Original Article

Prevalence of High-dose Antipsychotic Prescribing in Schizophrenia: A Clinical Audit in a Regional Queensland Mental Health Service

Abstract

Background: Antipsychotic medication is widely recognized as a critical intervention in both acute and ongoing treatments of schizophrenia. Guidelines endorse the routine practice of monotherapy with antipsychotic medication at the minimum effective dose. Despite the recommendations, high-dose antipsychotic prescribing and polytherapy appear to be common practice. **Objective:** The objective of this study was to determine the prevalence of high-dose antipsychotic prescribing in adult patients with schizophrenia in a regional Queensland hospital and to know if the prescribing practices are in keeping with the international guidelines and with the local policy introduced in December 2017. **Methods:** This was a cross-sectional survey/clinical audit of 358 adult patients with schizophrenia open to the service in both community and inpatient settings. The individual prescribing practices of psychiatrists were also examined. **Results:** A minority (15%) were prescribed high doses (high-dose single agent and high dose by polytherapy) and 20% were prescribed polytherapy (including high dose and within normal dose range). **Conclusion:** Eighty-five percent of the patients with the diagnosis of schizophrenia open to the service were prescribed antipsychotic within the dose range. In this respect, prescribing was aligned with current evidence-based guidelines.

Keywords: *High-dose antipsychotic, polytherapy, prescribing practices, schizophrenia*

Shalini Luthra, Lorna Duggan[1], Aanchal Agrawal, Gurpreeti Kaur[2], Neeru Luthra[2]

Central Queensland Hospital and Health Service, [1]Mental Health Alcohol and Other Drugs Services, Central Queensland Hospital and Health Service, Rockhampton, Australia, [2]Department of Anaesthesia, Dayanand Medical College and Hospital, Ludhiana, Punjab, India

Introduction

Schizophrenia forms a significant treatment burden even in modern-day psychiatry. Treatment interventions often involve antipsychotic medications and are recognized as a critical intervention in both acute and ongoing treatments of schizophrenia.[1]

Established guidelines recommend monotherapy at minimum effective dose for the treatment of schizophrenia. The evidence does not justify the routine use of high-dose antipsychotic medication, either with a single agent or combined antipsychotics. The use of more than one agent is only recommended for specific conditions such as treatment-resistant schizophrenia with partial response to clozapine, contraindication, or intolerance to clozapine or when switching treatments from one agent to another.[2] Support for antipsychotic polypharmacy is largely restricted to case reports and open-label trials, with most randomized controlled trials limited to combinations of drugs that include clozapine.[3,4]

People with psychotic disorders are known to have higher rates of metabolic risk factors,cardiovascular disease and diabetes, emerging evidence suggests that antipsychotics are a contributing factor.[5] The majority of antipsychotic adverse effects are dose related. High doses may increase the likelihood and severity of side effects such as extrapyramidal side effects, tachycardia, postural hypotension, sedation, hyperprolactinemia, and risk of seizures. Side effects associated with high-dose antipsychotics may limit benefit by reduction in concordance. The risk of corrected QT prolongation and associated arrhythmias is also significantly increased with high-dose antipsychotics. Case reports of arrhythmias and sudden death highlight the risk of high-dose prescribing and rapid dose escalation.[6] Metabolic monitoring is a key performance indicator (KPI) for all patients with an International Classification of Diseases 10th Edition diagnosis between F20.0 and F25.9 within Queensland.[7]

The most common reason for prescribing combined and high-dose antipsychotics in acute adult, high dependency units, and high-secure settings is for the management

How to cite this article: Luthra S, Duggan L, Agrawal A, Kaur G, Luthra N. Prevalence of high-dose antipsychotic prescribing in schizophrenia: A clinical audit in a regional Queensland mental health service. Int J App Basic Med Res 2023;13:70-6.

