The prevalence of and factors associated with antipsychotic polypharmacy in patients with serious mental illness: Findings from a cross-sectional study in a low-middle income country

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Declaration

I, Dr. K. Armstrong hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Rationale: Antipsychotic polypharmacy (APP) appears to be a common practice worldwide despite treatment guidelines advising against the practice for most patients in view of lack of evidence and possible risk of harm. Our study aimed to address deficiencies in local and international research by examining the current prevalence of APP in a South African context and investigating a broad range of patient, illness and treatment characteristics that may be associated with the practice. In doing so, we aimed to provide an indication of possible areas to be addressed in order to improve local mental health care practice.

Methods: We conducted a cross-sectional study of discharge records using Valkenberg Hospital's electronic patient database. We collected data on patient, illness and treatment characteristics for patients discharged on one or more antipsychotic agent from January to June 2014. Hierarchical multivariable logistic regression analysis was conducted to assess the relationship between APP and demographic and clinical variables and prescription patterns were analysed.

Results: Discharge records of 565 patients were examined. The prevalence of APP in our study population was 29.03% (95% CI= 25.31%-32.96%). Analysis of demographic and clinical characteristics revealed that age>29, male sex, diagnosis of schizophrenia compared to bipolar and substance-induced disorders, co-morbid intellectual disability, co-morbid substance use, greater number of hospital admissions and high-dose prescribing were significantly associated with APP. While highest rates of APP in patients with schizophrenia and schizoaffective disorders occurred, APP was also observed in a number of patients with bipolar and substance-induced disorders. Prescription patterns demonstrated the prominent use of first-generation antipsychotics and long acting injectables in APP combinations. Patients receiving APP were significantly more likely to have anticholinergic agents and sodium valproate co-prescribed in their treatment regimen.

Discussion: The prevalence of APP found in our study is fairly high in comparison with international rates. Antipsychotic prescription patterns reflect a complex interplay among patient, illness and treatment characteristics of our population. Our findings indicate that patients receiving APP may be those with greater illness severity, complexity, chronicity and treatment resistance, with complicating factors including co-morbid substance use involved. While APP is most common in patients with schizophrenia, antipsychotics may also be used in combination to manage mood and psychotic symptoms in patients with schizoaffective, bipolar and substance-induced disorders. The frequent use of long acting injectables in combinations may suggest concern over compliance in our population. The positive associations of APP with high-dose prescribing and co-prescription of anticholinergic medication contributes to concern over the safety of APP.

Conclusion Our study suggests concern over current local practice in that combination antipsychotic agents were prescribed for a number of patients with a range of psychiatric diagnoses without sufficient evidence for efficacy of this practice and at possible cost of increased adverse effects. Additional research is needed examining the practice of APP across diagnoses, focusing on the multiple aspects affecting local practice and various contributing factors that could be targeted for intervention. This would be a positive step towards improving the quality of our service and providing optimal patient management in a resource-limited setting.

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Research supervisor, Dr Henk Temmingh, provided valuable input at all stages of the research project and assisted with data analysis. His contribution was greatly appreciated.

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Abbreviations

AOR	Adjusted odds ratio
APM	Antipsychotic monotherapy
APP	Antipsychotic polypharmacy
FGA	First-generation antipsychotic
LAI	Long acting injectable
SGA	Second-generation antipsychotic

Chapter 1: Research Protocol and Literature review

1 Research Protocol

1.1 Background

The term antipsychotic refers to a group of agents that have a variety of actions, with individual antipsychotic drugs possessing various properties, including antipsychotic, antimanic and mood-stabilizing properties.(1) Antipsychotic agents are used in the treatment of psychotic and mood disorders. They have demonstrated efficacy in acute episodes of schizophrenia and for maintenance treatment by reducing the risk of relapse.(2) Clinical practice guidelines for the treatment of schizophrenia (2-6) advocate an approach of antipsychotic monotherapy in the majority of cases. They recommend avoiding antipsychotic polypharmacy (APP) which can be defined as co-prescription of more than one antipsychotic drug for a given patient,(7) except for short periods when switching agents or in treatment resistant settings when augmentation of clozapine with another antipsychotic agent may be considered, although supporting evidence for this remains weak.(8) Treatment guidelines recommend use of certain antipsychotics as first-line treatment options for acute mania, acute bipolar depressive episodes and for long-term maintenance/prophylactic treatment in bipolar disorder.(9,10) In bipolar patients with residual symptoms or frequent relapses on antipsychotic treatment, these guidelines advocate switching to an alternative monotherapy, or using an antipsychotic agent in combination with a mood stabilizer (lithium or sodium valproate). APP is not recommended in bipolar disorder. Use of antipsychotic agents in the treatment of psychosis with coexisting substance misuse (dual diagnosis) is advised in accordance with guidelines on schizophrenia or bipolar disorder.(13)

Despite treatment guideline recommendations, APP appears to be a common practice worldwide. APP rates range between 10 – 50 % in different settings.(14-19) A previous systematic review examined the prevalence and correlates of APP looking at studies published between 1970 to 2009 from different geographical regions.(20) This review found that global rates of APP remained similar over time (decades), with a median prevalence rate of APP of 19.6%. However, there were significant differences in rates of APP across geographical regions. APP rates in Asia and Europe were found to be consistently higher compared to Oceania and North America for the past four decades. The pooled median APP rate across decades for Asia was 32% (interquartile range 19.2% - 53.0%), with Europe's rate being 23% (interquartile range 15.0 % - 42.1%), compared to Oceania with a

median rate of 16.4% (interquartile range 9.8% - 20.0%) and North America with a median rate of 16% (interquartile range 7.2% - 24.4%). Rates of APP showed different trends across time in different regions. The rates in North America increased progressively from 12.7% in the 1980s to 17.0% in the 2000s, as did the rates in Europe with an increase from 17.6% in the 1980s to 26.3% in the 1990s and then a plateau to 25% in the 2000s. The rates in Oceania showed a large increase in APP from 2% in the 1980s to 17.7% in the 2000s. In contrast, rates of APP in Asia decreased substantially from 55.5% in the 1980s to 19.2% in the 2000s. Reasons for geographical differences and trends across time remain uncertain.(20)

While substantial rates of APP have been described, there is a lack of robust evidence to support the routine use of combined antipsychotics.(7,8,21-23) Evidence in support of antipsychotic combination therapy in schizophrenia consists mostly of small, open-label studies and case series,(7,8,21,23-26) although randomized controlled trials on the subject have also been conducted. A meta-analysis published in 2009 reviewed evidence from 19 randomized controlled trials that compared antipsychotic monotherapy to co-treatment with a second antipsychotic in patients with schizophrenia.(23) Findings suggested that, in certain clinical situations, APP may be associated with superior benefit compared with monotherapy regarding all-cause discontinuation and general measures of efficacy. However, much of the evidence in support of combination treatment came from clozapine augmentation studies, many conducted in China. The authors acknowledged there was evidence of publication bias supporting positive results and that database was too heterogeneous to derive strong clinical recommendations. In addition, it is not possible to determine whether improvement was due to potentiation or additive dosage effect.(27) Another meta-analysis of antipsychotic augmentation studies of clozapine only found benefit of APP in open, but not in blinded studies.(8) A recent well-designed randomised controlled trial of aripiprazole augmentation of risperidone or quetiapine showed no improvement in symptoms in patients receiving combined antipsychotic treatment compared to monotherapy. (28) Research on efficacy of APP in disorders other than schizophrenia is lacking.

In addition, there is evidence for harm associated with APP. A previous systematic review examined the safety and tolerability of this practice.(29) Findings from this review and other studies suggested an association of APP with increased adverse effects compared to treatment with one antipsychotic agent. The evidence was strongest with regard to increased extrapyramidal side-effects (17,30,31) and hyperprolactinaemia.(32-34) These side-effects were likely related to higher total antipsychotic dose. APP was also associated with increased sexual dysfunction,(35) hypersalivation,(36)

sedation,(32) cognitive impairment,(37) glucose elevation,(38) diabetes,(39,40) metabolic syndrome(41,42) and possibly dyslipidaemia.(40,41) Evidence for weight gain was mixed.(38,40,43) The exception to this trend of increased side-effects associated with APP came from some studies on aripiprazole augmentation of another antipsychotic agent which found a decrease in certain side-effects including hyperprolactinaemia, sexual dysfunction, weight gain and dyslipidaemia in particular settings.(43-45) Studies examining QTc prolongation presented different outcomes.(34,46) Of concern was the finding of increased risk of sudden cardiac death associated with APP and further increased by higher doses found in a large database study.(47) Studies reporting on association of APP and mortality produced conflicting results but of concern were results of increased mortality demonstrated in two cohort studies.(48,49) Additional concerns relating to APP include drug-drug interactions, problems in determining cause and effect of different combined treatments, decreased compliance as a result of complex drug regimens and significantly greater cost.(50)

Research has been conducted in order to gain insight into factors contributing to the practice of APP despite the adverse risk/benefit evidence. Antipsychotic prescription patterns seem to reflect a complex interplay among patient, illness, treatment and prescriber factors.(50) A previous systematic review conducted an evaluation of relevant correlates of APP, focussing on these factors.(50) This review and other studies found that patient characteristics associated with APP were younger age,(14,30,51-55) male sex (16,18,20,51,56) and unmarried patients,(30,51,57) with mixed results from studies examining race.(44,48,50,52,58) Illness variables associated with increased APP included diagnosis of schizophrenia or schizoaffective disorder,(18,20,51,55,56) earlier age of onset,(31,55,59) longer duration of illness,(16,20,60,61) greater illness severity,(51,54,55,59-61) treatment resistance,(60,61) psychiatric comorbidity,(56) mental retardation (55) and mixed results from only a few studies for comorbid substance use.(30,54,55) With regard to treatment variables, APP was found to be associated with inpatient setting/hospitalization,(20,30,62) longer inpatient stay,(18,31) APP at baseline,(51,61) higher total dose of antipsychotic,(7,14-16,31,55,63) treatment with quetiapine,(15,31,42,63) use of long acting injectables (LAIs),(17,20,64) first-generation antipsychotic (FGA) treatment,(16,20,37,55) anticholinergic treatment,(7,20,30,42,64) with mixed evidence regarding antidepressant treatment,(18,30,55,59) anxiolytic treatment (30,55,59) and mood stabilizer treatment.(30,55) Combinations of FGAs and second-generation antipsychotics (SGAs) were most common in studies on APP,(15,19,20) although studies reporting greater use of FGA combinations as well as SGA combinations were also found.(17,53) Provider variables including healthcare policies, drug

availability and cost, psychiatric education and experience and prescriber preference also influenced rates of APP.(65,66)

There is a paucity of research on APP in South Africa. Only one previous study has examined antipsychotic prescription patterns in a South African setting.(67) This study was published in 2008 and reviewed data on antipsychotic drug prescriptions for Xhosa patients with schizophrenia and schizoaffective disorder in three catchment areas in the Western Cape, particularly in terms of clozapine use. At the time of data collection FGAs were the only first line treatment available for use in the public sector in the Western Cape and clozapine the only freely available SGA. This study found that there was an overall low rate (10%) of clozapine use and a relatively high frequency of APP (28.6% of patients). The lower than expected rate of clozapine use could possibly be related to clinician concerns about treatment adherence, side-effect profile and the need for regular leukocyte counts to monitor the risk of agranulocytosis, a monitoring requirement that may be problematic in a low resource setting.(67) High rates of APP may be partially explained by high rates of LAI use (49.4% of patients), with the most frequently used antipsychotic combination being haloperidol and a LAI (54.2% of combinations). The study did not examine rates of high-dose antipsychotic usage. It is likely that there have been significant changes in antipsychotic drug prescriptions in the Western Cape since the time of this study as several additional SGAs have become widely available in the South African public sector and are commonly used in clinical practice. This may have resulted in an increase in rates of APP in view of research findings that use of SGAs is common in APP as previously discussed.

As evident above, APP is a practice generally viewed in the context of schizophrenia. Previous research into APP commonly restricts the study to a specific psychiatric population, usually patients with diagnosis of schizophrenia, or sometimes examines APP broadly across all patients prescribed antipsychotic treatment, without accounting for different psychiatric diagnoses included in this population.(56) While studies examining the relative prevalence of APP by diagnosis are limited, some research has adopted this approach. These studies confirmed that rates of APP are highest in patients with a diagnosis of schizophrenia, but also found varying lower rates of APP in patients with schizoaffective disorder and bipolar disorder.(14,27,30,55,68) To the best of our knowledge there is a lack of research investigating the occurrence of APP in other diagnoses, such as substance induced disorders, with this diagnosis either being excluded from studies as a primary diagnosis or not mentioned. Only a few studies reported on comorbid substance abuse and these produced mixed results on association with APP as mentioned previously. (30,54,55)

Our study attempted to address deficiencies in local and international research by examining recent antipsychotic prescribing patterns across diagnoses. It included information on comorbid conditions such as substance abuse, as well as other patient, illness and treatment characteristics associated with APP, including high-dose prescribing. This allowed for development of greater insight into the prevalence of and factors associated with APP in a hospital population in the Western Cape, increasing understanding of the complexity of the practice of APP in our setting.

1.2 Definition

APP was defined as the prescription of any two or more antipsychotics (oral and LAIs included) on discharge from hospital in the same patient.

1.3 Study aims

- To determine the prevalence of APP in patients discharged from Valkenberg Hospital.
- To determine the patient, illness and treatment factors associated with APP compared to monotherapy.

1.4 Study objectives

- We used an electronic patient record database to obtain information on patients prescribed one or more antipsychotic agent at time of discharge and used this information to determine the prevalence of APP in our study population.
- We used an electronic patient record database to obtain information on socio-demographic and clinical variables of patients in our study population in order to assess the patient and illness factors that may be associated with APP.
- We examined the nature and extent of pharmacotherapies prescribed to these patients from information on the electronic patient record database in order to assess related treatment variables associated with APP.

1.5 Hypotheses

Based on previous research we hypothesized that:

- There would be a fairly high rate of APP in our study population.
- The current rate of APP may be higher than that seen in previous years as several additional SGAs have recently become widely available in the South African public sector and are commonly used in clinical practice.
- Compared with monotherapy, APP would be more likely to occur in patients of younger age, male sex and single/unmarried patients.
- APP would be more likely in patients with diagnosis of schizophrenia, comorbid psychiatric diagnosis, comorbid substance use disorders, long length of hospital stay, increased number of hospital admissions, and longer time from first hospitalization to most recent discharge.
- Compared to patients with schizophrenia, lower rates of APP would be found in patients with schizoaffective disorder, bipolar disorder and substance induced disorders but these disorders would contribute significantly to the prevalence of APP in our population.
- APP would be positively associated with treatment variables of FGA use, use of LAIs, FGA-SGA combinations, high dose prescribing, concomitant anticholinergic use and possibly co-prescription of mood stabilizer and benzodiazepines. We expected antidepressant use to possibly show a negative association with APP.

