ORIGINAL ARTICLE

Predictors of high-dose antipsychotic prescription in psychiatric patients in Hong Kong

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Objective To determine the factors associated with high-dose antipsychotic prescribing for psychiatric patients in Hong Kong.

Design Retrospective cross-sectional study.

Setting Psychiatric in-patients and out-patients in the New Territories West Cluster, Hong Kong.

Patients A total of 1129 in-patients and 7520 out-patients who received antipsychotic medications on the study date.

Main outcome measures Demographic and clinical data were compared for patients receiving 'normal' and high dosages of antipsychotic medications.

Results High dosages were prescribed for 104 (9.2%) of the in-patients and 137 (1.8%) of out-patients. Antipsychotic polypharmacy was the most powerful predictor of high-dose prescribing, with an odds ratio of 8.88 for in-patients and 10.82 for out-patients.

Conclusion Antipsychotic polypharmacy was the main determinant of high-dose antipsychotic prescribing in this study. Further studies should be conducted to look for other variables contributing to such prescribing in Hong Kong.

Introduction

The prescription of antipsychotic medications above recommended levels is a well-documented phenomenon; a recent in-patient survey in the United Kingdom revealed a rate of about 20%.[1] At least five English-speaking countries have published guidelines or consensus statements advising against the use of high doses except in special circumstances.[2-5] Local guidelines published by the Hospital Authority also advise against such use and against polypharmacy.[6] The high-dose antipsychotic prescription rate has even been advocated as a proxy measure of the overall quality of clinical care provided by a mental health service.[7]

Recent literature reviews failed to show any clinical benefit in prescribing high doses of antipsychotic medications.[8,9] There is no clear relationship between neuroleptic dose and clinical response.[10] However, there is clear evidence showing the harm of high-dose antipsychotic therapy. Antipsychotic medications are associated with cardiac conduction defects and sudden death,[11] and there is evidence linking mortality with antipsychotic dosage and polypharmacy.[12,13] The association of diabetes mellitus with second-generation ('atypical') antipsychotics is also a matter of concern.[14,15]

Studies have examined the relationship between high-dose antipsychotic prescribing and various patient and prescriber characteristics. Patient factors include treatment non-responsiveness, duration of illness, and history of violence[16-19]; prescriber factors include inadequate knowledge, reliance on personal experience, skepticism about algorithms, and the use of polypharmacy.[1,19,20]

This study examined the rate of high-dose antipsychotic prescribing and its predictors in a large sample of in-patients and out-patients in Hong Kong.

Methods

All in-patients and out-patients receiving psychiatric services in the New Territories West Cluster in Hong Kong, who received antipsychotic medications on 15 November 2006, were included in this study. Out-patients receiving prescriptions prior to 15 November 2006 were included if antipsychotic medications were to be taken by the patient on that day.

Key words
Antipsychotic agents; Risk factors

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影響醫生為香港精神病患者處方高劑量抗精神病藥的因素

目的 確定香港的醫生為精神病患者處方高劑量抗精神病藥的相關因素。

設計 回顧性橫斷面研究。

安排 香港新界西聯網住院和門診的精神病患者。

患者 在研究進行當日接受抗精神藥物治療的1129位住院病人和7520位門診病人。

主要結果測量 比較接受‘正常’劑量和高劑量藥物治療的患者，與人口有關的數據和臨床資料。

結果 共有104位(9.2%)住院病人和137位(1.8%)門診病人的藥物是高劑量處方。抗精神藥複方用藥是影響高劑量處方的最主要因素，在住院病人的比值比為8.88，在門診病人中則為10.82。

結論 本研究發現，抗精神病複方用藥是高劑量處方抗精神藥物的主要決定因素。至於其他影響因素，仍有待進一步研究。

Patient data retrieved included: age, gender, history of violence, number and dosage of antipsychotics prescribed (including 'as required' antipsychotics). A history of violence was defined using the Priority Follow-Up registry established in Hong Kong in 1982, which registers psychiatric patients with a history of violence or assessed to have a violent disposition. In addition, the following information was obtained for in-patients: body mass index, detention status under the Mental Health Ordinance, psychiatric diagnosis using the International Classification of Diseases–10th edition,[21] number of psychiatric admissions in Hong Kong, and the number of years in contact with the mental health services. The psychiatric diagnosis was not obtained for out-patients, due to a significant proportion of missing data in the computer records.

