An Audit of High Doses of Antipsychotics

by

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Abstract

Prescription of high dose antipsychotics remains a common practice, contrary to available evidence. Studies have found that, on average, high daily doses of antipsychotics are no more effective or are less effective than are moderate doses, and have indicated that higher doses are associated with a greater incidence of side effects which may be worse than with a moderate dosage range in the treatment of schizophrenia. The objectives of the study were to examine the safety of high dose antipsychotic use in treating patients with psychotic illnesses in hospital settings in Edmonton and to examine different variables which are associated with treatment resistant schizophrenia in patients who received high-dose antipsychotics and which could be of predictive value for determining poor response to antipsychotics. Results showed that a statistical difference was reached with regard to the non-improvement with high doses versus regular doses, confirming that increasing the doses above recommended ranges does not lead to further amelioration of symptoms. Also, a statistical difference was reached with regard to concurrent medical conditions being more frequent in the high dose group versus regular dose group. The high dose group had a higher number of previous episodes.

Preface

This thesis is an original work by Simona Folescu. The research project, of which this thesis is a part received ethics approval from the University of Alberta Research Ethics Board, project name "An audit of high doses of antipsychotics", No Pro00006330, November17, 2009.

An audit of use of high doses of antipsychotics

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AAP	Atypical antipsychotics
BNF	British National Formulary
BPRS	Brief psychiatric rating scale
CGI	Clinical global index
CPS	Compendium of pharmaceuticals and specialties
CPZ	Chlorpromazine
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
EPS	Extrapyramidal side effects
PANSS	Positive and negative syndrome scale
RCT	Randomized controlled trials
SE	Side effects
SPC	Summary of Product Characteristics

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Chapter 1

1.1 Introduction

For psychotic illnesses, antipsychotic medications remain the mainstay of treatment. The doses being used have historically varied considerably in the last 30 years. For example, a maximum dose of 30 mg of haloperidol, daily, has replaced the 240 mg doses for “severe cases” that used to be used. There are though still uncertainties and inconsistencies in how high an antipsychotic doses should be and if there is any benefit on going above certain doses (15; 38). Although in clinical practice high doses of antipsychotics are being used frequently, the literature supporting this practice is sparse. The use of high doses is frequent and it comes with potential side effects (22; 23; 31; 51; 56; 58; 59)

There are a few challenges to be considered:

First, how do we know we have reached a high dose and what protocol needs to be followed before we go to high doses. Also, is there a certain type of population that tends to be put on high doses? And finally, what trials have been conducted so far that looked at high doses vs. regular doses?

For potential answers to these questions I conducted a literature review.

1.2 Review of the literature

1.2.1 Defining high doses of antipsychotics

A high dose is one that exceeds the maximum dose stated in the manufacturer's summary of product characteristics for that drug. It can be defined in chlorpromazine (CPZ) equivalents or British National Formulary (BNF) percentages. If more than 1000 mg CPZ equivalents or more than 100% of the maximum recommended dose in the BNF are being used, then this is considered a high dose.

Should we use CPZ equivalents or BNF percentages? The research done in the area shows more than 90% concordance rates. For example, Hung and al. (25) found a 97.2% concordance between these two methods and Yortson and al. (58) reported a 93% concordance rate.

A 'high-dose' is defined as 'a total daily dose of a single antipsychotic which exceeds the upper limit stated in the Summary of Product Characteristics (SPC) or BNF ' or 'a total daily dose of two or more antipsychotics which exceeds the SPC or BNF maximum using the percentage method'(RCP London, 2006)(46; 47)

What are the current recommendations of high doses being used?

According to the American Psychiatric Association, in clinical practice doses of several second-generation drugs, including olanzapine, quetiapine, and ziprasidone, have been extended above their recommended ranges. In determining the target dose, the psychiatrist should consider the patient's past history of response and dose needs, clinical condition, and severity of symptoms (1).If the patient is able to tolerate a higher dose of antipsychotic medication without significant side effects, raising the dose for a finite period, such as 2–4 weeks, can be tried, although the incremental efficacy of higher doses has not been well established. If

dose adjustment does not result in an adequate response, a different antipsychotic medication should be considered.

According to the Canadian Psychiatric Association (13), dosages should be maintained within the recommended range, and reasons for going outside the range should be clearly documented and justified".

The Consensus Working Group of the Psychiatric Association (London) recommends the following definition for high dose: a total daily dose of a single antipsychotic which exceeds the upper limit stated in the BNF (published by the British Medical Association & Royal Pharmaceutical Society of Great Britain) or a total daily dose of two or more antipsychotics which exceeds the *BNF* maximum using the percentage method (see previous section on Definition of high dose). Current evidence does not justify the routine use of high-dose antipsychotic medication in general adult mental health services, either with a single agent or combined antipsychotics. If high doses are to be used in an individual case, this should only be after evidence-based strategies have failed, and as a carefully monitored therapeutic trial. The decision to prescribe a high dose (of either an individual agent or through combination) should be taken seriously and should involve an individual risk–benefit assessment by a fully trained psychiatrist. This should be undertaken in consultation with the wider clinical team and the patient and a patient advocate, if available, and if the patient wishes their presence. Supplementary prescribers should not make the decision to proceed to the use of high dose. The decision to prescribe a high dose should be documented in the case notes, including the risks and benefits of the strategy, the aims, and when and how the outcome will be assessed. Dose escalation should be in relatively small increments and allow adequate time for response, and this includes prescribing once the high-dose threshold has been passed. Careful watch should be kept on the dose in terms of total percentage arising from drug

combinations, and the use of PRN (as required) medication. Local systems should be developed to alert the responsible psychiatrist/clinical team of patients currently being administered or at risk of receiving high doses.