1.6 Methodology

1.6.1 Study design

We conducted a cross-sectional study of discharge records using Valkenberg Hospital's electronic patient record database, *Clinicom*.

1.6.2 Study setting

Valkenberg Hospital is a large, government-funded psychiatric hospital in the suburb of Observatory, in Cape Town, South Africa. The hospital provides psychiatric services to the Cape Peninsula and is a major specialist referral centre of the Western Cape Province. It is the principal teaching hospital for the University of Cape Town's Department of Psychiatry. The hospital currently comprises 340 inpatient beds, of which 200 are dedicated to acute psychiatric services, 125 to forensic psychiatric services and 15 to a smaller therapeutic component. Patients admitted to the acute psychiatric units are commonly involuntary admissions with severe mental illness posing a risk to themselves or others and are unable to be managed on an outpatient basis.

1.6.3 Study population

We reviewed information on patients discharged from Valkenberg Hospital's acute and therapeutic units. We included patients with non-affective psychotic disorders and major affective disorders prescribed one or more antipsychotic agents at time of discharge. We included patients with diagnoses of schizophrenia (F20), acute and transient psychotic disorder (F23), delusional disorder (F22), schizoaffective disorder (F25), bipolar disorder (F31) and substance-induced mood and psychotic disorders (F10 - F19). We excluded patients with primary diagnoses relating to a medical condition, dementia, anxiety disorder, major depressive disorder, intellectual disability or personality disorder as these diagnoses were unlikely to feature significantly in our study population or contribute meaningfully to rates of APP in our setting. We examined the 6 month time period of January 2014 to June 2014. We estimated a total sample size of approximately N=500 to be sufficient as previous research in South Africa used a sample of 510 patients and international research on the subject has used study populations ranging from low hundreds to many thousands in large database studies.

1.6.4 Measurements

We accessed discharge records on Valkenberg hospital's electronic patient record database, *Clinicom*, to attain data on the variables below. We extracted the data on an electronic data collection sheet.

(a) Patient variables

- Age – number in years
- Gender – male or female
- Marital status – single, married, divorced, widowed
- Occupation – employed, unemployed

(b) Illness variables

- Diagnosis – recorded from ICD-10 coding in database

- Comorbid psychiatric diagnosis – gathered both from ICD-10 coding and information contained in discharge summaries completed electronically for each patient by their attending psychiatric registrar at time of discharge. Where the attending case manager commented on the presence of significant co-existing depressive symptoms, anxiety symptoms, evidence of personality disorder or traits or mild intellectual disability, these were captured as psychiatric comorbidities.
- Comorbid substance abuse – gathered from ICD-10 coding and clinical descriptors within patient discharge summaries; included comorbid alcohol (F10), cannabis (F12), methamphetamine (F15), methaqualone (F13), heroin (F11) and cocaine (F14) misuse
- Length of stay in hospital – number of days; as a proxy indicator of illness severity
- Number of Valkenberg hospital admissions – as a proxy indicator of illness severity
- Time from first hospitalization at Valkenberg Hospital to most recent discharge – number of days; indicator of duration of illness or time in treatment number of days/months

(c) Treatment variables

- Antipsychotic agent(s) prescribed
- Type of antipsychotic agent – FGA or SGA. Agents classified in our FGA group included haloperidol, chlorpromazine, trifluoperazine, flupentixol, zuclopenthixol and fluphenazine. SGA agents included amisulpiride, clozapine, olanzapine, risperidone, quetiapine and aripiprazole.
- Prescribed daily dose (PDD)/Defined daily dose (DDD). To compare doses of different antipsychotic drugs, the prescribed daily dose (PDD) in milligrams was divided by the defined daily dose (DDD) to give a PDD:DDD ratio. The DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults.(69) For LAIs, the DDD is based on the average recommended dose divided by the dosing interval.(69) This is the standard international unit recommended by the World Health Organization for drug utilization studies.(69) In keeping with previous studies, the PDD/DDD ratio for APP was calculated as the sum of the individual PDD/DDD ratios of all antipsychotics prescribed to a patient and high dose prescribing was defined as PDD/DDD of greater than 1.5.(15,58,61,70)

Note: Literature suggests three methods for calculating antipsychotic dose: Chlorpromazine equivalents, percentage of British National Formulary (BNF) maximum dose, and Defined Daily Dose (DDD).(58) Recent studies have shown that there is coherence between these different methods and all are reliable ways for standardizing antipsychotic doses in drug utilization research.(58,71) However, the use of Chlorpromazine equivalents methods has disadvantages in that values differ across literature (72) and may be of limited accuracy for atypical antipsychotics.(58,73) The BNF

method uses recommended maximum doses from the British National Formulary which may differ from those in other countries and are not internationally adopted.(58) The DDD method was chosen for this study because it uses values published by the WHO and is widely available and internationally recognized as a reliable tool.(58,69)

- Route of administration - oral or LAI
- Co-prescription of mood stabilizer(s)
- Co-prescription of antidepressant(s)
- Co-prescription of benzodiazepine(s)
- Co-prescription of anticholinergic(s)

1.7 Data analysis

We inspected data for normality using histograms and Shapiro Wilks' test for normality. Continuous variables were analysed using student's t-test for normal data and Wilcoxon-ranksum test for skewed data. For categorical variables we used Chi-square tests to analyse data, with Fisher's exact test where appropriate. Confidence intervals for prevalence rates were calculated using the normal approximation of the binomial distribution.

The main outcome of interest was the presence of antipsychotic polypharmacy (APP), as previously defined. We coded a positive outcome (i.e. the presence of APP) as "1" and a negative (no APP) as "0". We conducted a hierarchical multivariable logistic regression analysis in order to model the response variable of antipsychotic polypharmacy as a function of a number of demographic and clinical variables. Independent (predictor) variables were categorised into multilevel categorical variables using dummy coding to obtain reference level categories. Cut-points for continuous variables were decided on the basis of what constituted meaningful clinical categorisations. We followed a forward selection and backward elimination procedure and determined model fit using a combination of Likelihood-ratio Chi-square tests and the Akaike Information Criterion (AIC). We entered each variable into the model one at a time starting with demographic and then clinical variables. We removed variables one at a time if model fit did not improve by their addition, based on the likelihood Chi-square tests and AIC. The final model included all variables except reported symptoms of anxiety and depression and length of inpatient stay. Model fit for the final model was determined using the Pearson Chi-Square Goodness of Fit test. Statistical significance was set at $p<0.05$ for two-sided tests. We used Stata version 13 for Windows to analyse the data.

1.8 Structured literature review for studies on APP

In order to examine previous research on the prevalence and relevant correlates of APP we conducted an electronic search in PubMed (last updated September 2015) using the following key words: "(antipsychotic OR antipsychotics OR neuroleptic OR neuroleptics) AND (polypharmacy OR combination OR polytherapy) AND (prevalence OR correlates OR association)." In addition, reference lists from retrieved articles and relevant reviews were inspected to identify additional studies.

Inclusion criteria were human subjects, English language, adult population (age 16-65 years), articles published in peer reviewed journals, articles reporting explicitly of prevalence of APP in the study population and articles that reported explicitly on associations between APP and patient, illness and treatment characteristics. No restriction was placed on publication years included in the search. We excluded articles not conducted in English, studies in paediatric or geriatric populations, articles published in non-peer reviewed journals, intervention studies aimed at decreasing APP and studies reporting on psychotropic polypharmacy, without specific mention of APP.

Articles were first analysed in tabular format. Study findings pertinent to our review were documented. The quality of articles was assessed in accordance with STROBE guidelines.(74) Study design, population and methods were examined. Limitations affecting quality of research were commented upon. An extensive summary of the literature was then provided.

1.9 Limitations

- Restricting the study population to patients discharged from Valkenberg hospital may have produced results that are not readily generalizable to the general population in view of previous findings of hospitalization being associated with APP.(20,30,62)
- While discharge prescriptions should have reflected the plan for ongoing maintenance treatment in most patients, some APP may have resulted from certain patients discharged during a process of cross titration while changing antipsychotic agents.
- The variables examined in our study were limited to information captured on the hospital's electronic patient record database, *Clinicom.* We anticipated that data may be incompletely captured in some cases. In addition, we realized that certain relevant variables may not be directly recorded. We attempted to overcome this problem by examining related variables. Length of time from first hospitalization to most recent discharge was used to provide some

indication of duration of illness or time in treatment, although we acknowledge that the patient may have been diagnosed with mental illness prior to first hospital admission. Number of previous admissions and length of stay were recorded as indicators of illness severity and possibly treatment resistance, although we realize that these are not direct substitute measures.

- Our literature search was not exhaustive as it was limited by search terms and the database (PubMed) used. We excluded studies not conducted in the English language, which may introduce language bias. It was structured literature review and not a comprehensive systematic literature review.

1.10 Ethical considerations

1.10.1 Risks and benefits

The study entailed a cross-sectional review of discharge records (ie. secondary data) and did not involve direct participation of patients. This removed the risk of possible harm to patients that may be involved in studies requiring interaction with participants. Findings from the study will benefit patients in the future by increasing awareness and understanding of the practice of APP and identifying possible need for further audits, protocol development on APP practices and need for reflection on prescription practices.

1.10.2 Privacy and confidentiality

We made use of the data captured on Valkenberg Hospital's electronic patient record database in such a way that patient privacy and confidentiality was ensured. We used a password protected computer and ensured safekeeping of non-electronic related documents so that the researcher alone had access to patient information. Patient identifying data was removed prior to data analysis to safeguard patient privacy and confidentiality.

1.10.3 Ethical and regulatory compliance

We conducted the study in accordance with the ethical principles that are contained in the World Medical Association Declaration of Helsinki (75) and in the Department of Health's document, Ethics in Health Research, Principles, Structures and Processes.(76) We attained approval from the University Of Cape Town Faculty Of Health Sciences Human Research Ethics Committee, the Faculty of Health Sciences and the Department of Health prior to commencing our research.

1.11 Resources

We made use of Valkenberg Hospital's electronic patient record database, *Clinicom*, to attain relevant data for our study. The principle researcher captured the data and her supervisor assisted with data analysis. We made use of existing resources and did not require additional funding.

1.12 What happens at the end of the study?

By conducting this study we demonstrated the prevalence and patterns of APP at Valkenberg Hospital. We were able to assess whether current clinical practice is comparable with standard international guidelines and trends using this information. In addition, we identified the patient, illness and treatment characteristics that may be associated with APP in our setting. This provided an indication of possible areas that need to be addressed in order to improve local mental health care practice and enhance safe and effective patient management in the future. We aim to disseminate the study findings through public lectures to health professionals and publication in peer-reviewed journals.

1.13 Timeline for study

February – June 2014: Protocol development, protocol presentation (3 June)
June – December 2014: Attain approval, literature review, data collection
January – June 2015: Data collection
June – December 2015: Data analysis and report development
January – June 2016: Report development and completion

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2 Structured literature review

2.1 Objectives

The objectives of the structured literature review were as follows:

- To assess the prevalence of antipsychotic polypharmacy (APP) in previous international literature.
- To assess the patient, illness and treatment characteristics associated with APP in previous international literature.

2.2 Literature search strategy

We conducted an electronic search in PubMed for prevalence and correlates of APP (last updated September 2015) using the following key words: "(antipsychotic OR antipsychotics OR neuroleptic OR neuroleptics) AND (polypharmacy OR combination OR polytherapy) AND (prevalence OR correlates OR association)." In addition, reference lists from retrieved articles and relevant reviews were surveyed to identify additional studies.

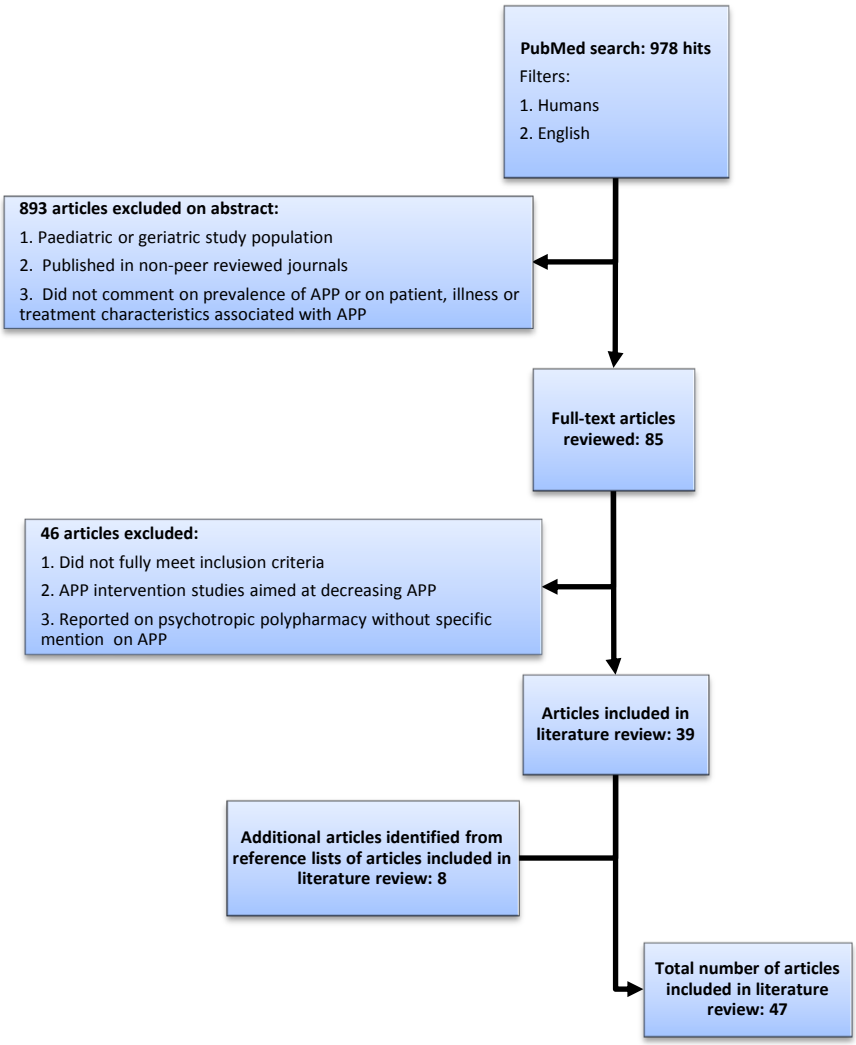
2.2.1 Inclusion criteria

- Human subjects
- English language
- Adult study population (18 – 65 years)
- Articles published in peer reviewed journals
- Articles reporting explicitly on prevalence of APP (co-prescription of more than one antipsychotic drug for a given patient) in study population
- Articles reporting explicitly on associations between APP and patient, illness and treatment characteristics. These included observational studies with cross-sectional, case control or cohort design and previous systematic reviews.
- Any study published prior to September 2015 (no restriction placed on publication years included)

2.2.2 Exclusion criteria

- Not in English
- Paediatric or geriatric study population
- Articles published in non-peer reviewed journals
- Intervention studies aimed at decreasing APP
- Studies reporting on psychotropic polypharmacy, without specific mention of APP

2.3 Flowchart of search strategy



2.4 Appraisal of quality and relevant content of studies

Articles included in our review were first analysed in tabular format (Annexure 1). The quality of articles was assessed in accordance with STROBE guidelines.(1) Study design was examined as different levels of evidence and advantages/disadvantages are associated with different study

designs. Study population was reviewed, with population factors including study size, duration of study and method of sampling affecting quality of studies. Statistical methods used in data analysis were explored in order to assess for measures taken to reduce the effects of confounders and reflect strength of associations. Limitations affecting quality of research were commented upon. Study findings pertinent to our review were documented.