Submitted: 04-Sep-2022
Revised: 19-Feb-2023
Accepted: 19-Apr-2023
Published: 17-Jul-2023

Address for correspondence:
Dr. Gurpreeti Kaur, Department of Anaesthesia, Dayanand Medical College and Hospital, Ludhiana, Punjab, India.
E-mail: grewal.preeti@gmail.com

Access this article online

Website: https://journals.lww.com/IJAB

DOI: 10.4103/ijabmr.ijabmr_504_22

Quick Response Code:

of acute behavioral disturbance.[8] There is, however, a paucity of research evidence specifically examining the efficacy and safety of high doses to tranquilize rapidly. Administration of pro re nata (PRN) medications has the potential to raise the total daily dose of antipsychotic above high-dose threshold and hence should be used cautiously.

Despite the recommendations, high-dose antipsychotic prescribing including polytherapy appears to be a common practice.[9]

Most of the evidence for high-dose antipsychotic prescribing has been derived from studies completed in the United Kingdom (UK). Several surveys conducted in the UK over the past decade, involving a total of 4200 inpatients, found that approximately one-quarter of patients were prescribed antipsychotic polytherapy.[9] For the great majority of these, high dose was prescribed by virtue of antipsychotic polytherapy.

The largest UK audit of antipsychotic polypharmacy was conducted by the Prescribing Observatory for Mental Health (POMH-UK).[10] A baseline audit of 3492 patients on 218 wards found that 43% were prescribed antipsychotic polytherapy, and over one-third were prescribed a high dose of antipsychotic medication.

There are few Australian studies addressing this issue. The second Australian National Survey of Psychosis completed in 2010 identified that 28% of participants with schizophrenia were taking two or more antipsychotics.[11]

A 2017 clinical audit at an acute Australian mental health unit in a metropolitan area revealed that 20.5% of patients discharged from a mental health inpatient unit were on high-dose antipsychotics and 32.5% were on antipsychotic polytherapy.[12]

An audit in 2013 of antipsychotic polypharmacy at Graylands Hospital, Western Australia, using a similar methodology to POMH-UK found that 89.8% of patients were prescribed more than one antipsychotic and 79% of patients were prescribed a high dose. 39.2% of high-dose prescribing was attributable to "as required" (PRN) medication.[13] The results from this audit demonstrate a worrying increase in the prevalence of antipsychotic polytherapy/high-dose prescribing. Previous audits at Graylands Hospital revealed that the prevalence of antipsychotic polytherapy had increased from 37% in 2002 to 55% in 2007, and 89.8% in the current audit.

In a New Zealand-based study, there was a high rate (33.7%) of multiple antipsychotic prescriptions, and lower than expected clozapine use (20%); Maori people were prescribed clozapine more frequently than non-Maori (24% vs. 13%, respectively).[14]

Several variables have been implicated in previous studies for high-dose polytherapy including the clinical beliefs and experience of the prescribing psychiatrist.[15] A survey of prescribers found that both high and low antipsychotic polypharmacy prescribers were reluctant to convert to monotherapy.[16]

Patients with longstanding illness, prolonged hospital stay, and those treated involuntarily are more likely to receive a higher than the recommended dose. Compulsory treatment was associated with more use of injectable medication and increased length of stay in hospital.[17-20]

An audit is a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and implementation of change. The aim of this audit is to determine the prevalence of high-dose antipsychotics in schizophrenia in a regional mental health service (MHS) and compare the same against published standards. Additionally, this audit evaluates the individual prescribing practices of psychiatrists in the service in light of a new policy on high-dose antipsychotic prescribing being introduced.

Methods

Literature review

A literature review was undertaken utilizing PubMed, Cochrane Library, PsycINFO, and Google Scholar. Keywords included high dose antipsychotic polytherapy, polypharmacy, and prescription practices in schizophrenia, to scope out the field and identify other audit methodologies.

Study design

The study was a cross-sectional clinical audit of antipsychotic prescribing for adults (18–65 years), with a diagnosis of schizophrenia (F20.0) open to the service including both inpatient and community patients. This includes inpatients and patients receiving long-term care throughout the community mental health team. The public mental health system in Australia provides long-term care for community patients with chronic illness like schizophrenia and they remain actively open to the service.