A high dose was defined as a total daily dose of a single antipsychotic exceeding the upper limit stated in the British National Formulary (51st edition).[22] Where two or more antipsychotics were used, the prescribed dose was converted to a percentage of the maximum recommended dose for each drug. If the sum of the percentages exceeded 100%, the patient was deemed to be receiving a high dose.[2,23] For trifluoperazine, which does not have a maximum dose in the British National Formulary,[22] a maximum daily dose was set at 50 mg which was also used in another similar study.[1] For thioridazine, thiothixene, and ziprasidone, which are not available in the United Kingdom, the maximum doses were obtained from the product inserts. This method of calculation has been recommended by the Royal College of Psychiatrists as being less ambiguous and easier to use than the chlorpromazine equivalent method.[2] There was a 97.2% concordance and Spearman's rank correlation of 0.92 between these two methods, using data obtained in a study.[24]

Data were analysed using the Statistical Package for the Social Sciences (Windows version 13.0; SPSS Inc, Chicago, US). The in-patient and out-patient groups were analysed separately. The differences in characteristics between patients receiving 'normal' doses and high doses were tested by Chi squared tests for categorical variables and independent Student's *t* tests for continuous variables, with a significance level at a P value of less than 0.05. Logistic regression analysis was used to identify the most significant predictive factors for high-dose antipsychotic prescribing and the Hosmer-Lemeshow test to assess goodness of fit. The regression was repeated using backward modelling to test for model stability. Finally, linear regression was performed with the antipsychotic dose expressed as a continuous variable (percentage of the maximum recommended dose). The entire study was approved by the New Territories West Cluster Clinical and Research Ethics Committee.

Results

Demographic and prescription data were obtained from 1254 in-patients and 19 986 out-patients. Antipsychotic medications were prescribed to 1129 (90.0%) of the in-patients and 7520 (37.6%) of the out-patients, and the daily dosage was noted to be high in 104 (9.2%) and 137 (1.8%) of the patients, respectively. The characteristics of these patients are summarised in Table 1. For in-patients, a diagnosis of schizophrenia, schizotypal and delusional disorders (F20-29) and antipsychotic polypharmacy were significantly more common in those prescribed high dosages. For out-patients, younger mean age, male gender, history of violence, and antipsychotic polypharmacy were significantly more common in those prescribed high dosages. No association was noted between high dosage and the number of psychiatric admissions or duration of contact with the mental health services.

Logistic regression was performed to determine predictors most associated with high-dose antipsychotic prescribing (Table 2). The Hosmer-Lemeshow goodness-of-fit test indicated that the models created were an appropriate fit for the data (for in-patients, P=0.223; for out-patients, P=0.763). Compulsory detention, schizophrenic or delusional disorder, and antipsychotic polypharmacy were associated with high-dose antipsychotic prescribing for in-patients. History of violence and antipsychotic polypharmacy predicted high-dose prescribing in out-patients. For both samples, antipsychotic polypharmacy was the most powerful predictor of high dosages; the odds ratio was 8.88 for in-patients (95% confidence interval, 5.70-13.83; P<0.001) and 10.82 for out-patients (7.48-15.66; P<0.001).

TABLE 1. Characteristics of patients prescribed 'normal' and high doses of antipsychotic medications

Characteristic	'Normal' dosage	High dosage	P value
In-patients			
Mean (SD) age [years]	46.1 (14.4)	43.3 (11.7)	0.053‡
Mean (SD) dose*	46.2 (29.6)	128.8 (25.0)	<0.001†
Mean (SD) body mass index (kg/m²)	23.3 (4.5)	24.0 (4.3)	0.135‡
Mean (SD) No. of psychiatric admissions	5.2 (4.3)	5.8 (3.8)	0.174‡
Mean (SD) duration of contact with mental health services (years)	18.3 (12.5)	18.5 (10.5)	0.830‡
Patient No. (%) [n=1129]	1025 (90.8)	104 (9.2)	
Sex			
Male	663 (64.7)	75 (72.1)	0.129†
Female	362 (35.3)	29 (27.9)	
Smoking status			
Non-smoker	790 (77.1)	76 (73.1)	0.358†
Smoker	235 (22.9)	28 (26.9)	
History of violence			
No	637 (62.1)	56 (53.8)	0.098†
Yes	388 (37.9)	48 (46.2)	
Compulsory detention			
No	783 (76.4)	242 (23.6)	0.218†
Yes	85 (81.7)	19 (18.3)	
Schizophrenic or delusional disorder			
No	235 (22.9)	11 (10.6)	0.002†
Yes	790 (77.1)	93 (89.4)	
Antipsychotic polypharmacy			
No	852 (83.1)	37 (35.6)	<0.001†
Yes	173 (16.9)	67 (64.4)	
Out-patients			
Mean (SD) age [years]	50.3 (17.7)	44.1 (12.6)	<0.001‡
Mean (SD) dose*	23.3 (22.6)	130.1 (25.1)	<0.001‡
Patient No. (%) [n=7520]	7383 (98.2)	137 (1.8)	
Sex			
Male	3591 (48.6)	80 (58.4)	0.015†
Female	3792 (51.4)	57 (41.6)	
History of violence			
No	6812 (92.3)	109 (79.6)	<0.001†
Yes	571 (7.7)	28 (20.4)	
Antipsychotic polypharmacy			
No	6202 (84.0)	44 (32.1)	<0.001†
Yes	1181 (16.0)	93 (67.9)	

* Expressed as a % of the maximum recommended dose
† Chi squared test
‡ *t* test

Linear regression using the dosages of antipsychotics expressed as a percentage of the maximum of those recommended yielded similar results. For in-patients, when polypharmacy was excluded from the linear regression model, the other nine characteristics in combination only explained 3.1% of the variance in high-dose prescribing. Including polypharmacy in this model explained 16.6% of the variance (R^2=0.166, F=23.485, P<0.001). For out-patients, age, gender, and history of violence explained 5% of the variance for high-dose prescribing, and when polypharmacy was included, the model explained 37.3% of the variance (R^2=0.373, F=894.9, P<0.001).