1.2.2 Prevalence of high doses of antipsychotics

The use of high doses in clinical practice remains frequent with most research being done in inpatient settings. The prevalence is reported to vary between: 6.8% (52) to 36% (43).Seven surveys, conducted in the UK over the past decade, involved a total of 4200 in-patients (15; 32; 58). About one quarter of patients included in these studies were prescribed a high dose of antipsychotic medication. For the great majority of these, a high dose was prescribed by virtue of polypharmacy; only 5% of those prescribed a high dose (about 1% of all in-patients) were prescribed a single antipsychotic at a dose above *BNF* limits. Compared with acute psychiatric wards, the prescribing of high doses appears to occur more frequently in psychiatric intensive care units (19), rehabilitation wards and medium secure units (33).Prescriptions of high-dose antipsychotics for a sample of 2136 patients with schizophrenia from six countries and territories (mainland China, Hong Kong, Korea, Japan, Taiwan and Singapore) were evaluated in 2004 and compared with data obtained for 2399 patients in 2001. Overall, the comparison between 2001 and 2004 showed a significant decrease in high-dose antipsychotic use from 17.9 to 6.5%

1.2.3 Current research on individual antipsychotics used in high doses

1.2.3.1 Olanzapine:

Olanzapine is used in clinical practice at doses of 10-15 mg, with maximum being 20 mg.

A few trials examined potential benefits of increasing the doses of olanzapine above the recommended range. Citrome and Kantrowitz (17) analyzed case study trials done between 1997 and 2006. The conclusion was that overall the dose of 20 mg should not be exceeded but that also it is possible to see some benefits for selected patients who are treatment resistant, have high levels of psychopathology or who are acutely agitated. Meltzer et al. (39) compared regular doses of clozapine with high doses of olanzapine and found no benefit in increasing the dose of olanzapine versus having patients on regular doses of clozapine. Mitchell et al. (40) found no additional benefit to increasing the dose to 30-40 mg but did notice more akathisia at the higher doses.

Table 1: Summary of findings from 3 trials on olanzapine

	Trial 1	**Trial 2**	**Trial 3**
Source	Citrome L, Kantrowitz JT	Meltzer HY, Bobo WV, Roy A, Jayathilake K, Chen Y, Ertugrul A, Anil Yağcioğlu AE, Small JG	Mitchell M, Riesenberg R, Bari MA, Marquez E, Kurtz D, Falk D, Hardy T, Taylor CC, Mitchell CP, Cavazzoni P.
Site	Nathan S Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Orangeburg, NY 10962, USA	Department of Psychiatry, Vanderbilt University School of Medicine, Nashville, Tenn., USA	Lilly Research Centre, Eli Lilly and Co. Ltd., Windlesham, Surrey, United Kingdom
Type of trial	Review of trial between 1997 and 2006	Double blind randomized control trial. A comparison between high doses of Olanzapine and regular doses of Clozapine in treatment resistant schizophrenia	double blind randomized control study
Nr of participants		40 participants	37 participants

Results Trial 1	Case reports of patients receiving doses up to 60 mg/day describe a favorable benefit-risk ratio. Double-blind clinical trials that have examined doses of olanzapine greater than 20 mg/day are limited in number, but suggest that these doses may be helpful in selected patients who are treatment resistant, have high levels of psychopathology or who are acutely agitated. This must be balanced by an increased risk of weight gain and elevated prolactin that was observed among those receiving 40 mg/day in a large randomized clinical trial comparing doses of 40 versus 20 versus 10 mg/day. In conclusion, dosing of olanzapine in clinical practice is higher than what has been established in the registration program for schizophrenia or bipolar disorder. This is somewhat supported by double-blind, controlled clinical trial evidence, but only for selected patients with severe and/or persistent symptoms.
Results Trial 2	Robust and significant (mostly $p < .001$) improvement in multiple measures of psychopathology, mainly between 6 weeks and 6 months of treatment, was found in both treatment groups, with no significant difference between the 2 treatments except for the Global Assessment of Functioning score, which favored clozapine ($p = .01$). Improvement in some domains of cognition was significant-and equivalent for both drugs, as well. Nonsignificantly different improvement in Verbal List Learning-Immediate Recall ($p < .05$), Controlled Word Association Test ($p < .05$), and Digit Symbol Substitution Test ($p < .001$) was found. There were no significant differences in extrapyramidal symptoms. Weight gain was significantly ($p = .01$) greater with olanzapine. Olanzapine, at higher than customary doses, demonstrated similar efficacy to clozapine in treatment-resistant schizophrenia and schizoaffective disorder in this study. However, the small sample size precludes definitively concluding that the 2 treatments are equivalent, at these doses, in treatment-resistant schizophrenia. The metabolic side effects of olanzapine are a limitation in its use

Table 1(Continued)

Results Trial 3	Of the 53 subjects who entered the study, 16 were excluded (7 because entry criteria were not met, 6 because of subject's decision, and 3 for other reasons). Subjects were primarily men (group A, 75%; group B, 55%; group C, 79%), approximately 40 years old (mean [SD] age: group A, 40.6 [8.6]; group B, 37.9 [8.6]; group C, 39.4 [9.2] years), and black (group A, 83%; group B, 55%; group C, 64% [the remainder were white]). Mean (SD) baseline weight was 84.0 (17.5) kg for group A, 82.1 (12.0) kg for group B, and 100.9 (23.3) kg for group C. By day 20, dose-proportional increases were observed in plasma olanzapine Cmax,ss and AUC. Geometric mean (percent coefficient of variation) values for groups A, B, and C at day 20 were as follows: Cmax, 57.8 (40.2), 75.6 (86.7), and 94.1 (50.2) ng/mL, respectively; and AUC: 997 (38.5), 1220 (88.0), and 1630 (53.9) ng. H/mL, respectively. The most frequently reported adverse events were weight gain (group A, 2/12 [17%]; group B, 3/11 [27%]; group C, 2/14 [14%]) and sedation (group A, 3/12 [25%]; group B, 2/11 [18%]; group C, 2/14 [14%]). Mean (SD) weight gain from baseline to end point was 3.5 (2.81) kg for group A, 3.0 (3.15) kg for group B, and 3.1 (2.22) kg for group C. Changes in glucose tolerance, vital signs, or laboratory parameters did not appear to be dose dependent. During double-blind therapy, 7 subjects experienced akathisia (spontaneously reported, n=3 [group C]; categorically defined, n=3 [group B]; both, n=1 [group C]). Of the subjects with categorically defined akathisia, 2 had a history of akathisia and the other had a score of 1 (questionable) on the Barnes Akathisia Scale at baseline. No cases of parkinsonism were observed at any time. Conclusion: Among these subjects with psychiatric illnesses, olanzapine at doses of 30 and 40 mg/d displayed a pharmacokinetic profile consistent with that of 20 mg/d. Higher-dose olanzapine exhibited a tolerance profile similar to that of 20 mg/d; however, akathisia may be more likely to occur at higher doses, particularly in subjects with a history of akathisia.