Setting

The regional MHS in Queensland is a service that caters to the need of regional and multiple rural settings over a vast geographical area of 114,000 km^2, covering a catchment area of 230,000 people.[21] It has twenty three adult patient unit beds and eight older persons inpatient unit beds.

Information was obtained for patients open to the MHS on March 22, 2018, with a diagnosis of schizophrenia (F20.0). A member of the administrative staff ran a report of patients with this diagnosis, and there were 358 adult patients open to the service on that date.

Ethical approval was obtained from the local Human Research Ethics Committee (HREC/17/QCQ/44).

There is a local hospital policy regarding high-dose antipsychotic medication prescribing that was finalized

in December 2017. This policy is compliant with the Royal College of Psychiatrists guideline (as there are no Australian guidelines).[22] The draft versions (since June 2017) and finalized version had been circulated among the medical officers' group on a regular basis for suggestions and implementation, respectively.

The completion of this audit was considered a timely activity for evaluation of clinical practice following the promulgation of the policy.

Data collection procedure

Collation of data was from consumer-integrated mental health application, the statewide electronic records used in Queensland. The data were collected by the trainee. The electronic record was used to collect patient characteristics, Mental Health Act (MHA) status, and antipsychotic prescription. The last medical review/case review summary was used to gather this information. Data were de-identified at the time of collection and entered.

In the audit, high dose was calculated by using the Australian Medicines Handbook (AMH) and the maximum figures as 100% [Table 1].[23] AMH is an independent, evidence-based, national drug reference and an important clinical resource for health practitioners concerned with the quality use of medicines. The principles of the British National Formulary (BNF) were used regarding the calculation of high-dose antipsychotic therapy. As it was an Australian audit, the AMH doses were referenced.

The comparative drug information makes it unique among drug reference tools, as it allows users to compare drugs and make informed prescribing choices.

Table 1: Australian Medicines Handbook licensed maximum doses of antipsychotics

Oral	mg/day	Depot	Dose range (mg)	Dose interval (weeks)
Amisulpride	1200	Aripiprazole	300–400	4
Aripiprazole	30	Flupenthixol	20–40	2–4
Asenapine	20	Haloperidol	25–200	4
Chlorpromazine	800	Olanzapine	300–400	2–4
Clozapine	900	Paliperidone	25–150	4
Haloperidol	10	Risperidone	25–50	2
Lurasidone	160	Zuclopenthixol	200–400	2–4
Olanzapine	20			
Paliperidone controlled release	12			
Quetiapine	800			
Risperidone	6			
Trifluoperazine	20			
Ziprasidone	160			

A high-dose regimen can result from either the use of a single agent above the AMH limit or from a combination of two or more antipsychotics where each is within the maximum dose, e.g., if 2 antipsychotics are used, one at 50% of maximum and the other at 70% of maximum the total is 120%, i.e., high dose. Cross-titration, augmentation, and use of antipsychoyics as needed, were considered high-dose antipsychotic therapy because patients were prone to a higher risk of side effects. A similar calculation was used for depot/long-acting injections.

Information about prescribing practices of individual psychiatrists was collected. This aspect was thoroughly considered in the senior medical officers' meeting and all psychiatrists consented for these data to be collected. To ensure confidentiality, the psychiatrists were designated colors and the code was only available to the researcher. The results were to be fed back anonymously. The merit of doing this was to provide accurate timely information to the consultant psychiatrists about their high-dose prescribing.

The data collection included patient characteristics: inclusive of gender, indigenous status, smoking status, MHA status, and antipsychotic doses.

Statistical analysis

Data were described in terms of frequencies (number) and relative frequencies (percentages) as appropriate. Percentage of patients with antipsychotic prescriptions of more than 100% AMH. Each outcome was reported as a proportion of the total patient group. All statistical calculations were done using (Statistical Package for the Social Sciences) SPSS 21 version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

Results

Three hundred and fifty-eight patients were identified as open to the service with a diagnosis of F20.0., of which 22.6% (81/358) of the population were indigenous.