TABLE 2. Characteristics identified by logistic regression analysis for high-dose antipsychotic prescription

Characteristic	Odds ratio (95% CI)	P value
In-patients		
Compulsory detention	1.72 (1.02-3.08)	0.042
Schizophrenic or delusional disorder	1.99 (1.01-3.92)	0.047
Antipsychotic polypharmacy	8.88 (5.70-13.83)	<0.001
Out-patients		
History of violence	2.04 (1.31-3.16)	0.002
Antipsychotic polypharmacy	10.82 (7.48-15.66)	<0.001

Discussion

Of all patients receiving antipsychotic medications, 9.2% of in-patients and 1.8% of the out-patients were prescribed high dosages. Such dosing was considerably less than the 20% reported in a recent large survey in the United Kingdom, which also studied an in-patient sample, the majority of whom were diagnosed to have schizophrenia, schizotypal and delusional disorders (F20-29).[1] Multi-national investigations in Asia[25] and Europe[26] revealed that 18% and 28% of the respective samples received high dosages of antipsychotic medications, but these two studies only included patients with schizophrenia. A diagnosis of schizophrenic or delusional disorder doubled the odds of high dosing for in-patients. A comparison with the out-patient sample was not possible in this study.

The strong association between antipsychotic polypharmacy and high-dose prescribing has been shown in several surveys[1,17,27] and was replicated in this study (odds ratio of 8.88 for in-patients and 10.82 for out-patients). Compulsory detention increased the odds of a high-dose prescribing 1.72 fold, which may reflect the severity of the illness.

For out-patients with a history of violence, the odds of high-dose antipsychotic prescribing was doubled. The odds for high-dosing in-patients with a history of violence was not statistically significant, contrary to the findings of similar in-patient studies in the United Kingdom.[16,23] There are two explanations for this finding. Firstly, using the Priority Follow-up registry does not identify all patients with a history of violence, as this is dependent on information provided to the psychiatrist and on the latter's decision to placing the patient on the registry, as a means of providing more intensive monitoring. Second, Castle Peak Hospital contains a significant proportion of long-stay in-patients and the patient mix may not be comparable to that in the United Kingdom.

There were no associations between high-dose antipsychotic prescribing and age, gender, body mass index, or smoking status, which are variables with the potential to affect drug pharmacokinetics in these patients. Similarly, there was also no association between high dosages and the number of prior psychiatric admissions or the duration of contact with the mental health services.

The fact that all variables combined explained only 16.6% of the variance for high-dose antipsychotic prescribing among in-patients and 37.3% among out-patients, points to the existence of other significant patient and/or prescriber variables in Hong Kong that were not assessed in this study. Several studies have examined prescribing practices of psychiatrists[19,20] and treatment settings[19,28] as possible variables affecting high-dose prescribing. The severity of illness, adherence to treatment, and psychosocial factors may also be of relevance. This study was cross-sectional and did not examine the reasons for high-dose antipsychotic prescribing.

From a legal perspective, the prescription of high-dose antipsychotic medications amounts to off-label use of these medications. The clinician is likely to be held liable and accountable should harm arise. Interestingly, the Royal College of Psychiatrists has recently published a report, "Use of Licensed Medicines for Unlicensed Applications in Psychiatric Practice",[29] which targets this problem.

Clinicians should be aware of the perils of prescribing high doses of antipsychotic medications, and should consider alternatives, including changing to different agents (eg clozapine) for treatment-resistant schizophrenia.[2-5] The Royal College of Psychiatrists now recommends that prescription of high-dose antipsychotic medications for the purpose of limited therapeutic trials (<3 months) should only be continued if there is evidence of clinical improvement and if benefits are believed to outweigh risks.[2] In view of the increased cardiac mortality associated with high-dose antipsychotic medication,[11] close monitoring of side-effects, including regular electrocardiography, was also recommended.[2]

Conclusion

This study found antipsychotic polypharmacy to be the factor most strongly associated with high-dose prescribing. Clinicians should exercise greater care when prescribing more than one antipsychotic medication to a patient. Better detection of high-dose antipsychotic prescribing and increased awareness of established clinical guidelines through regular clinical audits may facilitate better practice in this respect. More studies in this area should be conducted to discover other variables contributing to high-dose antipsychotic prescribing in Hong Kong.

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