2.5 Results

We attained a search result of 978 hits using our key words: "(antipsychotic OR antipsychotics OR neuroleptic OR neuroleptics) AND (polypharmacy OR combination OR polytherapy) AND (prevalence OR correlates OR association)" after the filters of human population and English language were applied. We excluded 893 studies on abstract level when it became apparent that the studies were conducted in paediatric or geriatric study populations, published in non-peer reviewed journals or did not comment on the prevalence of APP or on patient, illness or treatment characteristics associated with APP. We thus reviewed 85 full-text articles. An additional 46 of these were excluded because they did not fully meet inclusion criteria, were found to be intervention studies aimed at decreasing APP or reported on psychotropic polypharmacy without specific mention on APP. 39 studies remained appropriate for our literature review. We identified 8 additional relevant studies from the reference lists of these articles, which resulted in a total of 47 studies included in our literature review. Table 1 provides an overview of the relevant content and quality of studies included in our review.

2.5.1 Quality of included studies

Several limitations affecting the quality of literature were found across a number studies (see Table 1). The majority of studies were cross-sectional in design, which prevented assessment of treatment changes over time, with factors such as switching between antipsychotic agents possibly influencing results. Many studies were limited in available data due to their retrospective nature. In several studies, APP data was included but was not the main focus of the research conducted. Other factors limiting quality of studies included small sample sizes, limited duration of studies and restricted study populations, affecting validity and generalizability. Some studies failed to comment explicitly on methods of random selection used to select study population, leaving us unable to exclude selection bias. Several studies did not perform adjustment in multivariate analyses on results, with confounding factors possibly influencing their findings.

2.5.2 *Prevalence of APP in previous international literature*

Studies included in the literature review reflected a diverse range of settings and revealed varying rates of APP. Of the 44 observational studies that reported explicitly on prevalence of APP, 15 were conducted in Europe,(2-16) 16 in North America,(17-32) 7 in Asia,(33-39) 4 in Oceania,(40-43) and 2 in Africa.(44,45) Differences in rates of APP across geographical regions were evident. Prevalence rates of APP were highest across Asian studies, ranging from 12% to 78.6%. European studies reflected APP prevalence rates between 0% and 67.7%. Studies conducted in Oceania and North America generally revealed lower prevalence rates ranging from 14.2% to 43.2% and 0% to 49.3% respectively. Only two previous studies conducted in Africa were found, with an APP prevalence rate of 7% found in a Nigerian study (44) and 28.6% in a South African study.(45)

The majority of studies in our review reflected APP prevalence rates from 2000 onwards. Several studies had a retrospective comparative component examining APP prevalence rates prior to 2000. These studies showed a trend of increasing APP from between 1989 into the early 2000s.(9,14,15,28,30) Two studies in our review showed decreasing rates of APP during the 2000s.(39,42)

Another aspect of study setting influencing APP prevalence rates in our review was inpatient versus outpatient treatment. Inpatient studies generally showed higher rates of APP across geographical areas and times. Asian studies demonstrated inpatient prevalence rates ranging from 12% to 78.6%,(34,38,39) compared to rates ranging from 19.2% to 50.4% in outpatient studies.(35-37) European inpatient studies revealed APP prevalence rates between 0% and 67.7% (2,6-14) compared to rates between 6.3% and 56.2% found across outpatient studies.(3-5,15,16) Studies conducted in North America reflected prevalence rates ranging from 0% to 49.3% across inpatient studies (18,23,26,30) and 5.7% to 40% in outpatient studies.(17,19-22,24,25,27-29,31,32) The Oceanian studies revealed prevalence rates of 43.2% and 31% in inpatient studies (40,41) compared to rates ranging from 14.2% to 18.3% in outpatient studies.(42,43)

Study design should also be noted when considering rates of APP. Most studies included in our review were cross-sectional. Studies with longitudinal examination of rates in the same population showed that APP prevalence rates decreased when continued use over time was examined.(4,15,17,20)

2.5.3 Patient characteristics associated with APP in previous international literature

Age, sex/gender and marital status were the patient characteristics most frequently examined in studies reviewed. While some studies failed to demonstrate statistical significance with regard to the association of age and APP,(3,4,8,10,16,17,19,33,35,37,40,41,46) there were a number of studies that provided evidence for the significant association of younger age and APP.(6,12,13,26,27,29,31,34,38,39) The majority of studies examining sex/gender found male sex to be positively associated with APP. Although the association was non-significant in many studies,(3,8,10,12,17,19,21,26,29,31,33-35,38-40,46,47) several studies did reflect a statistically significant association of male sex and APP.(6,13,16,27,41) APP was significantly associated with being single/unmarried in 4 studies,(3,6,19,31) with one study reflecting a non-significant association of marital status and APP.(35)

Other patient characteristics less commonly captured in studies included in our literature review were race/ethnicity, living circumstances, education and employment. Results for race and ethnicity were inconclusive. One study showed a positive association with African-American race and APP,(26) while another found the association to be negative.(31) A single study showed increased APP in Asians compared to whites.(27) The association of race/ethnicity and APP was non-significant in other studies.(17,19,41,47) The few studies that examined living circumstances found no significant association with APP.(4,6,46) Likewise, education, occupation and employment generally failed to show significant associations with APP.(4,6,35)

2.5.4 Illness characteristics associated with APP in previous international literature

While the majority of studies restricted their study population diagnosis, several examined APP across different diagnoses. Diagnosis of schizophrenia was most commonly associated with APP.(2,6,27,31,41,47) Schizoaffective disorder was found most commonly with APP in one study.(18) Some studies adopted broader diagnostic categories and demonstrated a positive association between APP and psychotic disorders.(3,26,29,46) While diagnoses of schizophrenia, schizoaffective disorder or psychotic disorders were most prevalent in patients receiving APP, some studies demonstrated substantial occurrence of APP in bipolar disorder (6,18,24,26,46) and even some use of APP in major depressive disorders, although APP use in major depressive disorders was

consistently far lower than other diagnoses.(6,18,24,26,46) No studies specifying APP rates in patients with diagnosis of substance-induced disorder were found.

Few studies reported on associations of APP and co-morbidities. One study showed a positive association between APP and psychiatric co-morbidity in general.(27) Another showed a negative association between APP and co-morbid depression.(31) No significant association between anxiety and APP was found.(31,37) Co-morbid personality disorder was found to be associated with APP in one study,(12) with co-morbid mental retardation showing a non-significant relationship with APP in the same study. While a single study demonstrated a significant positive association of APP and co-morbid substance use,(2) other studies failed to show statistical significance of this association.(6,12,27)

APP was significantly associated with earlier illness onset in one study (33) and longer illness duration in two studies,(34,38) with the relationship being non-significant in another three.(10,33,35) Greater illness severity was positively associated with APP in two studies,(6,33) however no significant association was seen in others.(4,12,38,47) Positive and negative symptoms were significantly associated with APP in one study,(39) but relationships were found to be non-significant in other studies.(12,33,37)

2.5.5 Treatment characteristics associated with APP in previous international literature

Studies included in our review revealed a positive association between hospitalization and APP,(12,31,32,47) with increased rates of APP in patients with greater numbers of previous admission found in some studies,(10,26,46) although not reaching statistical significance in others.(35,37) Longer inpatient stay was significantly associated with APP in four studies,(16,40,41,46) with non-significant findings in two.(8,10) Antipsychotic monotherapy and APP on admission (at baseline) were found to be positively associated with APP at discharge in several inpatient studies.(4,6,16,46) High-dose prescribing was consistently associated with APP,(4,6,13,18,33,35,38,39,41) as was long acting injectable (LAI) antipsychotic use.(2,35,37,39,47) First-generation antipsychotic (FGA) use was positively associated with APP in three studies.(33,39,47) Neither studies that examined second-generation antipsychotic (SGA) use,(33-35,38,39), nor those comparing clozapine use (37,47) found significant associations with APP.

On analysis of APP prescription patterns reflected in articles included in our review, FGA-SGA combination treatment was most common,(2,4,7,10-12,14,17,19,20,26,28,47) followed by SGA-SGA combinations,(3,13,18,29,32,33,46) then FGA-FGA combinations which predominated in several studies.(8,35,44,45) Two studies that examined combination types over time both demonstrated a move from FGA-FGA combinations to more FGA-SGA combination treatment in recent years.(15,39) Agents commonly used in combinations varied across studies, with haloperidol,(26,34,44,45) chlorpromazine,(17,44) olanzapine,(5,10,29) risperidone (3,5,14,29,33,46) and quetiapine (3,13,17,18,29,46) appearing most frequently. There was diversity amongst studies with regard to most common agent combinations, with haloperidol-olanzapine,(20,30) risperidone-quetiapine (3,5,29) and quetiapine-aripiprazole (18,46) being the only combinations that were found to be most prominent in more than one study.

With regards to co-prescribed medications, a consistent positive association of concomitant anticholinergic prescription and APP was evident.(35,38,41,47) APP was found to be significantly associated with co-prescription of mood stabilizers in two studies,(18,31) with non-significant results in another.(47) Co-prescription of benzodiazepines showed a positive association with APP in two studies.(18,31) However, a negative association of APP and benzodiazepine use was found in another study.(33) Concomitant antidepressant use was associated with decreased APP in two studies,(6,47) with one study showing non-significant findings.(31)

2.6 Discussion

2.6.1 Prevalence of APP in previous international literature

A previous systematic review that examined the prevalence and correlates of APP in studies published between 1970 to 2009 from different geographical regions was included in our review.(47) This article showed a global median prevalence rate of APP of 19.6% across time with significant differences in rates of APP across geographical regions. APP rates in Asia and Europe were found to be consistently higher compared to Oceania and North America. The pooled median APP rate across decades for Asia was 32%, with Europe's rate being 23%, compared to Oceania with a median rate of 16.4% and North America with a median rate of 16%. African studies did not feature in this review. While studies included in our review revealed a range of prevalence rates, findings and geographical trends were similar to those found in this previous review.

Reasons for geographical differences in rates of APP are not clear. It has been suggested that higher rates in Asia may be partially explained by the Asian traditional medicine belief that a mixture of medical remedies is superior to a single compound.(48) Higher rates in Europe compared to North America could be as a result of higher use of LAIs or additional use of low potency FGAs to replace adjunctive benzodiazepines.(47) Lower rates of APP in Oceania may be related to higher use of clozapine in this region.(47)

Our findings of APP prevalence rates increasing over time from 1989 into the early 2000s were also in keeping with findings of the previous systematic review referred to above. This previous review reflected rates of APP in Europe, North America and Oceania increasing progressively from the 1980s to the 1990s and into the early 2000s.(47) These increasing trends may have been partly related to increased availability of SGAs over time, which broadened treatment options and may have been seen as more acceptable to use in combination with other agents with different profiles.(47) Two fairly recent studies in our review found decreasing APP prevalence rates as we progress further into the 2000s,(39,42) possibly as a result of greater awareness of treatment protocols advocating monotherapy and the risks associated with APP.

Additional consistencies with previous literature were our findings of higher APP prevalence rates in inpatient studies compared to outpatient studies, with inpatient status being positively correlated with APP in numerous previous studies.(47,49) Possible reasons for this include greater illness severity in inpatients, inpatients in the process of switching between antipsychotic agents and antipsychotics used for behavioural control or sedation in hospitals.(49)

The decreasing rates of APP found in longitudinal studies were commented upon in our findings. One reason for this trend may be that cross-sectional studies may reflect inflated prevalence rates of APP as a result of capturing patients in the process of switching between antipsychotics, as well as antipsychotics prescribed for behavioural or sedation purposes, both in the inpatient and outpatient setting.

2.6.2 Patient characteristics associated with APP in previous international literature

Our review findings on patient characteristics associated with APP were similar to those of a previous systematic review that focussed on correlates of APP.(49) While this previous systematic review was descriptive in nature and did not perform statistical analysis on findings, it suggested

substantial evidence for the positive association of APP with younger age, male sex and unmarried patients. It is possible that younger age at onset could be associated with increased illness severity, leading to increased APP in this population. An alternative explanation could be that younger patients are undergoing more treatment changes, reflected as increased rates of APP when overlapping antipsychotic switches are captured in cross-sectional studies.(49) It has been suggested that the association of male sex and APP could be related to greater illness severity, chronicity or dangerousness in males.(49) The same may hold for unmarried status, which has been found to be associated with both younger age and greater illness severity/chronicity.(49) Results on race were inconclusive in this previous review, and no mention made of other patient factors examined in our review, likely as a result of paucity of studies exploring these associations.