Gender

The majority of patients in the cohort were males (272/358; 76%).

Smoking status

Eighty-five percent (307/358) of the cohort were smokers. Seventy percent (61/86) of females in the study population and 90% of males (246/272) were smokers.

Mental Health Act status

Almost half of the patients were under the MHA (157/358; 44%). MHA is an act to provide for the treatment and care of a person with mental illness who does not have the capacity to consent to be treated. Patients under the MHA have an involuntary status.

Antipsychotic medications

Of the 358 patients that were audited, 15% had been prescribed high-dose antipsychotic (54/358). 20.3% (11/54) were prescribed high dose through a single antipsychotic and 79.6% (43/54) were prescribed high dose through antipsychotic polytherapy. Of these, 75% (41/54) were prescribed between 100% and 150%, 16.6% (9/54) were prescribed between 150% and 200%, and 7% (4/54) were prescribed more than 200% of the high-dose limit.

There was another 8.3% (30/358) prescribed polytherapy but not high dose, making the total patients on polytherapy 20% (73/358) [Figure 1].

Clozapine was prescribed for 25% (89/358) of the study population. Clozapine was prescribed in combination with other antipsychotics in 18.5% (10/54) of the population receiving high-dose antipsychotic.

Patient characteristics for antipsychotic prescribing

Gender

Eighty three point three percent (45/54) of the study population prescribed high doses were males and 9/54 (16.6%) were females.

Indigenous status

Twenty percent (16/81) of the patients on high-dose antipsychotic were indigenous and 14% (38/277) were nonindigenous. Five of these patients were female and 11 were males.

Mental Health Act

Fifty nine point two percent (35/54) of the patients prescribed high-dose antipsychotic were treated under the MHA (Treatment Authority and Forensic Order).

Prescribing practices

A bar chart [Figure 2] comparing the prescribing practices of individual psychiatrists was constructed. Psychiatrists were assigned colors to ensure confidentiality. Of the nine psychiatrists whose prescribing practices were audited, psychiatrist cyan and psychiatrist green did not have patients on high-dose antipsychotics and they had two and seven patients with schizophrenia open to them respectively.

Red psychiatrist had 25% (15/60) high-dose antipsychotic prescribing, psychiatrist orange 18.75% (6/32), psychiatrist gray 16.66% (3/18), psychiatrist yellow 16% (9/36), psychiatrist purple 13.33% (6/45), and psychiatrist pink 12.9% (4/31) followed by psychiatrist blue 10.1% (11/101).

Of the 54 patients on high dose, no reference was found in the notes to high-dose antipsychotic prescribing policy. Of these, 32 patients (59.2%) were subject to regular metabolic monitoring; however, metabolic monitoring is a KPI for Queensland Health (QH).

Discussion

The study found that 85% of the patients with the diagnosis of schizophrenia open to the service were prescribed antipsychotic within the dose range. In this respect, prescribing was aligned with current evidence-based guidelines. The few Australian studies show much higher rates and internationally the figures are highly variable. However, 15% of the patients were prescribed high doses either with a single agent or by polytherapy and 20% were prescribed polytherapy (including high dose and within normal dose range). Seventy-five percent of the high doses were within 150% high-dose prescribing.

Consequently, a number of patients were at risk of adverse outcomes not only because of receiving high doses but also due to drug interactions associated with polytherapy.