Table 1(continued)

1.2.3.2 Quetiapine:

Quetiapine is usually used at doses of 600 mg, the maximum being 800 mg.

Honer and MacEwan(24) found no added benefit to increasing the dose to 1200 mg, but noticed also more Parkinsonian side effects and also metabolic side effects. Lindenmayer and Citrome(35) also confirmed no additional benefit to 1200 mg of Seroquel. Boggs and Kelly (11) found that a 1200 mg dose was safe and helped positive symptoms further. However it only had 12 participants.

Table 2: Summary of findings from 3 trials on quetiapine

	1	2	3
Source	Honer WG, MacEwan GW, Gendron A, Stip E, Labelle A, Williams R, Eriksson H; STACK Study Group	Lindenmayer JP, Citrome L, Khan A, Kaushik S, Kaushik S	Boggs DL, Kelly DL, Feldman S, McMahon RP, Nelson MW, Yu Y, Conley RR
Site	19 referral centres	Manhattan Psychiatric Centre, New York	Yale University
Type of trial	The 8 week, double-blind study compared continuation of quetiapine 800 mg/d (n = 43) versus 1,200 mg/d (n = 88). The primary outcome measure was emergent or worsening parkinsonism (Simpson-Angus Scale). Secondary outcomes were adverse events, metabolic side effects, and increased symptom severity	RCT double blind study	RCT double blind study
Number of participants	131 participants	60 participants	12 participants

Results Trial 1	The results did not demonstrate any advantage for use of quetiapine outside the approved dose range.
Results Trial 2	No significant differences were observed between the high dose (n = 29) and standard dose (n = 31) groups in change from baseline to endpoint on extrapyramidal symptoms, electrocardiographic changes, or most laboratory measures between groups. There was a significant difference between groups for triglycerides (P = 0.035), and post hoc tests revealed a decrease in triglycerides from baseline (mean [SD], 162.7 [59.3] mg/dL) to endpoint (mean [SD], 134.8 [62.7] mg/dL) for the 600 mg/d group (P = 0.019). The mean change in the Positive and Negative Syndrome Scale total score did not differ between groups. In conclusion, quetiapine at 1200 mg/d, although reasonably tolerated, did not confer any advantages over quetiapine at 600 mg/d among patients who had failed to demonstrate an adequate response to a prospective 4-week trial of 600 mg/d.
Results Trial 3	the 1200 mg dose was found to be safe and well tolerated and appeared to further improve positive symptoms

Table 2 (continued)

1.2.3.3 Risperidone

Risperidone is usually used at doses of 2-6 mg, with maximum being 8 mg.

Three trials, of fairly short duration, that compared regular doses with high doses were identified (34):

- 8 week trial (n=513) involving 4 fixed doses of RISPERDAL® (2 mg/day, 6 mg/day, 10 mg/day, and 16 mg/day, on a twice-daily

schedule) The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses(18).

- In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1 mg/day, 4 mg/day, 8 mg/day, 12 mg/day, and 16 mg/day, on a twice-daily schedule). The most consistently positive responses were seen for the 4 mg dose group (37).
- In a 4-week, placebo-controlled dose comparison trial (n=246), by involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a once-daily schedule), the results were generally stronger for the 8 mg than for the 4 mg dose group(45).

1.2.3.4 Clozapine:

Clozapine is usually used at doses of 300-600 mg, maximum being 900 mg.

Surprisingly few trials of high doses of clozapine have been done, most of them being case reports. Keller and Drexler (29) published a case report of successfully administering electroconvulsive therapy (ECT) to a patient on 1800 mg of clozapine. The case of a 19-year-old man with paranoid schizophrenia was reported; he responded only partially to treatment with daily doses of clozapine, 1800 mg; aripiprazole, 20 mg; and clonazepam, 6 mg. Clozapine was reduced to 1600 to 1700 mg, maintaining therapeutic serum levels, and a course of ECT was added that included 24 treatments. Therapeutic results were minimal. However, adverse effects were limited to mild cognitive disturbances. This experience adds to other reports suggesting that clozapine and ECT can be combined without causing excessive adverse effects.

Maccall and Billcliff (36) stated that above 900 mg, clozapine could be used with additional benefits. Patients may fail to respond to clozapine treatment despite use of the maximum licensed UK dosage (900 mg/day) because of ultra-rapid metabolism of the drug. Findings of a study of a national clozapine/norclozapine assay service for the period 1997-2005 and three individual case studies of patients treated with clozapine in doses greater than 900 mg/day were presented. The findings suggested that clinicians should be alerted to the possibility of treatment failure because of rapid clozapine clearance secondary to genetic factors and heavy cigarette consumption. This may necessitate the use of clozapine in doses up to 1400 mg/day, notably in young male smokers. Doses of greater than 900 mg/day are rarely justified in women. Anyone given relatively high-dose clozapine (600 mg/day or more) should be monitored regularly for adverse events and changes in smoking habits.

1.2.3.5 Aripiprazole:

Aripiprazole is usually used at doses of 10 mg, maximum being 30 mg.

Chavez and Poveda (16) suggested that switching to high doses of aripiprazole could be potentially beneficial. A 57-year-old man with a 30 year history of schizophrenia had been taking olanzapine for 4 years, with the dosage titrated to 20 mg/day, to control the psychosis. After he had gained significant weight with olanzapine (the highest was 102.7 kg), his treatment was switched to aripiprazole. The patient required a high dose of aripiprazole (60 mg/day) to achieve full control of the psychiatric symptoms, and during aripiprazole therapy, he lost the weight he had gained while on olanzapine, weighing 85.9 kg within 7 months after the therapy switch. Dosages of atypical antipsychotics higher than those recommended by the Food and Drug Administration are often used

in clinical practice for refractory patients, despite the lack of evidence. High-dose aripiprazole (60 mg/day) was well tolerated and controlled this patient's symptoms effectively. In addition, he lost weight that was gained while being treated with olanzapine. High-dose aripiprazole may be beneficial and safe in refractory patients; however, large, double-blind, randomized clinical trials are needed.