2.6.3 Illness characteristics associated with APP in previous international literature

Highest rates of APP in patients with diagnoses of schizophrenia/schizoaffective disorder were to be expected in view of antipsychotics being the established mainstay of treatment for these disorders. The substantial rates of APP in bipolar disorder found in a few studies in our review was of interest and may likely be the result of increasing evidence for efficacy and increased use of atypical antipsychotics in the treatment of bipolar disorder. There is a need for further studies investigating this practice. No studies specified substance-induced disorders amongst diagnoses. There was also a lack of studies examining associations with co-morbid conditions. Previous systematic review similarly reflected paucity of studies examining APP across different diagnoses and co-morbidity associations and recommended future studies pursue these areas.(49)

Our review suggested possible association of APP with earlier illness onset, longer illness duration, greater illness severity and more positive and negative symptoms. These findings are consistent with previous systematic reviews that have suggested that illness characteristics demonstrated an association of APP with greater illness severity, chronicity and treatment resistance,(47,49) with additional antipsychotics added possibly as a result of poor response on monotherapy.

2.6.4 Treatment characteristics associated with APP in previous international literature

Similarly to patient and illness characteristics, treatment variables associated with APP have also been found to point towards greater illness severity, chronicity and refractoriness,(49) evidenced by

our findings of a possible positive association of APP with hospitalization, greater numbers of previous admission, longer inpatient stay and high-dose prescribing. It has been suggested that the positive association of APP with use of LAIs may result from the difficulty performing fine adjustments with LAIs alone, leading to oral medication being added for this purpose.(49) Concerns over compliance likely also contribute to the association between APP and LAI prescription.

APP prescription patterns reflected in our review were in keeping with those of a previous systematic review, which found a positive association of APP with FGA use, with a move from FGA-FGA combinations to more FGA-SGA combinations over time and FGA-SGA combination treatment being most prevalent.(47) Increased FGA-SGA trends could be explained by wider availability of SGAs in recent years which has increased treatment options available to prescribers as a result of their more varied pharmacodynamic profiles.(47) Psychiatrists may combine FGA agents with SGA antipsychotics with different profiles in hope of better outcomes and fewer extrapyramidal side-effects.(47) Prescriber practices vary widely amongst different health care systems and settings,(47) likely contributing to the variety of agents found to be used in combination in our review.

Consistent positive association of concomitant anticholinergic prescription with APP reflects an increased risk of extrapyramidal side-effects in patients treated with APP. This may be related to our findings of the positive associations of APP with high-dose prescribing and FGA use, factors which may also increase risk for extrapyramidal side-effects. The association of APP and co-prescription of mood stabilizers may be linked to high rates of APP in schizoaffective disorder,(18) and use of mood stabilizers to manage residual mood symptoms, aggression and hostility in difficult patients.(47) Co-prescription of benzodiazepines may reflect use in this population for sedation and behaviour control,(47) but results in this regard have been inconsistent. It has been suggested that antidepressants may be used to manage depressive and negative symptoms that may otherwise increase APP in a subgroup of patients,(47) possibly explaining the findings of decreased rates of APP in patients receiving concomitant antidepressant treatment. Previous review findings regarding concomitant medication use were similar to those revealed in our review.(47)

2.6.5 Previous literature on APP in South Africa

Only one previous study has examined antipsychotic prescription patterns in a South African setting.(45) This study used data collected between 2002 and 2005 and reviewed antipsychotic drug prescriptions for Xhosa patients with schizophrenia and schizoaffective disorder in three catchment areas in the Western Cape, particularly in terms of clozapine use. At the time of data collection FGAs

were the only first line treatment readily available for use in the public sector in the Western Cape and clozapine the only freely available SGA. This study found that there was an overall low rate of clozapine use (10%) and a relatively high frequency of APP (28.6% of patients). The lower than expected rate of clozapine use could possibly be related to clinician concerns about treatment adherence, side-effect profile and the need for regular leukocyte counts to monitor the risk of agranulocytosis, a monitoring requirement that may be problematic in a low resource setting.(45) High rates of APP may be partially explained by high rates of LAI use (49.4% of patients), with the most frequently used antipsychotic combination used being haloperidol and a LAI (54.2%) of combinations). The study did not examine rates of high-dose antipsychotic usage or factors associated with APP in their study population. It is likely that there have been significant changes in antipsychotic drug prescriptions in the Western Cape since the time of this study as several additional SGAs have become widely available in the South African public sector and are commonly used in clinical practice.

2.7 Relevance for our study

APP appears to be a relatively common practice worldwide, with geographical location and time of study influencing prevalence rates. In contrast to the fairly substantial international literature on APP, there is a paucity of research on APP from Africa, with only one previous study examining rates of APP in a South African setting conducted in 2008. There is clearly a need for investigation into this practice in the current South African health care climate. While inpatient, cross-sectional studies may be more feasible to conduct, the influence of clinical setting and study design on prevalence rates requires consideration.

There have been no previous studies examining patient, illness and treatment characteristics associated with APP in South Africa. Patient, illness and treatment factors associated with APP have been examined in previous international literature but inconsistencies and gaps in the evidence remain. Patient characteristics of age, sex and marital status have received most attention, with fewer studies examining other patient factors possibly associated with APP. There is a lack of information on illness characteristics in the context of APP. APP is a practice generally examined in the context of schizophrenia/schizoaffective disorders, with fewer studies investigating the occurrence of APP in bipolar disorder and no previous studies examining APP rates in substance-induced disorders found. There is a deficiency in the literature on co-morbidities associated with APP. Antipsychotic prescriptions seem to vary widely in different contexts and there is a need for further studies investigating associations with concomitant psychotropic prescriptions.

Our study will attempt to address deficiencies in local and international research by examining the current prevalence of APP in a South African context and investigating various patient, illness and treatment characteristics that may be associated with the practice. We will examine antipsychotic prescribing patterns across diagnoses, including bipolar disorder and substance-induced disorders. We will provide information on a broad range of patient, illness and treatment characteristics that may be associated with APP, including co-morbid conditions such as substance abuse, high-dose prescribing and concomitant psychotropic prescribing. Our study will provide greater insight into the prevalence of and factors associated with APP in a study population in the Western Cape, increasing understanding of the complexity of the practice of APP in our setting and hopefully offering a meaningful contribution to both local and international literature.

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Table 1

Analysis of studies included in literature review according to study design, population, prevalence of antipsychotic polypharmacy (APP), factors associated with antipsychotic polypharmacy (APP), most common antipsychotic polypharmacy (APP) combinations and study limitations

Study	Design	Population	Prevalence of APP	Factors associated with APP	Most common APP combinations	Study limitations
Adesola et al. 2014	Cross-sectional	Inpatients receiving at least one antipsychotic agent in March 2012, all diagnoses included, Federal Neuropsychiatric Hospital, Uselu, Benin City, Nigeria, N = 171	7%	Not examined	FGA-FGA (haloperidol-chlorpromazine)	Cross-sectional study, factors such as switching between antipsychotics may have affected results Focused on high-dose prescribing, main focus not APP Small study size Short duration of study, validity affected Single centre hospital study, generalisability affected
Aparasu et al. 2009	Cross-sectional	Outpatients prescribed at least one antipsychotic at outpatient visit in 2003-2004 NAMCS and 2003-2004 NHAMCS, all diagnoses included, United States National Ambulatory Medical Care Survey (NAMCS) and the outpatient department portions of the National Hospital Ambulatory Medical Care Survey (NHAMCS), N = 2860	9%	**Increased association:** Age < 65 years Diagnosis of psychosis **No significant association:** Sex	SGA-SGA (risperidone-olanzapine, risperidone-quetiapine)	Cross-sectional study, factors such as switching between antipsychotics may have affected results Limited data set, scope and validity affected Outpatient study in specific care systems, generalisability affected
Arilla et al. 2010	Cross-sectional	Inpatients treated with at least one antipsychotic in 2006, all diagnoses included, psychiatric inpatient unit at Royo Villanova Hospital, Zaragoza, Spain, N = 136	On admission: 44% On discharge: 51%	**Increased association:** Diagnosis of schizophrenia LAI use Co-morbid substance use disorder	FGA-SGA (specific agent combinations not given)	Cross-sectional study, factors such as switching between antipsychotics may have affected results Small study size Limited data set, scope and validity affected Multivariate analysis not performed, results not adjusted for confounding Single centre hospital study, generalisability affected
Atik et al. 2008	Cross-sectional	Outpatients prescribed antipsychotics in outpatient clinic in Sept 2005 - Sept 2006, all diagnoses included, Zonguldak Karaelmas University, Medical Faculty Hospital, Department of Psychiatry, Turkey, N = 444	6.3%	**Increased association:** Unmarried Diagnosis of psychosis **No significant association:** Age Sex	SGA-SGA (risperidone-quetiapine)	Cross-sectional study, factors such as switching between antipsychotics may have affected results Focused on antipsychotic prescription patterns in general and characteristics of patients prescribed different drug classes, main focus not APP Limited data set, scope and validity affected Multivariate analysis not performed on APP data, results not adjusted for confounding Single centre hospital outpatient study, generalisability affected

Barbui et al. 2006	Longitudinal	Outpatients with diagnosis of schizophrenia with clinical instability receiving antipsychotic medication recruited from psychiatric services serving four geographical catchment areas , Croydon (UK), Verona (Italy), Amsterdam (Netherlands), and Leipzig (Germany), part of a bigger international European clinical trial, the QUATRO study, N = 375	Baseline: 23% Persistent use at 1 year follow-up: 13%	**Increased association:** Living alone APP at admission Higher total dose of antipsychotic **Decreased association:** Number of antipsychotic drugs received the 12 months before enrolment in study **No significant association:** Age Sex Accommodation Employment Length of antipsychotic treatment Psychopathology scores Study site	FGA-SGA (specific agent combinations not given)	Small study size Participants recruited first interviewed and only included if gave written, informed consent, potential source of bias Outpatient study in schizophrenic patients with clinical instability, generalizability affected Recruiting sites not randomly selected, part of a bigger international European clinical trial, the QUATRO study, potential source of bias and generalizability affected
Bernardo et al. 2012	Longitudinal	Outpatients regularly prescribed antipsychotics in the Catalan Health Service during 2007, all diagnoses included, Barcelona Health Region, Catalonia, northeast Spain, N = 71004	13.9%	Not examined	FGA-SGA, SGA-SGA (haloperidol-risperidone, risperidone-quetiapine)	Limited data set, scope and validity affected Examined antipsychotic prescription patterns in general and focused on use of clozapine and depot antipsychotics, main focus not APP Associations with APP not measured in statistical analysis Study population excluded patients prescribed antipsychotics in private practice or inpatient services, generalisability affected

Biancosino et al. 2005	Longitudinal and cross-sectional components	Inpatients receiving antipsychotics at discharge from Jan 1998 to Dec 2003, regardless of diagnosis, voluntary psychiatric inpatient facility in Ferrara, northern Italy, N = 358	28%	**Increased association:** Male sex Younger age Single/unmarried Unemployed Earlier illness onset Diagnosis of schizophrenia APP at admission Higher illness severity Higher total dose of antipsychotic **Decreased association:** Antidepressant use at admission **No significant association:** Education Living with family Co-morbid substance use Benzodiazepine use at admission Mood stabilizer use at admission	Not examined	Medication examined at time of discharge, factors such as switching between antipsychotics may have affected results Small study size Inpatients admitted on voluntary basis, potential source of bias Severity scores interviewer-dependent, potential source of bias Single centre hospital study, generalizability affected
Bret et al. 2009	Cross-sectional	Inpatients prescribed antipsychotics on a single day in June 2004, all diagnoses included, 13 French psychiatric hospitals, members of the PIC network, N = 2192	49.3%	Not examined	FGA-SGA (cyamemazine-risperidone)	Cross-sectional study, factors such as switching between antipsychotics may have affected results Examined antipsychotic prescription patterns in general and focused on factors associated with SGA use compared to FGA use, main focus not APP Limited data set, scope and validity affected Single day duration, validity affected In-patient hospital study, generalisability affected
Centorrino et al. 2008	Cross-sectional	Inpatients prescribed antipsychotics for at least 3 consecutive days between March 1 and May 31, 2004, selected from computer-based pharmacy records using a computerized random-selection algorithm, all diagnoses included, McLean Psychiatric Hospital in Belmont, Massachusetts, USA, N = 305	23.3%	**Increased association:** Diagnosis of schizoaffective disorder Higher total dose of antipsychotic Co-prescription of mood stabilizer Co-prescription of sedative	SGA-SGA (aripiprazole-quetiapine)	Cross-sectional study, factors such as switching between antipsychotics may have affected results Small study size Computerized random sampling method used to select participants, details thereof not given, potential source of bias Limited data set, scope and validity affected Short duration of study, validity affected Single centre hospital study, generalisability affected

Clark et al. 2002	Longitudinal with point prevalences calculated	1995 paid Medicaid claims used to identify beneficiaries with diagnosis of schizophrenia and schizoaffective disorder, filled prescriptions for this group tracked over the subsequent 5 years, from 1 Jan 1995 to 31 Dec 1999, New Hamshire Medicaid pharmaceutical claims database, N = 836	Dec 1995: 5.7% Dec 1999: 24.3%	Not examined	FGA-SGA (specific agent combinations not given)	Point prevalence observations, factors such as switching between antipsychotics may have affected results Examined prescription patterns in general, main focus not APP Relatively small study size Limited data set, scope and validity affected Single state study, participants under full Medicaid insurance, generalizability affected
Correl & Gallego 2012	Systematic review	Articles reporting on associations between APP and study design, patient, illness, treatment and prescriber characteristics, electronic search in PubMed to assess correlates of APP, N = 98 studies included	Mean APP prevalence across studies reporting on APP correlates = 29.9%	**Increased association:** Younger age Male sex Unmarried Diagnosis of schizophrenia/schizoaffective disorder/psychotic disorder Earlier illness onset Longer illness duration Greater illness acuity/severity Less illness insight Treatment resistance Hospitalization Longer inpatient stay Longer treatment duration APP at admission Higher total dose of antipsychotic LAI use FGA use Co-prescription of anticholinergic agent	Not examined	Descriptive review of studies, statistical analysis of findings not performed Studies included in review generally did not focus on correlates of APP, but rather on reporting prevalence - the reported associations likely did not capture all possible associations because such analyses were either not done or not reported in studies Most studies collected data on only some of the potential and relevant correlates, there has not been a comprehensive screening for all potential associations Many studies were cross-sectional in design and may have included ongoing antipsychotic switches Study commented on factors associated with APP but was often vague with regard to whether the associations were positive or negative