Overall, there is conflicting evidence for associations between patient characteristics and either antipsychotic polytherapy or high dosing, such as age and ethnicity.[24] Males have been reported to be at greater risk, or have higher rates of these outcomes.[25] The audit by McMillan *et al*. found no evidence that gender was associated with polytherapy or high-dose prescribing.[12]

Internationally, the rate of antipsychotic polypharmacy is high, ranging from 6% to 71% with an average rate of 10%–40% in different clinical settings.[26-28] A systematic

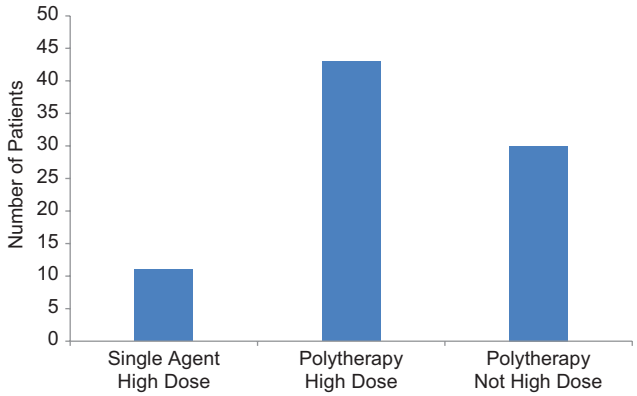

Figure 1: Patients on antipsychotic medications

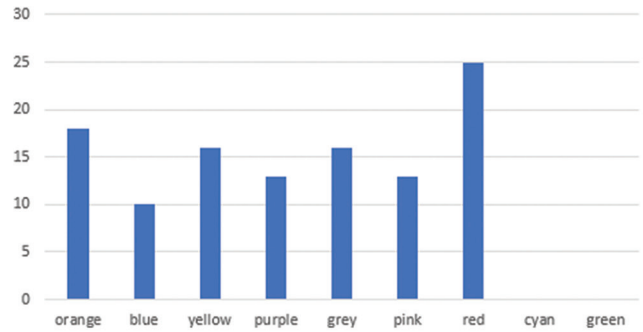

Figure 2: HDA% by consultant. HAD: High-dose antipsychotics

review of 147 studies reported that the global median antipsychotic polypharmacy rate was 19.6%. Although substantial variations exist between and within geographic locations, the practice of prescribing multiple antipsychotic drugs appears to be increasing.[5] A 5-year comparison study performed on Korean patients with schizophrenia from 2005 to 2010 saw an increase in polypharmacy from 37.1% to 48.3%.[29]

A recent Cochrane systematic review of antipsychotic combinations for schizophrenia concluded that there is very low-quality evidence that a combination of antipsychotics may improve the clinical response.[27] There was also very low-quality evidence that a combination of antipsychotics may make no difference at preventing participants from leaving the study early, preventing relapse, and/or causing more serious adverse events than monotherapy.

We found more males with a diagnosis of schizophrenia open to the service, a picture that is often seen. This audit provides further evidence that male patients were more likely to receive high doses of antipsychotics and that could be attributed to gender-related variations in the response and effects of antipsychotics. Female patients generally require lower doses of antipsychotics due to pharmacokinetic differences related to body fluid, weight, and body mass index. These principles would apply to high-dose prescribing where the threshold for high dose in women may be lower than their male counterparts. High-dose prescribing in pregnancy and women of childbearing potential requires careful assessment as dose-related side effects may be of greater consequence in this patient group (local policy). The results regarding association with gender are highly variable. The Australian audit had shown no variation associated with gender, but other studies have reported males to be at greater risk for high-dose prescribing.[12,15,30]

In our study, a greater number of indigenous people were receiving high-dose antipsychotics. This adds to the evidence that indigenous patients are at higher risk of receiving high doses.

