Antipsychotic dose: from research to clinical practice

Robert Chaplin and Sean McGuigan

A case note study of antipsychotic prescribing in an inner London hospital showed that although doses of individual drugs were below the *British National Formulary* limits, polypharmacy occurred in a third of cases. Multiple regression analysis showed high doses were associated with a current risk to the self or others and increasing number of previous admissions in patients with mania and treatment non-responsiveness in schizophrenia.

Recent interest surrounds the establishment of optimum antipsychotic doses in the treatment of psychosis. In their *Consensus Statement on the Use of High Dose Antipsychotics*, the Royal College of Psychiatrists (Thompson, 1994) addressed the dangers of exceeding the maximum recommended doses. In a comment on the statement, Kane (1994) concluded that doses above the equivalent of 15–20 mg of haloperidol (500–700 mg chlorpromazine) offered no advantage in the treatment of schizophrenic patients without a history of treatment refractoriness, while McEvoy *et al* (1991) stated that the median effective dose is 350 mg chlorpromazine equivalents per day. There is no systematic research that supports the value of high doses or polypharmacy.

The aims of this study were to document the patient characteristics associated with prescribed antipsychotic dose and, compare these doses with research into optimum dose regimes in the treatment of psychosis.

The study

All patients in the acute wards of Springfield psychiatric hospital, London, who were receiving regular antipsychotic medication were studied during a one month period in 1994. Case notes were examined to obtain data on sociodemographic details, diagnoses and history. This was supplemented, where necessary, by a brief discussion with the nurse in charge or the junior psychiatrist. Ward staff had no opportunity to modify prescribing. The current daily antipsychotic dose in mg/day chlorpromazine equivalents was calculated according to the method of Foster (1989). Six patients receiving only risperidone, for which there is no data on chlorpromazine equivalent dosage, were excluded from the analysis.

A psychiatric diagnosis was made from the information available in the case notes. Three diagnostic groups were formed: schizophrenia (including schizoaffective disorder, paranoid psychosis and other non-affective psychoses), mania (including mixed affective disorder), and 'other'. The broad classification of schizophrenia was used for comparison with studies of optimum antipsychotic dose.

Findings

The 107 patients currently receiving regular antipsychotic prescriptions are described in Table 1. Of the 67 (63%) of patients on single antipsychotic drugs, diagnoses were: 49 (73%) schizophrenia, 11 (16%) mania, and seven (11%) 'other'. Forty (37%) were prescribed two or more antipsychotics, four (4%) receiving three antipsychotics. Of those receiving multiple antipsychotic prescriptions, 36 (90%) suffered from schizophrenia and four (10%) mania.

Other psychotropic drugs additionally prescribed regularly to the sample included benzodiazepines (10 patients), lithium (19 patients), anticonvulsants (seven patients) and antidepressants (13 patients). Those with schizophrenia or mania who were additionally prescribed lithium or an anticonvulsant received a median dose of 1000 mg chlorpromazine equivalents and the three patients prescribed benzodiazepines received a median dose of 1900 mg.

Using multiple regression analysis, the doses in chlorpromazine equivalents prescribed to men (median 847 mg/day) and women (median 666 mg/day) were not significantly different. Patients with schizophrenia (median dose of 848 mg, 50% interquartile range 500–1250 mg) and those with mania (median dose 800 mg, 50% interquartile range 550–1200 mg), received strikingly similar doses but those with other diagnoses (most frequently depressive disorder) received a significantly lower dose (median 300 mg).

Within each diagnostic group an attempt was made using multiple regression analysis to model

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the variation of the antipsychotic dose in chlorpromazine equivalent with a range of socio-demographic and clinical factors. The multiple regression models proposed were of the form:

$$\text{antipsychotic dose} = \alpha + \Sigma \beta_i X_i$$

where X_i represented the variables age, gender, ethnicity, history of violence, risk of self-harm, risk of harm to others, Mental Health Act status, drug or alcohol history, acute disturbance, treatment unresponsiveness and number of previous admissions. In those with schizophrenia, the only variable with which higher antipsychotic dose was significantly associated at the 5% level was a history of treatment unresponsiveness. In those with mania, higher antipsychotic dose was significantly associated with a current risk to the self or others, and increasing numbers of previous admissions.