Covell et al. 2002	Longitudinal with cross-sectional "snapshot"	Random sample of outpatients in the Connecticut state mental health system with continuous prescription records from 7/1996 to 6/1998 with diagnosis of schizophrenia, Connecticut state public mental health system, N = 400 (total), N = 369 (snapshot)	11% (snapshot)	**Increased association:** High school diploma Unmarried **No significant association:** Age Sex Race	FGA-SGA (specific agent combinations not given)	Complicated study design with longitudinal and cross-sectional component, difficult to follow and interpret study results Focused on antipsychotic prescription patterns in general and characteristics of patients prescribed atypical agents and had medication changes, main focus not APP Small study size Prevalence of APP clearly reported in cross-sectional "snapshot" component only Method of random sampling used to select participants not explained, potential source of bias Participants limited to diagnosis of schizophrenia, other diagnoses not included Outpatient population, generalizability affected
Divac et al. 2007	Cross-sectional	Sample of randomly selected patients hospitalized for 28 days or longer between 2002 and 2005 with the diagnosis of psychosis, Institute of Psychiatry, Clinical Centre of Serbia (University hospital) in Belgrade, Serbia, N = 198	67.7%	**Decreased association:** More prior admissions **No significant association:** Age Gender Duration of hospitalization	FGA-FGA (specific agent combinations not given)	Cross-sectional study, factors such as switching between antipsychotics may have affected results Small study size Method of random sampling used to select participants not explained, potential source of bias Limited data set, scope and validity affected Single day duration, validity affected Multivariate analysis not performed, results not adjusted for confounding Single centre hospital study, generalisability affected
Edlinger et al. 2005	Longitudinal and cross-sectional components	Inpatients with diagnosis of schizophrenia hospitalized in the years 1989, 1995, 1998, 2001, Department of Psychiatry of the Medical University Innbruck, Austria, N = 333	1989: 3.4% 1995: 0% 1998: 2.0% 2001: 12.4%	Not examined	SGA-SGA, FGA-SGA (amisulpiride-clozapine, haloperidol-clozapine)	Cross-sectional examination of discharge prescriptions, factors such as switching between antipsychotics may have affected results Examined prescription patterns in general, including polypharmacy, types of antipsychotics prescribed and dosing regimens, main focus not APP Relatively small study size Unclear definition of APP, no details given as to which agents were included as "high potency" Rates not comparable to studies which include all agents regardless of potency Single centre hospital study, generalisability affected

Gallego et al. 2012	Systematic review	Articles published between 1970 and 05/2009 reporting frequency of APP in patients aged > 18 years, electronic search in PubMed and Google scholar to assess prevalence and correlates of APP across decades and regions, N = 147	Pooled median APP rate of 19.6% across all regions and decades	**Increased association:** Diagnosis of schizophrenia FGA use LAI use Co-prescription of anticholinergic agent Inpatient treatment Cross-sectional study design Study origin in Asia, Europe and countries other than North America **Decreased association:** Longer length of follow up Co-prescription of antidepressant **No significant association:** Race Sex Severity rating scores Clozapine use Co-prescription of mood stabilizer Co-prescription of anxiolytic Decade of study	FGA-SGA (specific agent combinations not given)	Studies had heterogeneous design, population characteristics, health care systems and treatment cultures Majority of studies included used cross-sectional APP definition, factors such as switching between antipsychotics may have affected results Many studies included did not focus on APP or reported with too little specificity, reducing the amount of data for meta-regression APP rates were heterogeneous between and within geographical location, limited generalizability of individual study results
Ganguly et al. 2004	Longitudinal	Medicaid beneficiaries with diagnosis of schizophrenia with filled prescriptions for antipsychotics between 1998 and 2000, California and Georgia Medicaid pharmaceutical claims database, N = 31435	Total APP: 40% Long-term APP: 23%	**Increased association:** Newer SGA and older FGA use **Decreased association:** Nil **No significant association:** Age Race Sex	FGA-SGA (specific agent combinations not given)	Limited data set, scope and validity affected Study limited to 2 states, participants under full Medicaid insurance, generalizability affected

Huffman et al. 2011	Case-control	Inpatients discharged on more than one regularly scheduled antipsychotic between 1 July 2008 - 31 August 2009, with comparison group of randomly selected adult patients discharged from the unit during this time who were not on multiple antipsychotics at time of discharge, Massachusetts General Hospital inpatient psychiatric unit, Boston, US, APP group N = 75, Comparison group N = 114	N/A	**Increased association:** Longer inpatient stay Department of mental health client Department of mental health supported housing Public or no insurance More than five prior hospitalizations Diagnosis of psychotic disorder Antipsychotic use on admission APP on admission **No significant association:** Age Sex Homelessness Race	SGA-SGA (aripiprazole-quetiapine, risperidone-quetiapine)	Study group consisted of cross-sectional sample, factors such switching between antipsychotics at time of discharge may have affected results Small study size Limited data sets, scope and validity affected Case-control study, methods of random selection of control group not provided and groups were not matched on baseline variables Multivariate analysis not performed, results not adjusted for confounding Single centre hospital study, generalisability affected
Humberston e et a.l 2004	Cross-sectional	All active outpatient files for the month of March 2000 reviewed and outpatients prescribed an antipsychotic included, all community mental health services in Auckland, N = 3178	16.4%	Not examined	Not examined	Cross-sectional study, factors such as switching between antipsychotics may have affected results Examined antipsychotic prescription patterns in general, main focus not APP Limited data set, scope and validity affected Outpatient study in a single region in Australia, generalisability affected
Jaffe & Levine 2002	Longitundinal	Inpatients receiving at least one antipsychotic medication for 28 days or longer during the year 1999, New York State Office of Mental Health psychiatric hospital system, N = 7482 inpatient episodes	37.3%	**Increased association:** Younger age African-American race (vs White and Hispanic) Previous hospitalization Diagnosis of psychotic disorder **No significant association:** Sex	FGA-SGA (specific agent combinations not given)	28 day overlap criterion, results may have been affected by very slow cross tapers Limited data sets, scope and validity affected Multivariate analysis not performed, results not adjusted for confounding Inpatient hospital study, generalisability affected

Jaracz et al. 2014	Cross-sectional	Patients with diagnosis of schizophrenia discharged from September-December 2011, six psychiatric hospitals in Poland, N = 207	47.3%	**Increased association:** Higher number of previous admissions **No significant association:** Age Sex Duration of illness Duration of present hospitalization Severity of symptoms Degree of clinical improvement	FGA-SGA (specific agents combinations not reported)	Cross-sectional study, factors such as switching between antipsychotics may have affected results Small study size Limited data set, scope and validity affected Severity of symptoms at admission and improvement on treatment assessed post hoc by psychiatrist of ward, potential source of bias Scanty information provided on study methods and statistical analysis Multivariate analysis not performed, results not adjusted for confounding Inpatient hospital study, generalisability affected
John et al. 2014	Cross-sectional	Inpatients with diagnosis of schizophrenia and schizoaffective disorder at discharge in 2010, Bentley Mental Health Service, Western Australia, N = 229	43.2%	**Increased association:** Longer inpatient stay **No significant association:** Age Sex Diagnosis of schizophrenia compared to schizoaffective disorder Co-prescription of other psychotropics and general medical drugs	Not examined	Cross-sectional study, factors such as switching between antipsychotics may have affected results Small study size Limited data set, scope and validity affected Multivariate analysis not performed, results not adjusted for confounding Antipsychotic prescription patterns not reported explicitly, difficult to interpret information on prescriptions Single centre hospital study, generalisability affected
Johnsen et al. 2004	Cross-sectional	Patients with registered antipsychotic prescriptions on a given date, regardless of diagnosis, two psychiatric hospitals in Norway, N = 174	Hospital A: 30% Hospital B: 27%	Not examined	FGA-SGA (specific agent combinations not given)	Cross-sectional study, factors such as switching between antipsychotics may have affected results Examined antipsychotic prescription patterns in general, including types of antipsychotics prescribed and co-prescription patterns, main focus not APP Small study size Limited data set, scope and validity affected Inpatient hospital study, generalisability affected
Koen et al. 2008	Cross-sectional	Xhosa inpatients and outpatients with schizophrenia or schizoaffective disorder receiving treatment in the three areas interviewed between 2002 and 2005, catchment areas of three state psychiatric hospitals and their affiliated community healthcare clinics in the greater metropole of Cape Town, N = 510	28.6%	Not examined	FGA-FGA (haloperidol-fluphenazine LAI)	Cross-sectional study, factors such as switching between antipsychotics may have affected results Examined prescription patterns, including clozapine, haloperidol and depot use, main focus not APP Relatively small study size, power affected Population restricted to Xhosa patients, generalizability affected
Kreyenbuhl et al. 2006	Longitudinal	Veterans with diagnosis of schizophrenia and schizoaffective disorder prescribed antipsychotics in 2000, VA facilities across the United States, data from VA's National Psychosis Registry, services provided to veterans with psychotic disorders in VA facilities across the US, N = 61257	90 or more days of overlapping treatment: 9.5% 60-89 days: 13.1% 30-59 days: 20%	Not examined	FGA-SGA (haloperidol-olanzapine)	Limited data set, scope and validity affected Use of LAIs not available on records, potential source of bias Study conducted in VA system, predominantly male population and single system of care, generalizability affected

Kreyenbuhl et al. 2007	Longitudinal	Veterans with diagnosis of schizophrenia and schizoaffective disorder prescribed antipsychotics for 90 days or more in 2000, VA facilities across the United States, data from VA's National Psychosis Registry, services provided to veterans with psychotic disorders in VA facilities across the US, N = 61257	9.5%	**Increased association:** Younger age Unmarried Military service-connected disability Diagnosis of schizophrenia compared to schizoaffective disorder Psychiatric hospitalization in past year More outpatient mental health visits Co-prescription of mood stabilizer Co-prescription of anxiolytic **Decreased association:** African American compared to white race Co-morbid depression Co-morbid substance use disorder Medical co-morbidity **No significant association:** Sex Co-morbid PTSD Co-prescription of antidepressant	Not examined	Limited data set, scope and validity affected Use of LAIs not available on records, potential source of bias Study conducted in VA system, predominantly male population and single system of care, generalizability affected
Kroken et al. 2009	Cross-sectional	Inpatients of acute psychiatric wards with diagnosis of schizophrenia discharged on antipsychotics during a 3 month period in 2005, 19 participating Norwegian hospitals, N = 449	35.6%	**Increased association:** Younger age Inpatient treatment during previous 12 months Co-morbid personality disorder **No significant association:** Sex Severity of symptoms Aggression Delusions/hallucinations Recurrent illness Outpatient treatment in previous 12 months Co-morbid substance use disorder Co-morbid mental retardation	FGA-SGA (specific agent combinations not given)	Cross-sectional study, factors such as switching between antipsychotics may have affected results Limited data set, scope and validity affected Severity scores at admission dependent on interviewer, potential source of bias Portion of patients in study transferred to longer stay wards, prescription at final discharge from inpatient treatment could differ from current study results Acute setting hospital study, generalisability affected

Latimer et al. 2014	Longitudinal	Patients with diagnosis of schizophrenia with public medical claims for antipsychotic prescriptions covering at least 11 months during 2004, Quebec province, Canada, N = 12150	10.4%	**Increased association:** Age 50-59 Psychiatrist assigned Physician assigned prescribes clozapine **No significant association:** Sex Public assistance receipt Hospital assigned Hospital type	Not examined	Limited data set, scope and validity affected Restricted to public health care medical claims, private system excluded, generalisability affected
Li et al. 2015	Cross-sectional	Inpatients and outpatients with diagnosis of schizophrenia receiving antipsychotics during July/Aug 2012, 45 psychiatric hospitals in China, N = 4239	34.2%	**Increased association:** Earlier illness onset Higher severity scores Higher total dose of antipsychotic FGA use **Decreased association:** Co-prescription of benzodiazepine Patient and family satisfaction **No significant association:** Age Sex Longer illness duration Inpatient treatment Having insurance Living with family Family history of psychiatric disorders Delusions or hallucinations Disorganized speech or behaviour Negative symptoms SGA use	SGA-SGA (specific agent combinations not given)	Cross-sectional study, factors such as switching between antipsychotics may have affected results Limited data set, scope and validity affected Patients unable to understand contents of survey excluded, potential source of bias Hospital based study, generalisability affected
Lopez de Torre et al. 2012	Cross-sectional	Inpatients with one or more antipsychotic prescription on 29 March 2011, Psychiatric hospital in Basque Country, Spain, N = 172	47.1%	**Increased association:** Younger age Male sex Higher total dose of antipsychotic	SGA-SGA (olanzapine-quetiapine, clozapine-quetiapine)	Cross-sectional study, factors such as switching between antipsychotics may have affected results Small study size Limited data set, scope and validity affected Single day duration, validity affected Multivariate analysis not performed, results not adjusted for confounding Single centre hospital study, generalisability affected

Mauri et al. 2005	Cross-sectional	Inpatients receiving antipsychotics during 1989, 1999 and 2002, regardless of diagnosis, Psychiatry Department of Milan's Ospedale Maggiore Hospital, N = 1696	1989: 18.57% 1999: 25,49% 2002: 21.5%	Not examined	FGA-SGA (haloperidol-risperidone) (2002)	Cross-sectional study, factors such as switching between antipsychotics may have affected results Compared antipsychotic prescription patterns in general and high-dose prescribing in 1989,1999 and 2002, main focus not APP Limited data set, scope and validity affected Difficult to follow and interpret findings, inconsistent reporting of results Inpatient hospital study, generalisability affected
McCue et al. 2003	Cross-sectional	Psychiatric inpatients hospitalized during 1995 and 2000, Woodhull Medical and Mental Health Centre, Brooklyn, New York, 1995: N = 459, 2000: N = 584	1995: 0% 2000: 15.9%	Not examined	FGA-SGA (haloperidol-olanzapine)	Cross-sectional study, factors such as switching between antipsychotics may have affected results Examined prescription patterns in general, main focus not APP Relatively small study size Limited data set, scope and validity affected Single centre hospital study, generalisability affected
McKean & Vella-Brincat 2009	Cross-sectional	Inpatients receiving antipsychotics during Feb to April 2008, regardless of diagnosis, Hillmorton Hospital and Seagar Clinic in Christchurch, New Zealand, N = 201	31%	**Increased association:** Male sex Longer inpatient stay Co-prescription of anticholinergic agent Diagnosis of schizophrenia Higher total dose of antipsychotic **No significant association:** Age Ethnicity History of type 2 diabetes Treatment for raised cholesterol/triglyceride	Not examined	Cross-sectional study, factors such as switching between antipsychotics may have affected results Small study size Limited data set, scope and validity affected Multivariate analysis not performed, results not adjusted for confounding Single centre hospital study, generalisability affected