Being under the MHA was found to be associated with increased risk of high-dose prescribing as evidenced by almost 60% of patients in this audit. Other studies including the Australian study by McMillan *et al*. and the study by Gisev *et al*. concluded that patients treated under the MHA were more likely to receive high-dose antipsychotic.[12,24]

The prescribing practices of the psychiatrists were similar and variance may be attributable to the patient group. Confidential feedback was provided to psychiatrists and was received well in a spirit of learning. Further study is needed to evaluate patient characteristics of those in the high-dose group, medication history and response to previous antipsychotics prescribed, clozapine trial, and concurrent use of illicit drugs. The circulation of the local draft High Dose Antipsychotic Policy to the prescribing cohort on a regular basis and ongoing education to the junior doctors has proven to be of benefit.[6]

The local policy is based on current evidence and indicates a requirement of approval by the consultant psychiatrist including clear documentation and justification of individual patient treatment decisions. The decision should be discussed with the multidisciplinary team including a pharmacist, the patient, and/or carer and valid consent obtained from the patient. The policy also indicates requirement of monitoring patients on high-dose regimens with recording of blood pressure, pulse, temperature, electrocardiogram's every 1–3 months, and monitoring for response and side effects. These monitoring requirements are more rigorous than those in place to meet the QH KPI of metabolic monitoring.

Additionally, it was noted that an alarming 84% of the study population were smoking tobacco. Tobacco smoking is one of the leading preventable causes of death and disability in Australia.[31] A nationally representative Australian study of people with a psychotic illness found that the prevalence of smoking was 73% for men and 56% for women far more than the prevalence of smoking in the Australian general population – which was around 26% at that time.[32] A recent QH initiative on smoking cessation advocates that all patients who express a desire to quit smoking and/or are inpatients assessed as nicotine dependent as part of the patient risk assessment or using a validated scoring tool such as the QH Smoking Cessation Clinical Pathway be offered free nicotine replacement therapy in accordance with the smoking cessation clinical pathway (clinicalexcellence.qld.gov.au).

The predisposition of people with psychotic illness to cardiometabolic risk factors along with risks associated with high rates of cigarette smoking makes them more vulnerable to the side effects of high-dose antipsychotics.[7] In 2007, a systematic review concluded that mortality rates in schizophrenia were significantly greater than in the general population, median standardized mortality ratio of 2.58 (10%–90% quantile, 1.18–5.76) and the mortality gap between schizophrenia patients and the general population had continued to increase during the 1970s and 1980s.[33]

While a majority of the patients of the service were receiving antipsychotics within the normal dose range, the audit emphasizes the need to develop further strategies to reduce these rates.

Strengths and limitations

The large sample size of 358 patients was a strength of the study and was an accurate reflection of the prescribing practices of the entire service. Data collection by a single trainee ensured a standardized process of recording data accurately and consistently.

The names of patients on high-dose antipsychotic were sent to individual psychiatrists and that ensured cross-checking

of the data and also making the psychiatrist aware of their prescribing practice and an opportunity to reflect.

There are very few Australian studies examining high-dose antipsychotic prescribing and majority have been completed in metropolitan areas. This audit is the first study in a regional center and therefore adds to the evidence base.

Limitations

As a cross-sectional study, the quality of data was dependent on the accuracy and completeness of clinical notes. The data were collected from the last medical review/case review; it may be that some patients were on two antipsychotics temporarily due to cross-titration, or were using an oral antipsychotic for short term while commencing a long-acting formulation. This information was not readily identifiable from the last medical review/case review and hence it is possible that rates of high-dose prescribing were overestimated.

This study only included patients with a diagnosis of schizophrenia and antipsychotic medications are used in schizoaffective and bipolar affective disorders and prescribed off-label for other psychiatric conditions, often in high doses.

Another study including the abovementioned diagnoses would further enhance the results. The data pertaining to this can be obtained from the electronic system for patients open to the service on March 22, 2018.

About additional psychotropic prescribing information, limited data regarding antidepressants, mood stabilizers, and benzodiazepine medications were collected; however, it was beyond the scope of a single trainee to collect all the information.

The AMH was used as a reference for antipsychotic prescribing dose ranges. The dose ranges are slightly different to those of BNF and it is likely that there could have been an overestimation/underestimation of the results.[8,34] The prescribers' preferred prescribing guide could have influenced this difference.

Conclusion

A majority (85%) of antipsychotic prescribing practices were aligned with clinical guidelines. It does show the positive effect of regular circulation of local policy and discussions during clinical governance sessions.