1.2.3.6 What about polypharmacy?

A systematic review was conducted in September 2012(49)

- Assessed the efficacy and safety of atypical antipsychotics combination therapy and high-dose monotherapy
- 30 RCT were included
- Common outcomes were PANSS, BPRS, CGI, response rates, cognition, withdrawals, and serious adverse events.

Combination treatment strategies:

- Clozapine plus AAP versus Clozapine : 11 randomized controlled trials (RCT)
- No statistical difference, except slight CGI improvement at 16 weeks
- More serious side adverse events with combinations
- More akathisia
- More weight gain

Non clozapine atypical antipsychotics vs. Non-clozapine monotherapy

- 2 RCTs, 16 weeks
- Risperidone plus aripiprazole vs risperidone and seroquel plus aripiprazole vs seroquel
- No difference in outcome
- More adverse effects with combination

Clozapine vs. high doses antipsychotics

- 8 RCTs
- Standard clozapine better than high dose risperidone in 1 trial , but the remaining 7 trials found no difference
- Standard clozapine was equal to high olanzapine but more weight gain and anticholinergic side effects with olanzapine, more siallorrhea with clozapine

High doses of atypical antipsychotics versus regular doses of antpsychotics

- 1 RCT
- High risperidone versus regular haloperidol: risperidone was better

Overall, the limitations of the review were that 27 out of the 30 RCT were rated as poor. The studies had short duration and low power, as well as poor documentation on dosing levels and treatment history.

Conclusions were that high doses of atypical antipsychotics or combinations were not more efficacious than standard doses of antipsychotics, but in fact it came with more side effects. The recommendation was also that longer studies should be done.

1.2.4 Factors influencing high dose use

There are a number of factors that have been postulated to influence high doses of antipsychotics being used:

- Smoking
- Adjunctive lithium, carbamazepine, benzodiazepines
- Racial differences
- Positive symptoms
- Aggression

Botts and al (12) examined variables associated with high olanzapine dosing in a state hospital. A retrospective review of all patients receiving olanzapine during an inpatient stay at a state psychiatric hospital in Kentucky during 2001 was conducted. Demographic information and smoking status were collected for all patients. Olanzapine doses of > 20 mg/day were considered high doses. Neither gender nor smoking status was associated with receiving a high dose of olanzapine. The association of increased length of stay with high dose suggests that treatment resistance may be an important factor in receiving high daily doses of olanzapine. Combinations of antipsychotics and the use of other medications as requested (prn) have been more often postulated to contribute to the use of high doses of antipsychotics, as opposed to monotherapy. According to Cherrie (1997), patients receiving additional lithium, carbamazepine or benzodiazepines were more likely to receive high doses of antipsychotics. Bakare (41) looked at racial differences in prescribing antipsychotics. According to Hung (25), polypharmacy and being an inpatient were predictors of high doses of antipsychotics being used. Barbui and Biancosino(7) reported that positive symptoms were associated with high doses of antipsychotics. Barnes reported that aggression and polypharmacy, with depot medications and other medications as requested (prn) were more frequent. Tungaraza (52) reiterated that polypharmacy is the most common factor implicated in the use of high doses.

Is ‘high-dose’ treatment better than ‘low-dose’? Are two antipsychotics better than one? We don't know. There has been a surprisingly low number of high dose trials conducted, with very few meet today's exacting standards for properly conducted studies. The only conclusion that can be drawn from these data is that a minority of patients may benefit from high doses as per Aubree & Lader(5). Against this is the observation that, in recent dose-finding studies of atypical drugs, there appears to be a threshold effect. That is, above

a certain dose limit all doses give rise to the same degree of response (risperidone and quetiapine are good examples). This threshold theory is supported by recent neuroimaging studies (Kapur *et al*, 2000) (28).

Kapur (2000) (28) examined the dopamine D2 receptor occupancy through imaging. Since all antipsychotics block dopamine 2 receptors, the authors investigated how well D 2 receptor occupancy in vivo predicts clinical response, extrapyramidal side effects, and hyperprolactinemia. In a double-blind study, 22 patients with first-episode schizophrenia were randomly assigned to 1.0 or 2.5 mg/ day of haloperidol. After 2 weeks of treatment, dopamine D2 receptor occupancy was determined with 11C raclopride and positron emission tomography, and clinical response, extrapyramidal side effects, and prolactin levels were measured. Patients who showed adequate responses continued taking their initial doses, those who did not respond had their doses increased to 5.0 mg/day, and evaluations were repeated at 4 weeks for all patients. The patients showed a wide range of dopamine D2 receptor occupancy (38%-87%). The degree of receptor occupancy predicted clinical improvement, hyperprolactinemia, and extrapyramidal side effects. The likelihood of clinical response, hyperprolactinemia, and extrapyramidal side effects increased significantly as dopamine D2 occupancy exceeded 65%, 72%, and 78%, respectively. The study confirms that dopamine D2 occupancy is an important mediator of response and side effects in antipsychotic treatment. The data are consistent with a "target and trigger" hypothesis of antipsychotic action, i.e., that the dopamine D2 receptor specificity of antipsychotics permits them to target discrete neurons and that their antagonist properties trigger within those neurons intracellular changes that ultimately beget antipsychotic response. While limited to haloperidol, the relationship between dopamine 2 occupancy and

side effects in this study may help explain many of the observed clinical differences between typical and atypical antipsychotics.

Is polypharmacy working? This has been poorly supported: the very few studies available do suggest that two drugs are effective where one alone is not (Yuzda, 2000) (59). The only exception is that of augmenting effect to clozapine. (Canales et al, 1999)(14).