Morrato et al. 2007	Longitudinal	Medicaid beneficiaries with diagnosis of schizophrenia with filled prescriptions for antipsychotics between 1998 and 2003, California, Nebraska, Oregon, Utah and Wyoming Medicaid pharmaceutical claims database, N = 55481	6.4% (prevalence of APP in the year after initiating antipsychotic medication)	**Increased association:** Male sex Asian race compared to white Number of psychiatric diagnoses Recent psychiatric hospitalization Diagnosis of schizophrenia **Decreased association:** Age > 34 Initiated on olanzapine Initiated on risperidone **No significant association:** Co-morbid substance use disorder Diagnosis of depression Diagnosis of bipolar disorder Initiated on clozapine Initiated on quetiapine	Not examined	Limited data set, scope and validity affected California represented majority of sample, although considered in data analysis methods and reporting, may have affect generalizability Participants under full Medicaid insurance, generalizability affected
Nielsen et al. 2010	Longitudinal	Patients diagnosed with first-episode of schizophrenia from Jan 1996 – Dec 2006, followed for observation period of 1 year following initial diagnosis, Danish Central Psychiatric Research Registry , N = 13600	"Total polypharmacy": 33.3% in 1996, 56.2% in 2005 "Long-term polypharmacy": 16.7% in 1996, 37.1% in 2005	Not examined	1996 & 1997: FGA-FGA 1998 - 2005: FGA-SGA (specific agent combinations not given)	Examined prescription patterns broadly, main focus not APP Unclear graphical presentation of prevalence rates, individual prevalence rates only provided in written content for 1996 and 2005 Examined APP in first-episode schizophrenia only, generalizability affected Outpatient study, generalizability affected
Procyshyn & Thompson 2004	Cross-sectional	All non-geriatric patients discharged between 1 January and 31 December 2000, regardless of diagnosis, Department of Psychiatry, Riverview Hospital, Port Coquitlam, Canada, N = 372	Schizoaffective disorder: 49.3% Schizophrenia: 44.7% Bipolar disorder: 29.9% Psychosis NOS: 22.5%	Not examined	Not examined	Cross-sectional study, factors such as switching between antipsychotics may have affected results Small study size Limited data set, scope and validity affected Single centre hospital study, generalisability affected

Procyshyn et al. 2010	Longitudinal	Outpatients receiving the same prescription for at least 90 days, community mental health services, British Columbia, Canada, N = 435	Schizoaffective disorder: 33.7% Schizophrenia: 31.7% Psychosis NOS: 20.0% Bipolar disorder: 16.9% Major depression: 14.3%	Not examined	Not examined	Cross-sectional study, factors such as switching between antipsychotics may have affected results Relatively small study size Limited data set, scope and validity affected Outpatient study in single province in Canada, generalisability affected
Sim et al. 2004	Cross-sectional	Inpatients with diagnosis of schizophrenia in July 2001, inpatient psychiatry units in 6 East Asian countries and territories (China, Hong Kong, Japan, Korea, Singapore and Taiwan), N = 2399	Overall: 45.7% Japan: 78.6% Singapore: 70.3% Korea: 35.5% China: 25.2% Taiwan: 22.2% Hong Kong: 12%	**Increased association:** Country Younger age Longer illness duration **Decreased association:** Nil **No significant association:** Sex Psychiatric compared to general hospital setting SGA use Co-prescription of anticholinergic agent	Not examined	Cross-sectional study, factors such as switching between antipsychotics may have affected results Heterogeneous data sets, scope and validity affected Inpatient hospital study, generalisability affected
Sim et al. 2004	Cross-sectional	Inpatients with diagnosis of schizophrenia admitted during July 2001, Institute of Mental Health/Woodbridge Hospital, Singapore, N = 300	71.7%	**Increases association:** High potency antipsychotic use Co-prescription of anticholinergic agent Younger age Longer illness duration Higher total dose of antipsychotic **No significant association:** Sex SGA use Illness severity score	Not examined	Cross-sectional study, factors such switching between antipsychotics may have affected results Small study size, power affected Short duration, validity affected Limited data sets, scope and validity affected Inpatient hospital study, generalisability affected

Soukas et al. 2013	Cross-sectional	All patients in Finland who had at least one hospitalization due to schizophrenia during the years 2000-2007, Finnish National Hospital Discharge Register, N = 16083	46.2%	**Increased association:** Male sex Longer inpatient stay Previous antipsychotic use **No significant association:** Age Previous anxiolytic, hypnotic and sedative use Previous antidepressant use Previous anticholinergic agent use	Not examined	Cross-sectional study, factors such as slow switching between antipsychotics may have affected results Limited data set, scope and validity affected Population consisted of patients with previous hospital admissions during the time period examined, generalizability affected
Sun et al. 2014	Longitudinal	Patients with schizophrenia or psychotic disorder with data from relevant systems, over 2005-2009 from VA system and 2002-2009 for other systems, Veterans Affairs' health care system (national data VA database), non-federal outpatient settings (national data from National Ambulatory Medical Care Survey), two large not-for profit healthcare systems in southwestern and Great Lakes areas of the US (data from Health Maintenance Organization Research Network Virtual Data Warehouse), VA selection: N = 119662, VA one-week selection: N = 47100, NAMS selection: N = 885 visits, (17596617 patients represented) HMORN site 1 selection: N = 699, HMORN site 2 selection: N = 4887	VA non-tapered: 29-31% VA tapered: 13-15% VA one-week sample: 20-22% NAMS: 19-31% HMORN site 1: 16-26% HMORN site 2: 21-26%	**Increased association:** Increased rates of 1-year admission (VA and HMORN samples - NAMCS lacked this data) **No other factors consistently associated across systems**	SGA-SGA (specific agent combinations not given)	Limited data sets, scope and validity affected Different levels of data available in different databases, may have contributed to differences in APP rates observed Data available on sample characteristics differed across studies and limited comparability Data only available for VA system for 2005-2009
Sweileh et al. 2013	Cross-sectional	Patients with diagnosis of schizophrenia receiving the same antipsychotic medication for the past 6 months, 4 governmental primary psychiatric healthcare centres in West Bank, Gaza Strip and East Jerusalem territories of Palestine, N = 250	50.4%	**Increased association:** LAI use Co-prescription of anticholinergic agent Higher total dose of antipsychotic **No significant association:** Age Sex Education Marital status Smoking Occupation Waist circumference Illness duration Number of hospitalizations Family history of diabetes SGA use	FGA-FGA (specific agent combinations not given)	Cross-sectional study, factors such as switching between antipsychotics may have affected results Small study size Restricted to 4 government public healthcare services, generalizability affected

Tsutsumi et al. 2011	Longitudinal	Outpatients visiting one of the participating sites for the first time between 1 Jan 2007 and 30 June 2008 and diagnosed with schizophrenia, 4 psychiatric clinics in Tokyo, Japan, N = 300	43.7%	Not examined	FGA-SGA (chlorpromazine-risperidone)	Study vague and difficult to follow at times Small study size Limited data set, scope and validity affected Significant drop out rate, reasons included loss to follow-up, referral to another clinic/hospital and hospitalization, potential source of bias Outpatient study with limited population, generalisability affected
Wang et al. 2000	Cross-sectional	Patients with diagnosis of schizophrenia or other psychotic disorder under the care of randomly recruited or volunteer psychiatrists participating in the PRN Study, 3 patients from each psychiatrist randomly selected from a patient log, 1997 American Psychiatric Association Practice Research Network (PRN) Data, N = 155	17%	Not examined	Not examined	Cross-sectional study, factors such as switching between antipsychotics may have affected results Examined antipsychotic prescription patterns with focus on use of newer antipsychotics, main focus not APP Small study size Methods of random sampling used to select participants not provided, potential source of bias Psychiatrists in study randomly selected and self-volunteers, potential source of bias Participants restricted to those under care of psychiatrists involved in study, generalizability affected
West et al. 2005	Cross-sectional	Patients with diagnosis of schizophrenia or other psychotic disorder under the care of randomly recruited or volunteer psychiatrists participating in the PRN Study, 3 patients from each psychiatrist randomly selected from a patient log, 1999 American Psychiatric Association Practice Research Network (PRN) Data, N = 151	16%	Not examined	Not examined	Cross-sectional study, factors such as switching between antipsychotics may have affected results Examined treatment patterns in general, including pharmacologic and psychosocial treatment, main focus not APP Small study size Methods of random sampling used to select participants not provided, potential source of bias Psychiatrists in study randomly selected and self-volunteers, potential source of bias Participants restricted to those under care of psychiatrists involved in study, generalizability affected
Wheeler et al. 2006	Cross-sectional	Outpatients with diagnosis of schizophrenia or schizoaffective disorder prescribed an antipsychotic at each of the three time points in study, 2 urban mental health service catchment areas of Auckland, Australia, March 2000: N = 1457, October 2001: N = 1575, March 2003: N = 1627	March 2000: 18.3% October 2001: 14.2% March 2003: 14.6%	Not examined	Not examined	Cross-sectional study, factors such as switching between antipsychotics may have affected results Examined antipsychotic prescription patterns in general, main focus not APP Limited data set, scope and validity affected Outpatient study in a single region in Australia, generalisability affected

Xiang et al. 2007	Cross-sectional	Clinically stable outpatients with schizophrenia, random selection methods used, 2 psychiatric outpatient clinics at university-affiliated hospitals in Beijing and Hong Kong, N = 505	19.2%	**Increased association:** LAI use Site Decreased association Nil **No significant association:** Age Number of hospitalizations Prescription of clozapine Positive symptoms Negative symptoms Anxiety symptoms	Not examined	Study vague and difficult to follow at times Cross-sectional study, factors such as switching between antipsychotics may have affected results Relatively small study size Limited data set, scope and validity affected Methods of random sampling used to select participants not provided, potential source of bias Population limited to clinically stable hospital outpatients in two of China's most developed cities, generalisability affected
Xiang et al. 2012	Cross-sectional samples in longitudinal study	Inpatients with schizophrenia, examined in 2001, 2004 and 2009, hospitals in 9 Asian countries and territories, N = 6761	2001: 46.8% 2004: 38.3% 2009: 43.4%	**Increased association:** Younger age Positive symptoms Negative symptoms Higher total dose of antipsychotic LAI use FGA use Site **No significant association:** Sex SGA use	2001: FGA-FGA 2004 & 2009: FGA-SGA (specific agent combinations not given)	Cross-sectional samples in study, factors such as switching between antipsychotics may have affected results Limited data set, scope and validity affected Study centres differed in some sites across the three time periods examined, may have distorted comparisons Inpatient hospital study, generalisability affected

Chapter 2: Publication-ready Manuscript

The prevalence of and factors associated with antipsychotic polypharmacy in patients with serious mental illness: Findings from a cross-sectional study in a low-middle income country

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Abstract

Background: Antipsychotic polypharmacy (APP) appears to be a common practice worldwide despite lack of evidence for efficacy and treatment guidelines advising against the practice for most patients. Our study aimed to address deficiencies in local and international research by examining the current prevalence of APP in a South African context and investigating a broad range of patient, illness and treatment characteristics that may be associated with the practice.

Methods: We conducted a cross-sectional study of discharge records using Valkenberg Hospital's electronic patient database. We collected data on patient, illness and treatment characteristics for patients discharged on one or more antipsychotic agents from January to June 2014. Hierarchical multivariable logistic regression analysis was used to assess the relationship between demographic and clinical variables and APP. We also analysed psychotropic co-prescription patterns associated with APP.

Results: Discharge records of 565 patients were examined. The prevalence of APP in our study population was 29.03% (95% CI= 25.31%-32.96%). Analysis of demographic and clinical characteristics revealed that age>29, male sex, diagnosis of schizophrenia compared to bipolar and substance-induced disorders, co-morbid intellectual disability, co-morbid substance use, greater number of hospital admissions and high-dose prescribing were significantly associated with APP. While highest rates of APP occurred in patients with schizophrenia and schizoaffective disorders, APP was also observed in a number of patients with bipolar and substance-induced disorders. Prescription patterns demonstrated the prominent use of first-generation antipsychotics and long acting injectable preparations in APP combinations. Patients receiving APP were significantly more likely to have anticholinergic agents and sodium valproate co-prescribed in their treatment regimen.

Conclusions: Our study suggests that current local practice deviates from standard local and international guidelines in that combination antipsychotic agents are prescribed for a number of patients with a range of psychiatric diagnoses and symptoms without sufficient evidence for efficacy of this practice and at possible cost of increased adverse effects. Patients receiving APP may be those with greater illness severity, complexity, chronicity and treatment resistance, with complicating factors including co-morbid substance use involved. Antipsychotic prescription patterns suggest a complex interplay of patient, illness and treatment factors relevant in our setting.

Keywords

Antipsychotics, polypharmacy, antipsychotic combination, psychiatric hospital

1 Background

Antipsychotic agents are used in the treatment of psychotic and mood disorders. Local and international clinical practice guidelines for the treatment of schizophrenia (1,2) advocate an approach of antipsychotic monotherapy in the majority of cases. Guidelines recommend avoiding antipsychotic polypharmacy (APP) which can be defined as co-prescription of more than one antipsychotic drug for a given patient,(3) except for short periods when switching agents or in treatment resistant cases, when augmentation of clozapine with another antipsychotic agent may be considered, although supporting evidence for this remains weak.(4,5) Treatment guidelines recommend use of antipsychotics as part of treatment options in bipolar disorder but do not advocate an approach of APP.(6,7) Use of antipsychotic agents in the treatment of psychosis with coexisting substance misuse is advised in accordance with the individual guidelines on schizophrenia or bipolar disorder.(8)

Motivation behind guidelines is the lack of robust evidence to support the routine use of combined antipsychotics.(3-5,9,10) In addition, there is evidence for harm associated with APP. Research has shown an association of APP with increased adverse effects including extrapyramidal side-effects,(11-13) hyperprolactinaemia,(14-16) sexual dysfunction,(17) hypersalivation,(18) sedation,(14) cognitive impairment,(19) and diabetes.(20,21) Possible increased risk of sudden cardiac death (22) and mortality (23,24) has been suggested. Additional concerns have been drug-drug interactions, problems in determining cause and effect of different treatments, complex drug regimens resulting in decreased compliance and greater cost.(25)

Despite these adverse aspects, APP appears to be a common practice worldwide. A recent systematic review found a global median prevalence of APP of 19.6% across time, with factors such as clinical setting, geographical location and time of study influencing prevalence rates.(26) In contrast to the fairly substantial international literature on APP, there is a paucity of research on APP from Africa, with only one previous study examining rates of APP in a South African setting conducted in 2008.(27) There is clearly a need for investigation into this practice in the current South African health care context.