The audit also emphasizes the need to ensure that 15% of the patients on high-dose antipsychotic therapy are regularly monitored in keeping with the local policy. The service providers need to aim toward decreasing antipsychotic polytherapy at every opportunity by introducing psychosocial interventions in addition to antipsychotics for holistic person-centered provision of care.

The plan is to present these data to the medical staff and to collaborate on an action plan to ensure that any high-dose prescribing is within the policy and to re-audit in 9 months by a medical officer of the service.

Further audit is required to investigate if regular monitoring of patients on high-dose antipsychotics is taking place as per the local policy. Ongoing education is required to ensure that new prescribers are conforming to the standards.

Ethical statement

Ethical approval was obtained from the Human Research Ethics Committee (HREC/17/QCQ/44) of Central Queensland Hospital and Health Service.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. National Institute for Health and Care Excellence (NICE). Psychosis and Schizophrenia in Adults: Treatment and Management. NICE Clinical Guideline 178. London: NICE; 2014. p. 301-79.
2. Ortiz-Orendain J, Castiello-de Obeso S, Colunga-Lozano LE, Hu Y, Maayan N, Adams CE. Antipsychotic combinations for schizophrenia. Cochrane Database Syst Rev 2017;6:CD009005.
3. Stahl SM. Antipsychotic polypharmacy, Part 1: Therapeutic option or dirty little secret? J Clin Psychiatry 1999;60:425-6.
4. Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, *et al.* Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry 2004;161:1-56.
5. Gallego JA, Bonetti J, Zhang J, Kane JM, Correll CU. Prevalence and correlates of antipsychotic polypharmacy: A systematic review and meta-regression of global and regional trends from the 1970s to 2009. Schizophr Res 2012;138:18-28.
6. High Dose Antipsychotic Medication Prescribing; Regional Hospital Data Queensland Health; 2017. (unpublished data available on request to maintain confidentiality).
7. Galletly CA, Foley DL, Waterreus A, Watts GF, Castle DJ, McGrath JJ, *et al.* Cardiometabolic risk factors in people with psychotic disorders: The second Australian national survey of psychosis. Aust N Z J Psychiatry 2012;46:753-61.
8. National Collaborating Centre for Mental Health. National Institute for Health and Care Excellence: Clinical Guidelines. In: Violence and Aggression: Short-Term Management in Mental Health, Health and Community Settings. London: British Psychological Society; 2015.
9. Patel MX, Bishara D, Jayakumar S, Zalewska K, Shiers D, Crawford MJ, *et al.* Quality of prescribing for schizophrenia: Evidence from a national audit in England and Wales. Eur Neuropsychopharmacol 2014;24:499-509.
10. Paton C, Barnes TR, Cavanagh MR, Taylor D, Lelliott P, POMH-UK project team. High-dose and combination antipsychotic prescribing in acute adult wards in the UK: The challenges posed by P.R.N. Prescribing. Br J Psychiatry 2008;192:435-9.
11. Waterreus A, Morgan VA, Castle D, Galletly C, Jablensky A, Di Prinzio P, *et al.* Medication for psychosis – Consumption and consequences: The second Australian national survey of