1.2.5 Side effects of high doses

Why should we worry about high doses of antipsychotics? The literature shows that there are some side effects that can appear when you exceed the proposed limit:

1) Prolongation of QT interval (3;9;20;21;28;50)
2) Increased EPS (2;8; 10)
3) Neuroleptic Malignant Syndrome (42)

A paradoxical increase in violence may occur due to severe akathisia or confusional states due to cholinergic blockade (Barnes & Bridges) (8).

Patients with the following are at high risk for cardiac problems:

1) Previous episodes of torsades de points

2) Left ventricular dysfunction

3) Left ventricular hypertrophy

4) Heart blocks.

5) Electrolyte abnormalities: a decrease in potassium, calcium and magnesium levels

6) Alcohol dependence

7) Women

8) Treatment with diuretics

Recommended monitoring:

All patients should be assessed for cardiovascular disease prior to the institution of antipsychotic drug therapy, regardless of dose. This should, whenever possible, include an ECG, which should be examined for evidence of ischemic heart disease, left ventricular hypertrophy and repolarisation abnormalities. The presence of such factors may affect the choice of antipsychotic drug or increase the frequency of monitoring required, as well as prompt a more detailed cardiac assessment.

An ECG prior to, and ECG monitoring during, antipsychotic therapy is particularly important where higher risk antipsychotic drug treatment is contemplated (for example, pimozide and haloperidol). Special precautions pertain for sertindole, and these are embodied in the summary of product characteristics. High-dose or parenteral antipsychotic drug therapy is not to be used if the patient receiving the medication has a history of cardiovascular disease. Urea and electrolytes should also be checked, particularly plasma potassium, especially in patients at higher risk of electrolyte abnormalities, due, for example, to anorexia nervosa, diuretic use or dehydration. ECGs should be performed every few days following initiation of such therapy or during a period of dose escalation, until it is judged that steady state concentrations have been reached. Thereafter, ECG and electrolyte assessment is recommended every few months, at times of acute illness, when potentially interacting drugs are introduced or if the patient experiences symptoms that could be due to arrhythmia, for example syncope or fits (Yap & Camm, 2000) (57).

Chapter 2:

2.1 Methodology

The methodology used for developing this retrospective study included a few steps:

a) Conception
b) Literature review
c) Proposal development
d) Data abstraction instrument
e) Development of protocols and guidelines for abstractions
f) Data abstraction
g) Sampling
h) Ethics
i) Pilot study

Analyzing the data:

The methodology of this research includes a 2 step approach:

The first part is a simple tabulation of the 'yes' and 'no' responses for the total sample as well as 2 x 2 tables for clinical indicators by the remaining variables. The yes and no responses refer to answering the question if the clinical indications for a patient being started on a high dose were documented or not. The idea is to look at which variables made a statistical difference reported to clinical indicators. Chi-squared test and Yates correction for continuity were used.

Chi-square is a statistical test commonly used to compare observed data with data we would expect to obtain according to a specific hypothesis.

In statistics, Yates' correction for continuity (or Yates' chi-squared test) is used in certain situations when testing for independence in a contingency table.

Second, we constructed a model to predict which variables can play a role in a patient being put on high doses. For this second part, a logistic regression model was used.

2.2 Building a logistic regression model

A goal of this research was to identify variables or combinations of variables that were influential in discriminating between high and low dose groups. Logistic regression was used for this purpose because this technique is based on the assumption of a binary-valued dependent variable. By considering dosage as binary-valued, i.e., high vs low, logistic regression is a natural choice for this analysis. A further advantage of logistic regression is that it does not require any assumptions about the probability distributions of the predictor variables and allows a mixture of both discrete and continuous variables which is the case for the data in this study. The method provides a statistical test of the individual regression coefficients as well as a test of the model fit as each predictor variable is added to the mode.

The nature of this research calls for a dichotomous outcome: whether a male or a female tends to be put on high doses of antipsychotics, whether having abnormal imaging results makes a difference.

The goal is to investigate those variables that are able to have predictive value for dosage: for example if abnormal imaging is a significant predictor whether individuals will be assigned to higher or regular dose group.

If *p* represents the probability of 'success' for a binary variable such as high dose in the present study, logistic regression involves

modeling the logit which is defined as the natural logarithm of the odds ratio which can be written as

$$\ln\left(\frac{p}{1-p}\right).$$

Given a set of *k* predictor variables, $x_1, x_2, \ldots x_k$, the overall logistic regression model can be written as

$$\ln\left(\frac{p}{1-p}\right) = \beta_\circ + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k$$

with the corresponding logistic curve then being of the form

$$p(x) = \frac{\exp\left(\beta_\circ + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k\right)}{1 + \exp\left(\beta_\circ + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k\right)}.$$

Estimation of the logistic regression coefficients is accomplished by optimizing the maximum likelihood equation associated with the equation for logistic curve (Johnson and Wichern, 2007) (26).

Once estimates of the regression coefficients have been obtained, an individual's scores on the predictor variables can then be used to predict membership in the high and low-dose groups.

2.3 Study protocol:

I was the only one to conduct the retrospective chart review and thus have access to patient information. I also applied the inclusion/exclusion criteria. The patient records reviewed consisted of the hospital admission records only, which contain printed medication lists. Therefore there was no need to request the pharmacy prescription records. Only patients who met the DSM-IV TR diagnostic criteria of psychotic disorders were included in the study.

Data recorded remained anonymous (data were coded numerically and contained no personal identifiers).

The review process was conducted as follows. The charts of patients admitted to the two psychiatric in-patient units at the University of Alberta Hospital were requested for review on a month-by-month basis. The estimated time frame for patient admission dates for the retrospective chart review was approximately one year. There was no firm temporal limitation concerning the admission date for chart review. Data collection was discontinued as soon as the target number of 100 cases per group was obtained.