Research into factors contributing to the practice of APP has shown that antipsychotic prescription patterns reflect complex interplay among patient, illness, treatment and prescriber factors.(25) However, inconsistencies and gaps in the evidence remain. Patient characteristics of age, sex and marital status have received most attention, with fewer studies examining other patient factors possibly associated with APP. There is a lack of information on illness characteristics in the context of APP. APP is a practice generally examined in the context of schizophrenia/schizoaffective disorders, with fewer studies investigating the occurrence of APP in bipolar disorder and no previous studies examining APP rates in substance-induced disorders found. There is a deficiency in the literature on co-morbidities associated with APP. Antipsychotic prescriptions seem to vary widely in different contexts and there is a need for further studies investigating associations with concomitant psychotropic prescriptions. Moreover, there have been no previous studies examining patient, illness and treatment characteristics associated with APP in South Africa.

Our study attempted to address these deficiencies in local and international research by examining the current prevalence of APP in a South African context and investigating a broad range of patient, illness and treatment characteristics that may be associated with this practice. In doing so, we were able to assess whether current local practice is comparable with standard local and international guidelines. We examined antipsychotic prescribing patterns across diagnoses, including bipolar disorder and substance-induced disorders. We provided insight into the prevalence of and factors associated with APP in a study population in the Western Cape, increasing understanding of the complexity of the practice of APP in our setting.

2 Methods

2.1 Study aims

We aimed to determine the prevalence of APP in patients discharged from Valkenberg Hospital and examine the patient, illness and treatment factors associated with APP compared to monotherapy.

2.2 Sample and setting

We conducted our study at Valkenberg Hospital, a large, government-funded psychiatric hospital in the suburb of Observatory, in Cape Town, South Africa. The hospital provides psychiatric services to the Cape Peninsula and is a major specialist referral centre of the Western Cape Province. It is the principal teaching hospital for the University of Cape Town's Department of Psychiatry. The hospital

currently comprises 340 inpatient beds, of which 200 are dedicated to acute psychiatric services, 125 to forensic psychiatric services and 15 to a smaller therapeutic component. Patients admitted to the acute psychiatric units are commonly involuntary admissions under the Mental Health Care Act (2002) with severe mental illness posing a risk to themselves or others and are unable to be managed on an outpatient basis.

We performed a cross-sectional study of discharge records using Valkenberg Hospital's electronic patient record database (Clinicom). The study was approved by the University of Cape Town's Human Research Ethics Committee, the Faculty of Health Sciences and the Department of Health. Data were collected for patients with serious mental illness prescribed one or more antipsychotic agents at the time of discharge from Valkenberg Hospital's acute and therapeutic units. We extracted discharge information for patients with diagnoses including schizophrenia (F20), acute and transient psychotic disorder (F23), delusional disorder (F22) schizoaffective disorder (F25), substance-induced mood and psychotic disorders (F10 - F19) and bipolar disorder (F31). We excluded patients with primary diagnoses relating to a medical condition, dementia, anxiety disorder, major depressive disorder, intellectual disability or personality disorder as these diagnoses were unlikely to feature significantly in our study population or contribute meaningfully to rates of APP in our setting. We examined the time period of January to June 2014.

2.3 Data and variables extracted

We used an electronic data extraction form to extract data from the electronic discharge database. Patient variables including age, gender, marital status and occupation of patients discharged on one or more antipsychotic agent were collected. These variables were routinely documented on the record database at time of admission.

Illness variables of length of hospital stay (measured in days from admission to discharge date), number of Valkenberg hospital admissions and time from first hospitalization at Valkenberg to most recent discharge (as approximate indicator of illness duration or time in treatment) were retrieved from the database.

Patient diagnoses recorded in the database using ICD-10 coding methods were collected. Data on co-morbid psychiatric conditions were gathered both from ICD-10 coding and information contained in discharge summaries completed electronically for each patient by their attending psychiatric registrar at time of discharge. Where the attending case manager commented on the presence of significant co-existing depressive symptoms, anxiety symptoms, evidence of personality disorder or

traits or mild intellectual disability, these were captured as psychiatric co-morbidities. Diagnoses and associated clinical features are discussed routinely (typically over 4-8 clinical case discussion ward rounds on average over the admission period) by members of a multidisciplinary team under consultant psychiatrist supervision and include multiple sources of information. All diagnoses are confirmed by a consultant psychiatrist in charge of each multidisciplinary team. Discharge records are routinely audited by consultant psychiatrists. Data on co-morbid substance use was likewise gathered from ICD-10 coding and clinical descriptors within patient discharge summaries. These included co-morbid alcohol (F10), cannabis (F12), methamphetamine (F15), methaqualone (F13), heroin (F11) and cocaine (F14) misuse.

Antipsychotic agents prescribed at discharge were recorded in patient discharge summaries and captured according to names, dosages, types of agents and route of administration. Agents classified by type as first-generation antipsychotics (FGAs) included haloperidol, chlorpromazine, trifluoperazine, flupentixol, zuclopenthixol and fluphenazine. Second-generation antipsychotics (SGAs) included amisulpiride, clozapine, olanzapine, risperidone, quetiapine and aripiprazole. Route of administration was captured as oral or long acting injectable (LAI). APP was defined as the prescription of any 2 or more antipsychotics on discharge from hospital in the same patient. To compare doses of different antipsychotic drugs, the prescribed daily dose (PDD) in milligrams was divided by the defined daily dose (DDD) to give a PDD:DDD ratio. The DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults.(28) For LAIs, the DDD is based on the average recommended dose divided by the dosing interval.(28) This is the standard international unit recommended by the World Health Organization for drug utilization studies.(28) In keeping with previous studies, the PDD/DDD ratio for APP was calculated as the sum of the individual PDD/DDD ratios of all antipsychotics prescribed to a patient and high-dose prescribing was defined as PDD/DDD of greater than 1.5.(29-31) In addition to antipsychotic agents, data on co-prescription of anticholinergic agents, mood stabilizers, antidepressants and benzodiazepines were captured.

2.4 Statistical analysis

We inspected data for normality using histograms and Shapiro Wilks' test for normality. Continuous variables were analysed using student's t-test or for normal data and Wilcoxon-ranksum test for skewed data. For categorical variables we used Chi-square tests to analyse data, with Fisher's exact test where appropriate. Confidence intervals for prevalence rates were calculated using the normal approximation of the binomial distribution.

The main outcome of interest was the presence of antipsychotic polypharmacy (APP), as previously defined. We coded a positive outcome (i.e. the presence of APP) as "1" and a negative (no APP) as "0". We conducted a hierarchical multivariable logistic regression analysis in order to model the response variable of antipsychotic polypharmacy as a function of a number of demographic and clinical variables. Independent (predictor) variables were categorised into multilevel categorical variables using dummy coding to obtain reference level categories. Cut-points for continuous variables were decided on the basis of what constituted meaningful clinical categorisations. We followed a forward selection and backward elimination procedure and determined model fit using a combination of Likelihood-ratio Chi-square tests and the Akaike Information Criterion (AIC). We entered each variable into the model one at a time starting with demographic and then clinical variables. We removed variables one at a time if model fit did not improve by their addition, based on the likelihood Chi-square tests and AIC. The final model included all variables except reported symptoms of anxiety and depression and length of inpatient stay. Model fit for the final model was determined using the Pearson Chi-Square Goodness of Fit test. Statistical significance was set at $p<0.05$. We used Stata version 13 for Windows to analyse the data.

3 Results

3.1 Antipsychotic polypharmacy: Prevalence, clinical and demographic associations

A total of 567 patient records met criteria for inclusion. We excluded 2 records where patients were diagnosed with acute and transient symptoms of psychosis (F23) and delusional disorder (F22), as these patients were low in number, resulting in a final sample of N=565. Of the total sample 60.71% were male and the median age was 32 (IQR: 25-32).

The prevalence of APP among our study population was 29.03% (95% CI= 25.31%-32.96%). The demographic and clinical characteristics of patients discharged on APP and antipsychotic monotherapy (APM) are shown in Table 1, with results of multivariable analyses examining associations between these characteristics and the likelihood of receiving APP reported as adjusted odds ratios (AOR). Patients in age category 30–44 were significantly more likely to receive APP than those in age category 18–29 (AOR=2.90, CI=1.65–5.11, p<0 .001), as were those aged 45–60 years (AOR=2.28, CI=1.06–4.90, p = 0.033). The odds of receiving APP was significantly higher in males (AOR=1.93, CI=1.09–3.41, p=0.023) and approached significance at the 5% level in patients who were unemployed (AOR=10.05, CI=0.82–121.90, p=0.070). There were no significant associations between marital status and APP; patients who were married or widowed did not differ significantly

from those who were single (AOR=0.43, CI=0.11-1.64, p=0.219 and AOR=0.48, CI=0.04–5.47, p=0.560 respectively), and neither did those who were divorced (AOR=2.02, CI=0.65–6.27, p=0.220).

When compared to patients with schizophrenia, patients with other diagnoses were less likely to receive APP, with an AOR of 0.55 for schizoaffective disorder (CI=0.27–1.14, p=0.111), and a significantly lower odds for APP of 0.32 for bipolar disorder (CI=0.15–0.65, p=0.002) and 0.40 for substance-induced disorder (CI=0.91–0.87, p=0.021). APP was more likely in patients with co-morbid personality disorders (AOR=2.50, CI=0.89–7.11, p=0.080), with this association approaching significance at the 5% level. Intellectual disability (AOR=3.94, CI=1.39–11.15, p=0.010), and substance use (AOR=1.82, CI=1.02–3.22, p=0.040) were both associated with a significant increased odds of APP. Co-morbid depressive and anxiety symptoms were not significantly associated with APP (not shown and omitted from model).

There was no significant association between illness duration and APP (measured as time from first admission to most recent discharge) for either patients with between 1-3 years of illness duration (AOR=0.85, CI=0.37–1.92, p=0.701) or patients with >3 years (AOR=1.05, CI=0.44–2.48, p=0.907) compared to those with illness duration of <1 year. Compared to patients with <3 prior admissions to Valkenberg hospital, the odds increased of having APP in those with higher numbers of Valkenberg admissions, with the AOR of 2.13 for patients with 3-6 admissions (CI =0.98–4.64, p=0.055), which approached statistical significance and 2.64 for patients with >6 admissions (CI=1.05–6.62, p=0.038), a statistically significant difference. Length of hospital stay did not show strong association with APP in bivariate analysis, and was omitted from the multivariable model.

Table 1 Comparison of demographic and clinical characteristics of patients discharged on antipsychotic polypharmacy (APP) and antipsychotic monotherapy (APM) (N=565)

Characteristic	APP		APM		Adjusted OR	95% CI	P value
	N	%	N	%			
Demographic							
Age (years)							
18 - 29 (reference)	52	31.71	187	46.63	ref (1.0)	ref	ref
30 - 44	81	49.39	135	33.67	2.90	1.65 - 5.11	< 0.001
45 - 60	31	18.90	79	19.70	2.28	1.06 - 4.90	0.033
Sex							
Female (reference)	38	23.17	184	45.89	ref (1.0)	ref	ref
Male	126	76.83	217	54.11	1.93	1.09 - 3.41	0.023
Marital status							
single (reference)	151	92.07	345	86.03	ref (1.0)	ref	ref
married	3	1.83	33	8.23	0.43	0.11 - 1.64	0.219
divorced	9	5.49	17	4.24	2.02	0.65 - 6.27	0.220
widowed	1	0.61	6	1.50	0.48	0.04 - 5.47	0.560
Occupation							
Employment (reference)	1	0.61	25	6.23	ref (1.0)	ref	ref
Unemployed	164	99.39	376	93.77	10.05	0.82 - 121.90	0.070
Clinical							
Diagnosis							
Schizophrenia (reference)	93	56.71	145	36.16	ref (1.0)	ref	ref
Schizoaffective disorder	36	21.95	43	10.72	0.55	0.27 - 1.14	0.111
Bipolar disorder	20	12.20	112	27.93	0.32	0.15 - 0.65	0.002
Substance-induced disorder	15	9.15	101	25.19	0.40	0.91 - 0.87	0.021
Psychiatric co-morbidities							
Personality disorder							
No personality disorder (reference)	152	92.68	385	96.01	ref (1.0)	ref	ref
Personality disorder	12	7.32	16	3.99	2.50	0.89 - 7.11	0.080
Intellectual disability							
No intellectual disability (reference)	152	92.68	390	97.26	ref (1.0)	ref	ref
Intellectual disability	12	7.32	11	2.74	3.94	1.39 - 11.15	0.010
Substance use							
No substance use (reference)	58	42.48	182	45.39	ref (1.0)	ref	ref
Substance use	219	54.61	106	64.63	1.82	1.02 - 3.22	0.040
Time from first admission to last dischargre (illness duration) (years)							
0 - 1 (reference)	39	23.78	208	51.67	ref (1.0)	ref	ref
1 - 3	26	15.85	74	18.45	0.85	0.37 - 1.92	0.701
> 3	99	60.37	119	29.68	1.05	0.44 - 2.48	0.907
Number of Valkenberg admissions							
< 3 (reference)	53	32.32	260	64.84	ref (1.0)	ref	ref
3-6	50	30.49	92	22.94	2.13	0.98 - 4.64	0.055
> 6	61	37.20	49	12.22	2.64	1.05 - 6.62	0.038
High-dose prescribing							
No high-dose prescribing (reference)	81	49.39	378	94.26	ref (1.0)	ref	ref
High-dose prescribing	83	50.61	23	5.74	11.34	6.20 - 20.74	< 0.001

3.2 Frequency, dosing and different types antipsychotic combinations

Prescription rates of individual antipsychotic agents are shown in Table 2. Of the 164 participants who were prescribed 2 or more antipsychotics, the majority (N= 161, 97.56%) were prescribed 2 antipsychotics and only 3 patients (2.44%) were prescribed 3 different antipsychotics. The most commonly prescribed agent amongst all patients discharged was haloperidol (36.64%), followed by risperidone oral preparation (27.96%) and zuclopenthixol LAI (17.17%). The most common agents among patients discharged on APM were haloperidol (35.91%), risperidone oral (31.67%) and olanzapine (7.48%). In those discharged on APP, zuclopenthixol LAI was prescribed in 50% of patients, followed by haloperidol (38.41%), flupentixol LAI (29.88%), risperidone oral (18.90%) and clozapine (16.46%). When associations were examined, APP was found to be significantly associated with use of flupentixol LAI ($p<0.001$), zuclopenthixol LAI ($p<0.001$), fluphenazine LAI ($p<0.001$), amisulpiride ($p<0.001$), clozapine ($p=0.001$), chlorpromazine ($p=0.003$) and risperidone oral preparation ($p=0.002$). The odds of APP was significantly higher with high-dose prescribing (AOR=11.34, CI=6.20–20.74, $p<0.001$).