psychosis. Aust N Z J Psychiatry 2012;46:762-73.
12. McMillan SS, Jacobs S, Wilson L, Theodoros T, Robinson G, Anderson C, *et al.* Antipsychotic prescribing for vulnerable populations: A clinical audit at an acute Australian mental health unit at two-time points. BMC Psychiatry 2017;17:139.
13. Luft B. Antipsychotic polypharmacy – Time to review practice. Graylands Hosp Drug Bull 2013;20:1-4.
14. Dey S, Menkes DB, Obertova Z, Chaudhuri S, Mellsop G. Antipsychotic prescribing and its correlates in New Zealand. Australas Psychiatry 2016;24:360-4.
15. Correll CU, Shaikh L, Gallego JA, Nachbar J, Olshanskiy V, Kishimoto T, *et al.* Antipsychotic polypharmacy: A survey study of prescriber attitudes, knowledge and behavior. Schizophr Res 2011;131:58-62.
16. Essock SM, Schooler NR, Stroup TS, McEvoy JP, Rojas I, Jackson C, *et al.* Effectiveness of switching from antipsychotic polypharmacy to monotherapy. Am J Psychiatry 2011;168:702-8.
17. Galletly C, Castle D, Dark F, Humberstone V, Jablensky A, Killackey E, *et al.* Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Aust N Z J Psychiatry 2016;50:410-72.
18. Connolly A, Taylor D. Factors associated with non evidence-based prescribing of antipsychotics. Ther Adv Psychopharmacol 2014;4:247-56.
19. Sim K, Su A, Fujii S, Yang SY, Chong MY, Ungvari GS, *et al.* Antipsychotic polypharmacy in patients with schizophrenia: A multicentre comparative study in East Asia. Br J Clin Pharmacol 2004;58:178-83.
20. John AP, Gee T, Alexander S, Ramankutty P, Dragovic M. Prevalence and nature of antipsychotic polypharmacy among inpatients with schizophrenia spectrum disorders at an Australian mental health service. Australas Psychiatry 2014;22:546-50.
21. Census of Population and Housing. Australian Bureau of Statistics; 2011. Available from: http://www.abs.gov.au/census . [Last accessed on 2014 Aug 03].
22. Royal College of Psychiatrists. Consensus Statement on High-Dose Antipsychotic Medication. London: Royal College of Psychiatrists; 2014. College Report CR190. Available from: www.rcpsych.ac.uk. [Last accessed on 2018 Jul 12].
23. AMH. Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2017.
24. Gisev N, Bell JS, Chen TF. Factors associated with antipsychotic polypharmacy and high-dose antipsychotics among individuals receiving compulsory treatment in the community. J Clin Psychopharmacol 2014;34:307-12.
25. Lelliott P, Paton C, Harrington M, Konsolaki M, Sensky T, Okocha C. The influence of patient variables on polypharmacy and combined high dose of antipsychotic drugs prescribed for in-patients. JPsyc Bull 2002;26:411-4.
26. Xiang YT, Wang CY, Si TM, Lee EH, He YL, Ungvari GS, *et al.* Antipsychotic polypharmacy in inpatients with schizophrenia in Asia (2001-2009). Pharmacopsychiatry 2012;45:7-12.
27. Arnold LM, Strakowski SM, Schwiers ML, Amicone J, Fleck DE, Corey KB, *et al.* Sex, ethnicity, and antipsychotic medication use in patients with psychosis. Schizophr Res 2004;66:169-75.
28. Goff DC, Dixon L. Antipsychotic polypharmacy: Are two ever better than one? Am J Psychiatry 2011;168:667-9.
29. Roh D, Chang JG, Kim CH, Cho HS, An SK, Jung YC. Antipsychotic polypharmacy and high-dose prescription in schizophrenia: A 5-year comparison. Aust N Z J Psychiatry 2014;48:52-60.
30. Sun F, Stock EM, Copeland LA, Zeber JE, Ahmedani BK, Morissette SB. Polypharmacy with antipsychotic drugs in patients with schizophrenia: Trends in multiple health care systems. Am J Health Syst Pharm 2014;71:728-38.
31. Collins D, Lapsley H. The Costs of Tobacco, Alcohol and Illicit Drug Abuse to Australian Society in 2004/05. Canberra: Department of Health and Ageing; 2008.
32. Cooper J, Mancuso SG, Borland R, Slade T, Galletly C, Castle D. Tobacco smoking among people living with a psychotic illness: The second Australian Survey of Psychosis. Aust N Z J Psychiatry 2012;46:851-63.
33. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? Arch Gen Psychiatry 2007;64:1123-31.
34. Joint Formulary Committee. British National Formulary (BNF) 69. London: BMJ Publishing group Ltd, Royal Pharmaceutical Society; 2015.