Two patient groups were studied: (1) patients who received a high dose of antipsychotic medication(s); (2) patients who received antipsychotic medication doses within the recommended dosage range. High dose antipsychotic medication was operationally defined as follows. The Compendium of Pharmaceuticals and Specialties (CPS, 2009) recommends a maximum dose or a dose range for all antipsychotic drugs. The CPA clinical practice guidelines (Canadian Psychiatric Association, 2005) for treatment of schizophrenia employ the CPS recommended doses of antipsychotics. The latter guidelines do not include recommendations regarding the use of high antipsychotic doses, however, aside from documenting and justifying the reason for exceeding the recommended doses. For the purposes of this study, we have chosen the CPS maximum recommended chlorpromazine (CPZ) (i.e., 1000 mg/day) dose for the definition of high antipsychotic dose. The chlorpromazine equivalents (Woods, 2003) (51) were considered together and used to calculate the cumulative daily dosage. A cumulative daily dosage exceeding 1000 mg/day CPZ equivalent will be operationally defined as a high dosage. Please also see Tables 3, 4, and 5.

Table 3: First generation antipsychotics included in the study
Adapted from CPS, 2009(13).

Drugs	Usual dose	Maximum dose
Chlorpromazine	200-400 mg/day	1000-2000 mg/day
Loxapine	20-100 mg/day	250 mg/day
Perphenazine	12-48 mg/day	48-64 mg/day
Zuclopenthixol	20–60 mg/day	100 mg/day
Flupenthixol	9-24 mg/day	12-24 mg/day
Fluphenazine	2.5–10 mg/day	20 mg/day
Pimozide	2–12 mg/day	12 mg/day
Trifluoperazine	6–20 mg/day	40 mg/day
Haloperidol	4–12 mg/day	20 mg/day
Thiothixene	15–30 mg/day	60 mg/day

Table 4: Second generation antipsychotics included in the study

Drugs	Usual dose	Maximum dose
Clozapine	300–600 mg/day po	900 mg/day
Olanzapine	10-15 mg/day	20 mg/day
Quetiapine	600 mg/day	800 mg/day
Risperidone	2–6 mg/day	8 mg/day
Risperdal Consta	25–37.5 mg im every 2 wk	50 mg im every 2 wk

Note: Ziprasidone and aripiprazole were not included in the original table. Adapted from CPS, 2009 (13).

Table 5: Reported minimum effective fixed doses and chlorpromazine dose equivalence ratios for haloperidol and atypical antipsychotics, Data from Woods, 2003 (54).

Antipsychotic Medication	Reported Minimum Effective Fixed Dose (mg/d)	Chlorpromazine 100 mg/d Dose Equivalence (mg/d)
Haloperidol	4	2
Risperidone	4	2
Olanzapine	10	5
Quetiapine	150	75
Ziprasidone	120	60
Aripiprazole	15	7.5

Health Research Ethics Board approval for this study was obtained (November 18, 2009).

Inclusion Criteria

1. Patients who meet the DSM-IV TR diagnostic criteria for psychotic disorders.

2. Adults 18 - 65 years of age.

3. Inpatient treatment.

Exclusion Criteria

1. Mood disorders with psychotic features.

2. Patients with history of brain injuries, brain tumors or any other structural brain pathology.

3. Patients who received ECT treatment during the same admission.

The patient's discharge date was used as the time point for review of medication information. Documentation in the case notes was used to complete a proforma consisting of the audit standards. This process is also known as "Clinical Quality Assessment" and/or "Clinical Audit".

The specific standards to be audited were as follows:

1. If a patient is prescribed a trial of high-dose antipsychotics, the clinical indications should be documented in the patient's notes.

2. Risk factors like obesity and advanced age (> 70 years of age) should be considered before prescription of high dose antipsychotics, and documented.

3. The potential for drug interactions must be considered and documented.

4. The decision to commence a patient on a high dose of antipsychotic medication is the responsibility of the patient's psychiatrist. A decision to start an elective trial of high-dose antipsychotic medication must be made by the patient's attending psychiatrist.

5. Patients should be informed that they are receiving a trial of a high dose of antipsychotics (or an explanation of why they were not informed should be documented).

6. If a decision to prescribe high dose medication is made, the dosage should be increased slowly and not more than once weekly.

7. Daily pulse, blood pressure and temperature checks should be carried out for 7 days after a change in dose, and then discontinued if within normal limits.

8. It must be ensured that the patient maintains adequate fluid intake.

9. An ECG test to exclude significant cardiac disease or prolonged QT intervals should be performed prior to commencing patients on high-dose antipsychotics. If not, an explanation for not doing so should be documented.

10. A repeat ECG should be performed at 3-month intervals for monitoring QT intervals, and antipsychotic dose should be reduced if QT intervals are abnormal.

Given the anonymous nature of data collection by one reviewer and the fact that the process will not affect the treatment process for patients in any way, a waiver of consent was therefore requested and was approved by Health Research Ethics Board. Further, it would be difficult and likely overly time-consuming to obtain consent from patients who have been discharged from hospital.

Clinical improvement with treatment was defined as either complete or partial remission of psychotic symptoms and functional recovery. This is the DSM-IV TR longitudinal course specifier and information needed to assess such was obtained from patient charts (i.e., Mental Status Exam outcome; Global Assessment of Functioning Scale score). A 2-point scale was used to assess clinical improvement with treatment, where 0 = worsening of symptoms or no change and 1 = clinical improvement (partial or complete remission of symptoms).

The groups of variables that were used for statistical analysis are described below.