High dose antipsychotic was defined as >1000 mg chlorpromazine equivalent per day and was prescribed to 34 (41%) patients with schizophrenia, 6 (37.5%) patients with mania but to none of those with other diagnoses. Only one patient was prescribed a single drug at higher dose than recommended by the *British National Formulary* (BNF; British Medical Association and Royal Pharmaceutical Society of Great Britain, 1993). A separate univariate analysis was used to examine the characteristics of the patients with schizophrenia receiving high dose antipsychotics. This was strongly associated with a history of violence (χ^2=8.41, d.f.=1, P=0.004), and a mental state characterised by a risk of self-harm, harm to others or severe disturbance (χ^2=4.91, d.f.=1, P=0.027).

Table 1. Patient characteristics and antipsychotic drug prescriptions

Patient characteristics	Male (*n*=66)	Female (*n*=41)
Age: Mean (s.d.)	35 years (15)	44 years (16)
Compulsory status (%)	36 (55%)	23 (51%)
Treatment unresponsive	14 (21%)	13 (31%)
History of violence	26 (39%)	3 (7%)
Current alcohol or drug use	16 (24%)	2 (5%)
High dose prescriptions, >1000 mg/CPZ daily	25 (40%)*	13 (33%)*
Median dose of total antipsychotic drugs (mg CPZ equivalent)		
Total (50% interquartile range)	847 mg (500–1250)	666 mg (375–1100)
Schizophrenia	967 mg (*n*=54)	720 mg (*n*=29)
Mania	733 mg (*n*=8)	950 mg (*n*=8)
Other diagnoses	267 mg (*n*=3)	300 mg (*n*=5)

*Excludes those prescribed risperidone as no data available on relative antipsychotic potency in mg chlorpromazine equivalents.
CPZ, chlorpromazine

Comments

This study shows that the guidelines in the Royal College *Consensus Statement* are being adhered to with regard to the use of individual antipsychotic drug doses within the maximum limits set by the BNF. However, antipsychotic polypharmacy occurred in nearly a third of all patients, and as a result high doses (>1000 mg chlorpromazine equivalents) were prescribed to 40% of patients with diagnoses of schizophrenia and mania.

The factors that predicted high dose prescribing can be divided into two groups. First, those that were prescribed for their sedative effects in patients suffering from schizophrenia with acute disturbance or a history of violence, and in patients with mania at risk of harming themselves or others. This suggests they are used in preference to benzodiazepines which were only regularly prescribed to 10% of the sample. Additionally, this cross-sectional data suggests that the use of other agents (e.g. mood stabilisers and benzodiazepines) is not associated with lower dose antipsychotic prescribing.

The other important indicator of high dose prescription was illness with a poor outcome. Measures of chronicity in patients with mania (increasing number of admissions) and treatment resistance in patients with schizophrenia were associated with increased prescribed dose. Alternative strategies for the management of treatment resistance (Royal College of Psychiatrists, 1994) include review of diagnosis and compliance, dose reduction, clozapine (only used in 3% of our sample despite 27% being treatment resistant), augmentation with mood stabilising drugs where appropriate, and re-evaluation of environmental stressors.

This study has addressed the patient characteristics associated with the receipt of high dose antipsychotic drugs but is of limited value in explaining the therapeutic rationale behind such decisions. Further studies are needed to investigate the attitudes of psychiatrists to the use of high dose antipsychotics and polypharmacy.

Conclusion

Patients are frequently prescribed higher doses of antipsychotics than supported by research findings, even though keeping within safe BNF limits. High dose treatment arises from polypharmacy and carries increased risk of toxic effects, for

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example Parkinsonism and akathisia, with subsequent risk of non-compliance and limited evidence of therapeutic advantage. It is recommended that psychiatrists reduce polypharmacy, consider alternative options for treatment refractory patients, attempt careful dose reductions in patients receiving high doses and locally audit their antipsychotic prescribing practices.

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