperidone + zuclopenthixol decanoate (Clopixol [®])	4 (11.76)	3	0
Chlorpromazine + risperidone + flupenthixol decanoate (Fluanxol [®])	3 (8.82)	2	0
Risperidone + flupenthixol decanoate (Fluanxol [®])	3 (8.82)	2	1
Risperidone + sulpiride	2 (5.88)	2	0
Risperidone + haloperidol	1 (2.94)	1	0

study conducted to determine the reasons for polypharmacy, practitioners indicated a belief that there was questionable therapeutic benefit in more than 50% of the patients being treated with multiple antipsychotic combinations. In addition, chart documentation showed that the majority of these patients did not receive an adequate trial of monotherapy with other atypical or typical agents, or clozapine prior to the combination antipsychotic regimen,⁹ similar to our patient population.

Another aspect to be considered in polypharmacy is receptor binding. Both risperidone and first-generation antipsychotics bind to the same receptor (D₂). Thus giving these drugs concurrently will lead to competitive antagonism and subsequently displacement from the receptor site.²⁶ The displacement of one drug will then result in the effect of only one drug being seen, which leads us back to square one. This will also then lead to increased adverse events. Furthermore, there are some physicians who argue that by using combination antipsychotics, the dose of each drug can be reduced and this will reduce the risk of adverse events. This is inaccurate in this group of drugs, as the dose–response relationships for these agents are unpredictable and reflect the wide variation in pharmacokinetic and pharmacodynamic responses among individuals. Thus the use of lower doses does not guarantee a reduced incidence of side effects.^{27,28}

Inappropriate prescribing of anticholinergics

Of the 79 patients on monotherapy with risperidone, nearly 60% were prescribed benzhexol. This is similar to the figure reported by Taylor SM *et al*,¹⁸ but nearly six times higher than that reported by Broekema *et al*.³ It must also be noted that more patients were on a scheduled dosing of benzhexol (34.18%) than were on dosing on an as-needed basis (24.05%), whereas in the study by Taylor *et al* more than 80% of the patients on monotherapy with an atypical antipsychotic were on a scheduled dosing of an anticholinergic.²⁰

With regard to the prescribing of anticholinergics in polypharmacy, our study again differed from that of Broekema *et al*,³ as approximately 85% of our patients were prescribed benzhexol, compared with less than 20% in the study by Broekema *et al*. However, our findings are congruent with those reported by Taylor *et al*¹⁸ and Sim *et al*,²² where combinations of typical and atypical antipsychotics were associated with increased use of anticholinergics. More patients in our study were also prescribed benzhexol on a scheduled basis than on an as-needed basis (76.47% vs. 8.82%), despite there being no indication that patients were experiencing EPS. This again was in contrast to the study by Taylor *et al*, in which more patients were being prescribed

anticholinergics on an as-needed basis than on scheduled dosing (c. 70% vs. c. 20%).²⁰

The practice of prescribing anticholinergics as prophylaxis is widespread, despite the fact that current guidelines do not recommend the use of the drugs as prophylaxis in long-term psychotic patients. With regard to risperidone specifically, it was found that at low doses there are few or no incidents of EPS.²⁹ This was noted in a study by Kapur *et al*³⁰, where the D₂-receptor occupancy was studied in 44 patients, consisting of 16 patients on risperidone (2–12 mg/day), 17 patients on olanzapine and 11 patients on clozapine. At the end of the study, it was found that receptor occupancy was 66%, 73%, 79% and 81% at doses of 2 mg, 4 mg, 6 mg and 8 mg, respectively. The authors concluded that doses of 4–6 mg/day achieve a D₂-receptor occupancy similar to that obtained with neuroleptics or first-generation antipsychotics. The authors also postulated that the occurrence of EPS at higher levels of D₂-receptor occupancy indicates that the high 5-HT₂ affinity of risperidone provides some protection against EPS. Other than that, the combined 5-HT₂ and D₂ occupancy and the avoidance of D₂-receptor overblockade are also believed to reduce the risk of EPS.³¹ Thus, given that the majority of the patients in our study were on doses of less than 4 mg/day, the risk of EPS is low.

Only a certain proportion of patients may develop EPS. Thus many patients receive prophylactic medication unnecessarily, increasing the risk of adverse drug reactions and drug–drug interactions, all of which will have a negative impact on treatment adherence, potentially leading to more relapses and rehospitalisations.^{22,32} There is also a high potential for abuse with this group of drugs, particularly by psychiatric patients, due to their stimulant, euphoriant and hallucinogenic effects.^{33,34} Furthermore, it has been found that anticholinergic load causes significant impairment in attention as well as memory.³⁵

In addition to this, of those patients who do develop EPS, the majority improve, as a result of either lowering antipsychotic dosages or their modifications. Those psychotic patients with risk factors (male gender, young and elderly patients, and those on high-potency antipsychotics) who continue to manifest EPS reasonably need at least 3 months of anticholinergic treatment. Subsequently, at follow-up visits, a trial of anticholinergic drug withdrawal would further guide whether or not to continue the drugs on a long-term basis.³⁴

Ideally, anticholinergics should be used only when EPS have actually developed and the reduction of antipsychotic dosage or the introduction of another antipsychotic drug with fewer parkinsonian effects has proved ineffective. If EPS are

under control for 3 months, an attempt must be made to withdraw the anticholinergic drug.³³ However, in high-risk patients, or when there is a dose increase, prophylactic treatment may be initiated and continued for about 7 days. After that, the dose of the anticholinergic drug should be reduced gradually.³⁶ Indeed studies indicate that the gradual withdrawal of anticholinergics will not produce a recurrence of EPS.³³

Limitations

The number of patients on risperidone was determined by examining all of the records available at the Psychiatry Unit, and was not based on a list. Therefore it cannot be established with certainty whether the figure obtained was accurate, as some files may have been misplaced, missing or currently being used. When comparing our results with other studies, we did not take into account the length of treatment defined in other studies. Also the definition of polypharmacy used in other studies was different from that in our study. Furthermore, the focus solely on patients who were being prescribed risperidone does not allow for proper inferences to patients on other atypical antipsychotics, such as quetiapine and olanzapine.

Conclusion

More efficient prescribing practices should be adopted in order to prevent unwanted side effects and reduce the burden on patients' quality of life. By optimising treatment in a rational manner, unwanted expenses can also be reduced and financial resources can be channelled towards more beneficial practices for the patient, such as increasing the number of patients on atypical antipsychotics.

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CONFLICTS OF INTEREST

None.

ADDRESS FOR CORRESPONDENCE

Dr SA Jacob, 28 Lorong Jambu Bol 1 kawasan 6, Teluk
Pulai 41100 Klang, Selangor Malaysia. Tel: +601
6288 1425; email: sabyj@hotmail.com

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