I. Clinical Variables

1. Previous episodes (YES/NO)

2. Presence of Positive symptoms (YES/NO)

3. Presence of Negative Symptoms (YES/NO)

4. Comorbid substance use disorder (YES/NO)

5. Depressive symptoms (YES/NO)

6. History of schizophrenia or psychosis in 1st-degree relatives (YES/NO)

7. Aggression (YES/NO)

8. Insight (YES/NO)

9. Concurrent general medical conditions (YES/NO)

10. Abnormal diagnostic imaging findings (YES/NO)

11. Clinical improvement with treatment (as defined above)

II. Psychosocial Variables

1. Race (Caucasian, African-American, Asian, Hispanic, other)

2. Gender (male; female)

3. Marital status (single, married, divorced)

4. Homeless (YES/NO)

5. Social Support (YES/NO) (defined as financial support)

6. Psychosocial stressors (YES/NO)

III. Continuous Variables

1. Chronological age (years)

2. Age of psychiatric illness onset (operationally defined as first psychiatric hospitalization)

3. Number of previous psychiatric episodes (if known)

4. Level of Education (years)

Chapter 3: Results

Results

A total of 590 charts were reviewed, and 194 of them were included in the study. The main reasons for exclusion of charts were: incorrect diagnosis, having received ECT during the admission, and uncertainties of the diagnosis. Sampling of charts was carried out to first identify patients on high doses of antipsychotics (N=94) and to then complement by a similar number (N=100) of patients on a regular dose (i.e., non-consecutive sampling).The main diagnosis was schizophrenia. The main single antipsychotic used in high dose was olanzapine, followed by quetiapine. With regard to combinations of antipsychotics, the usual combination was a typical depot first generation antipsychotic combined with an oral second generation antipsychotic. The usual add on oral antipsychotic was risperidone, followed by clozapine.

A. Factors associated with absence or presence of documentation of clinical indications in patients on high dose antipsychotics (N=94)

If a patient is prescribed a trial of high-dose antipsychotics, the clinical indications should be documented in the patient's notes. The nine variables in these analyses are listed in detail in the Methods section and included. Consideration of risk factors like obesity and advanced age, consideration of drug interactions, whether the

decision to commence a patient on a high dose of antipsychotic medication was made by the attending psychiatrist, whether the patient was informed of a change in dosage, whether a slow increase was made, whether daily pulse, blood pressure and temperature checks were carried out for 7 days after a change in dose, whether fluid intake was ensured, whether an ECG test to exclude significant cardiac disease or prolonged QT intervals was performed prior to commencing patients on high-dose antipsychotics and whether a repeat ECG was performed at 3-month intervals for monitoring QT intervals.

Table 6 summarizes the results of comparing these variables between patients with documentation of clinical indicators for their high dose antipsychotics versus no documentation.

Table 6: Factors associated with the absence or presence of documentation of clinical indications in patients on high dose antipsychotics (N=94).

		Clinical indications not documented N = 34 (max.)	Clinical indication documented N = 60 (max.)	Test statistic, significance, Number of patients
Risk factors considered	No	5	8	X^2 [1] = 0.016 p = 0.9 N = 94
	Yes	29	52	
Drug interactions considered	No	34	44	X^2[1] = 7.28 p = 0.007 N=91
	Yes	0	13	
Decision to start made by…	Attending psychiatrist	23	58	X^2[1] = 12.998 p < 0.001 N = 94
	Other than attending psychiatrist	11	2	
Patient informed	No	27	28	X^2[1] = 7.3963 p = 0.007 N = 92
	Yes	7	30	
Slow dosage increase	No	15	21	X^2[1] = 0.19 p = 0.69 N = 90
	Yes	19	35	
Daily checks for pulse. blood pressure, temperature	No	27	37	X^2[1] = 2.468 p = 0.116 N = 91
	Yes	6	21	
Adequate fluid intake	No	0	3	X^2[1] = 0.511 p = 0.475 N = 94
	Yes	34	57	

EKG performed prior to high dose	No	29	54	$X^2[1] = 0.121$ P = 0.728 N = 94
	Yes	5	6	
Repeat EKG at 3-months	No	33	58	$X^2[1] = 0.118$ p = 0.732 N = 93
	Yes	1	1	

Max. = Maximum number of patient charts available

In summary, in patients without proper documentation of clinical indications for starting a high dose antipsychotic, the decision to start a high dose belonged more often not to the attending psychiatrist than in patients with proper clinical documentation. Furthermore, in patients without proper documentation, drug interactions were more often not considered and patients were more often not informed of a high dose being started, compared to patients with proper documentation. No difference was noticed in the rest of the variables.

B. Comparing patients on high dose antipsychotics with patients on regular dose antipsychotics

A comparison of the 21 variables included in the study (see Methods section), between the regular dose group and high dose group was done. These comparisons are summarized in Table 7.

Table 7: Factors associated with the regular or high doses of antipsychotics

		Regular dose	**High dose**	**Test statistical significance**
Chronological age		38.2	38.4	T [190]=0.013 p=0.897
Age of onset		32.1	28.8	T [167]=1.73 p=0.084
Previous episodes	no	19	9	X^2 [1]= 3.161

	yes	81	82	p=0.075
Positive symptoms	no	3	1	X^2 [1]=0.84 p=0.36
	yes	97	90	
Negative symptoms	no	29	20	X^2 [1]=1.422 p=0.233
	yes	68	70	
Substance –use disorders	no	54	51	X^2 [1]=0.012 p=0.913
	yes	41	40	
Depressive symptoms	no	62	59	X^2 [1]=0.275 p=0.6
	yes	37	30	
Family history	no	61	56	X^2 [1]=0.264 p=0.608
	yes	15	11	
		Regular dose	**High dose**	**Test statistical significance**
Aggression	no	74	63	X^2 [1]=0.718 p=0.397
	yes	25	28	
Insight	no	95	83	X^2 [1]=1.809 p=0.179
	yes	4	8	
Concurrent general medical condition	no	61	40	X^2 [1]=5.979 p=0.014
	yes	37	50	
Abnormal diagnosis in imaging	no	56	40	X^2 [1]=2.122 p=0.145
	yes	11	15	
Improvement with treatment	no	16	30	X^2 [1]=7.549 p=0.006
	yes	83	60	
Homeless	no	92	92	X^2 [1]=5.816 p=0.016
	yes	6	0	
Social support	no	50	40	X^2 [1]=1.084 p=0.2978
	yes	47	51	
Psychological stress	no	3	3	X^2 [1]=0.003 p=0.957
	yes	91	87	
Gender	female	55	45	X^2 [1]=0.711 p=0.399
	male	45	47	
Race	Cauc	71	71	X^2 [4]=5.986 p=0.4247
	Hispanic	1	1	
	Asian	15	12	
	Aboriginal	10	3	
	Af.american	3	5	
Marital status	Single	63	63	X^2 [2]=1.142 p=0.565
	In relationship	21	14	
	Single but previously in a relationship	14	16	
Previous episodes	0	26	12	X^2 [2]=8.15

	1-7	43	55	p=0.017
	More than 7	23	14	
Education	School	12	7	X^2 [2]=3.883 p=0.2744
	High school	30	23	
	College	9	12	
	University	11	17	

Results showed that a statistical difference was reached with regard to the non-improvement with high doses versus regular doses, confirming that increasing the doses above recommended ranges does not lead to further amelioration of symptoms. Also, a statistical difference was reached with regard to concurrent medical conditions being more frequent in the high dose group versus regular dose group. The high dose group had a higher number of previous episodes.

The high dose group had a tendency to have any history of previous episodes, and was younger at disease onset, although these variables did not reach statistical difference, compared to the regular dose group.

Of note, homelessness was more frequent in the regular dose group than in the high dose group. However, this difference is likely spurious as none of the patients on high dose was currently homeless.

Next, we constructed a logistic regression model with select predictor variables to assess which of them, if considered together, would predict best whether a patient may be put on high doses of antipsychotics.

The dependent variable was: Group, dummy-coded as HIGH DOSE = 1 and LOW DOSE = 0.

(Of note, not all predictor variables were included because of small cell counts, i.e., almost all responses were '1's or in other cases almost all '0's. The variables not included in the model were: family history, abnormal diagnostic image, age of onset, number of previous episodes, education, positive symptoms, insight, homeless and psyco-social stress).

Model:

Group = previous episodes + negative symptoms + substance use disorders+

-depressive symptoms + aggression + concurrent general medical conditions + improvement with treatment + gender + social support (+error)

The results of this regression are summarized in Tables 8 and 9

Table 8: Coefficients

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-0.482	0.605	-0.796	0.426
Previous episodes	0.502	0.50	1.004	0.315
Negative symptoms	0.213	0.415	0.513	0.608
Substance use disorders	0.167	0.342	0.487	0.626
Depressive symptoms	-0.187	0.35	-0.534	0.594
Aggression	0.117	0.389	0.300	0.764
Concurrent general medical conditions	0.946	0.376	2.514	0.012*
Improvement with treatment	-0.925	0.394	-2.347	0.019*
Gender	0.319	0.354	0.903	0.367

	Estimate	Std. Error	z value	Pr(>|z|)
Social support	-0.221	0.377	-0.587	-0.557

* = $p < 0.05$

(Dispersion parameter for binomial family taken to be 1)

The null deviance was 232.52 on 167 degrees of freedom and the residual deviance was 215.12 on 158 degrees of freedom (24 observations deleted due to missing information).

Thus, two predictors were statistically significant, concurrent general medical conditions and improvement with treatment. Overall, the model could be a reasonable fit.

We then transformed the beta-estimates of each predictor into odds-ratios to show the relative risk to be put on high dose antipsychotics associated with each predictor. This was done by inverse log-transformation of the beta estimates from Table 9. Results of these transformations are shown in Table 10.

Table 9: Odds ratios for each predictor

Predictor	Odds-ratio
(Intercept)	(0.618)
Previous episodes	1.652
Negative symptoms	1.237
Substance use disorders	1.182
Depressive symptoms	0.83
Aggression	1.124
Concurrent general medical conditions	2.574

Predictor	Odds-ratio
Improvement with treatment	0.396
Gender	1.376
Social support	0.802

Interpreting the previous significant estimates only (i.e., concurrent medical condition and improvement with treatment), their odds ratio show that, all else being held equal, for each unit of increase in concurrent general medical condition there is a 2.57 times increase in the odds that a high dose will be prescribed. In the case of improvement with treatment, for each unit of improvement with treatment there is a 0.39 decrease in the odds of a high dose. Reversing the relationship by expressing the odds as the likelihood of receiving a low dose (i.e., 1/0.39=2.523), with improvement with treatment, it is 2.523 times more likely an individual will receive regular doses.

Chapter 4: Conclusion and discussions

4.1 Limitations of the present study

This is a retrospective study. As in all retrospective studies we can encounter an information bias, which could have led to missing, misinterpreted information that played a role in the results and how certain variables have been found to influence the two groups. In this study, we cannot control the outcome assessment, but instead need to rely on others for accurate record-keeping.

4.2 Summary of findings:

The majority did not have documentation of drug-drug interactions and of the fact that they were put on high dose. The majority were started on high doses by the attending psychiatrist. The potential for drug-drug interactions was not considered in most cases. Results showed that a statistical difference was reached with regard to the non-improvement with high doses versus regular doses, confirming that increasing the doses above recommended ranges does not lead to further amelioration of symptoms. Also, a statistical difference was reached with regard to concurrent medical conditions being more frequent in the high dose group versus regular dose group. The high dose group had a higher number of previous episodes.

The high dose group had a tendency to have any history of previous episodes, and was younger at disease onset, although these variables did not reach statistical difference, compared to the regular dose group.

Of note, homelessness was more frequent in the regular dose group than in the high dose group. However, this difference is likely spurious as none of the patients on high dose was currently homeless. As well, there was a trend for the regular dose group to be older in regards to age of onset. The education status was fairly

similar, although a potential trend for having a university degree in the high dose group was noticed.

4.3 Relevance of the study

The use of high doses of antipsychotics in clinical practice remains high, despite the lack of evidence indicating greater effectiveness. The study answers the question if going to higher doses leads to better outcomes and answer is no. Also, the study points towards certain variables: particularly having a concurrent general medical condition, but also having suffered previous episodes and more previous multiple episodes as portraying a certain type of patient that tends to be put on higher doses, although without better results. Also, the high dose group tended to be younger and not homeless.

4.4 Future areas of investigation

This being a retrospective study comes with limitations. Prospective studies, double blinded, will elucidate things further. Also certain variables, such as marital status, living situation, ECG follow-up and being repeated, could be left out, and smoking, for example should be added. Certain trends noticed, such as concurrent medical conditions, previous episodes and previous multiple episodes could be teased out with studies that have more power due to higher numbers. Similarly, potential trends such as age, homelessness and education could be teased out in studies that have higher numbers of participants.

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