Table 2 Antipsychotics prescribed to patients discharged on antipsychotic polypharmacy (APP) and antipsychotic monotherapy (APM) (N=565)

Antipsychotic	APP		APM		Total		Test- statistic	df	P-value
	N	%	N	%	N	%			
FGA									
Haloperidol	63	38.41	144	35.91	207	36.64	Chi-square = 0.31	1	0.575
Chlorpromazine	22	13.41	24	5.99	46	8.14	Chi-square = 8.59	1	0.003
Trifluoperazine	7	4.27	14	3.49	21	3.72	Chi-square = 0.19	1	0.658
Flupentixol (LAI)	49	29.88	7	1.75	56	9.91	Chi-square = 103.16	1	< 0.001
Zuclopenthixol (LAI)	82	50.00	15	3.74	97	17.17	Chi-square = 175.15	1	< 0.001
Fluphenazine (LAI)	22	13.41	3	0.75	25	4.42	Chi-square = 44.15	1	< 0.001
SGA									
Amisulpiride	13	7.93	4	1	17	3.01	Fisher's exact test	-	< 0.001
Clozapine	27	16.46	28	6.98	55	9.73	Chi-square = 11.90	1	0.001
Olanzapine	12	7.32	30	7.48	42	7.43	Chi-square = 0.00	1	0.946
Risperidone (oral)	31	18.90	127	31.67	158	27.96	Chi-square = 9.42	1	0.002
Risperidone (LAI)	1	0.61	3	0.75	4	0.71	Fisher's exact test	-	NS
Quetiapine	2	1.22	1	0.25	3	0.53	Fisher's exact test	-	0.203
Aripiprazole	0	0	1	0.25	1	0.18	Fisher's exact test	-	NS

NS = Non-significant ($p>0.05$)

The frequency of antipsychotic combinations prescribed at discharge is demonstrated in Table 3. The most common combination of antipsychotics was that of haloperidol and zuclopenthixol LAI, found in as many as 22.56 % of patients discharged on APP. This was followed by the haloperidol and flupentixol LAI combination which was present in 9.76% of combinations, chlorpromazine and

zuclopenthixol LAI in 8.54%, risperidone oral and flupentixol LAI in 7.93% and risperidone oral with zuclopenthixol LAI found in 7.32% of patients discharged on APP.

Table 3 Antipsychotic combinations in patients with antipsychotic polypharmacy (APP) at discharge (N=164)

Antipsychotic combination	**N**	**%**
Haloperidol + Zuclopenthixol (LAI)	37	22.56
Haloperidol + Flupentixol (LAI)	16	9.76
Chlorpromazine + Zuclopenthixol (LAI)	14	8.54
Risperidone (oral) + Flupentixol (LAI)	13	7.93
Risperidone (oral) + Zuclopenthixol (LAI)	12	7.32
Amisulpiride + Clozapine	9	5.49
Haloperdiol + Fluphenazine (LAI)	9	5.49
Clozapine + Zuclopenthixol (LAI)	7	4.27
Olanzapine + Zuclopenthixol (LAI)	7	4.27
Chlorpromazine + Flupentixol (LAI)	6	3.66
Olanzapine + Flupentixol (LAI)	5	3.05
Clozapine + Flupentixol (LAI)	4	2.44
Clozapine + Fluphenazine (LAI)	4	2.44
Risperidone + Fluphenazine (LAI)	4	2.44
Trifluoperazine + Fluphenazine (LAI)	3	1.83
Trifluoperazine + Zuclopenthixol (LAI)	2	1.22
Trifluoperazine + Flupentixol (LAI)	2	1.22
Chlorpromazine + Fluphenazine (LAI)	2	1.22
Haloperidol + Risperidone (oral)	1	0.61
Amisulpiride + Zuclopenthixol (LAI)	1	0.61
Quetiapine + Flupentixol (LAI)	1	0.61
Quetiapine + Zuclopenthixol (LAI)	1	0.61
Risperidone (oral) + Risperidone (LAI)	1	0.61
Amisulpiride + Clozapine + Flupentixol (LAI)	2	1.21
Amisulpiride + Clozapine + Zuclopenthixol (LAI)	1	0.60

As regards the nature of combinations according to type of antipsychotic agent class and route of administration, FGA oral and FGA LAI combinations predominated, being found in 55.49% of patients discharged on APP, followed by SGA oral and FGA LAI in 35.97% and a combination of 2 SGA oral agents in 5.49%, as shown in Table 4.

Table 4 Antipsychotic combination types in patients with antipsychotic polypharmacy (APP) at discharge (N=164)

Type and route of administration	N	%
FGA (oral) + FGA (oral)	0	0
FGA (oral) + FGA (LAI)	91	55.49
FGA (oral) + SGA (oral)	1	0.61
FGA (oral) + SGA (LAI)	0	0
SGA (oral) + SGA (oral)	9	5.49
SGA (oral) + SGA (LAI)	1	0.61
SGA (oral) + FGA (LAI)	59	35.97
SGA (oral) + SGA (oral) + FGA (LAI)	3	1.82

3.3 Co-prescriptions of other psychotropic medications with APP

Psychotropic co-prescriptions are displayed in Table 5. Anticholinergic agents, given to 44.51% of patients on APP regimens and 27.93% of patients receiving APM, were highly significantly associated with APP (P<0.001). In turn, sodium valproate also demonstrated a significant association with APP, being co-prescribed in as many as 53.05% of patients receiving APP, compared with 41.15% of patients prescribed APM (p=0.010). Lithium was significantly more commonly co-prescribed amongst patients on APM (16.71%) compared to patients on APP (9.76%) (p=0.034). Additional subgroup exploratory analysis confined to patients with APP (N=164) demonstrated a significant association between diagnosis and valproate co-prescription (p<0.001), with as many as 40.23% of sodium valproate co-prescriptions occurring in patients with diagnosis of schizophrenia, followed by 34.48% in schizoaffective disorder, only 17.24% in bipolar disorder and 8.05% in substance-induced disorders. Lithium co-prescriptions in those receiving APP occurred only in patients with diagnoses of bipolar and schizoaffective disorder, each contributing 50% of the total. Fluoxetine was the most frequently co-prescribed antidepressant, appearing in 3.66% of patients discharged on APP and 2.74% on AMP, but no significant associations between antidepressant co-prescriptions and APP were found. Similarly, benzodiazepines were prescribed to 4.88% of patients receiving APP and 7.48% of those on APM, a non-significant association.

Table 5 Psychotropics co-prescribed to patients discharged on antipsychotic polypharmacy (APP) and antipsychotic monotherapy (APM) (N=565)

Psychotropic co-prescription	APP		APM		Total		Test- statistic	df	P-value
	N	%	N	%	N	%			
Anticholinergic	73	44.51	112	27.93	185	32.74	Chi-square = 14.53	1	0.001
Mood stabilizer									
Sodium valproate	87	53.05	165	41.15	252	44.6	Chi-square = 6.67	1	0.010
Lithium	16	9.76	67	16.71	83	14.69	Chi-square = 4.48	1	0.034
Lamotrigine	1	0.61	2	0.50	3	0.53	Fisher's exact test	-	NS
Carbamazepine	1	0.61	2	0.50	3	0.53	Fisher's exact test	-	NS
Topiramate	0	0	1	0.25	1	0.18	Fisher's exact test	-	NS
Antidepressant									
Amitriptyline	0	0	1	0.25	1	0.18	Fisher's exact test	-	NS
Clomipramine	0	0	1	0.25	1	0.18	Fisher's exact test	-	NS
Citalopram	2	1.22	5	1.25	7	1.24	Fisher's exact test	-	NS
Fluoxetine	6	3.66	11	2.74	17	3.01	Fisher's exact test	-	0.591
Venlafaxine	1	0.61	0	0	1	0.18	Fisher's exact test	-	0.290
Benzodiazepine	8	4.88	30	7.48	38	6.73	Chi-square = 1.25	1	0.262

NS = Non-significant (p>0.05)

4 Discussion

The APP prevalence rate of 29.03% found in our study is fairly high in comparison to international rates, with a recent systematic review finding a global median prevalence of APP of 19.6% across time.(26) Our finding of a relatively high APP prevalence of 29.03% is similar to that of an earlier South African study published in 2008. This study reviewed data on antipsychotic drug prescriptions for Xhosa patients with schizophrenia and schizoaffective disorder, particularly in terms of clozapine use and found that there was an overall low rate (10%) of clozapine use and a relatively high frequency of APP (28.6% of patients).(27) The study suggested that high rates of APP may have been partially explained by high rates of LAI use (49.4% of patients), with the most frequently used antipsychotic combination used being haloperidol and a LAI (54.2% of combinations). While this study investigated APP in a limited population, our study examined the practice amongst all patients discharged on antipsychotic agents, without restricting race or diagnosis. Although findings were similar, our analysis of antipsychotic drug prescriptions examined prescription patterns in greater detail and included several additional SGAs that were not widely available in the South African public sector at the time of the previous study. In addition, we examined APP in the context of a range of patient, illness and treatment factors, increasing understanding of the complexity of the practice of APP in our setting.

Our study thus provides insight into various aspects that require consideration in relation to our relatively high rate of APP. The associations of APP with clinical and demographic characteristics

was statistically significant for age>29, male sex, diagnosis of schizophrenia compared to bipolar and substance-induced disorders, co-morbid intellectual disability, co-morbid substance use and greater number of hospital admissions. The positive association of APP with increased age is of interest in that it contrasts to data from several international studies that have showed an association of APP with younger age.(25) It is possible that older patients hospitalized in our setting are those with greater illness severity, complexity, chronicity and treatment resistance, factors which have been found to be associated with APP (25,26), with additional antipsychotics possibly added as a result of poor response on monotherapy. Likewise, the associations of APP with male sex and greater number of hospital admissions could also be linked to greater illness severity, complexity, chronicity and refractoriness in these patients,(25) as could the association with intellectual disability, with similar findings in previous studies and suggestion that individuals suffering from intellectual disability may be poorly responsive to antipsychotic treatments.(32)

While highest rates of APP in patients with diagnoses of schizophrenia and schizoaffective disorder were anticipated, it was of interest that APP was also observed in a fair number of patients with bipolar disorder and several patients with substance-induced disorders. Co-prescription of sodium valproate showed a significant positive association with APP, occurring significantly more often in APP patients with diagnoses of schizophrenia and schizoaffective disorders. In addition to its mood stabilizing action, sodium valproate may be used to treat residual psychotic symptoms and aggression in some cases.(11) There was a significant positive association between co-morbid substance use and APP, on a background of high rates of substance use in our population. It is evident that APP is a practice that warrants further investigation across diagnoses with careful attention to various contributing factors that could be targeted for intervention, including substance use.

Prescription patterns demonstrated the prominent use of FGAs and LAI formulations in APP combinations, which is in keeping with previous local and international literature.(26,27) However, our finding of FGA (oral) and FGA (LAI) predominantly used together in combinations differed from international trends that have demonstrated a move from FGA-FGA combinations to more FGA-SGA combinations over time, with FGA-SGA combination treatment being most common in recent studies.(26) FGAs remain common first-line prescriptions in our population, their lower cost making them particularly attractive in a resource-limited setting. SGA agents remain second-line choices in many cases, with restricted availability of certain agents including quetiapine and aripiprazole. LAIs are commonly used. They may frequently be added to existing regimens where concerns over compliance exist, contributing to their significant association with APP. In other cases, the positive

association of APP with use of LAIs may result from the difficulty performing fine adjustments with LAIs alone, leading to oral medication being added for this purpose.(25) Often, oral medication is used as initial lead in dosing for the first few weeks after LAI initiation while waiting for LAI plasma levels to reach steady state. As there is evidence that eventual discontinuation of the oral medication in such cases is often deferred and may even continue beyond its original purpose as lead-in medication,(33) an important aspect of treatment planning would include instructions to community clinics to taper and stop such medications and audits of whether such processes are in fact carried out. The majority of combinations found in our study remain unsupported by evidence, with the possible exception of clozapine augmentation strategies.(3,4)

The positive association of APP with clozapine and use of clozapine with amisulpiride in combinations recorded demonstrates attempts by some prescribers to follow treatment guidelines in managing treatment resistant patients. However, the rates of clozapine use in our study population (9.7%) remain relatively low in comparison to international rates.(34-37) Possible reasons for this include clinician concerns about treatment adherence, side-effect profile, the need for regular follow-up for monitoring of leukocyte counts required with clozapine treatment and difficulties related to reintroduction of clozapine after discontinuation for longer than 48 hours.(27)

The results of our study also contribute to concern over the safety of APP. There was a significant positive association of APP with high-dose prescribing, as well as with co-prescription of anticholinergic medication. This may suggest risk for increased extrapyramidal side-effects with APP, which in turn raises concerns about potential additional adverse effects possibly resulting from excess dopamine D2 blockade, including akathisia, tardive dyskinesia and hyperprolactinaemia amongst others.(11)

Our study does however have several limitations that should be noted when interpreting results. Restriction to a single centre hospital population may have produced results that may not be readily generalizable to the general population, with inpatient status found to be associated with APP in previous studies.(25) While discharge prescriptions should have reflected the plan for ongoing maintenance treatment in most patients, some APP may have resulted from certain patients discharged during a process of cross titration while changing antipsychotic agents or with oral medication being used as lead-in dosing with initiation of LAI as discussed. In addition, our study was cross-sectional in nature, with variables examined being limited to administrative data and information contained in discharge summaries completed electronically for each patient by their attending psychiatric registrar at time of discharge. In some cases, the attending clinician may have

failed to document co-morbid psychiatric symptoms or substance use. We did not extract information from case files on sequential antipsychotic medications used and reasons for medication changes during hospital stay, making it uncertain whether prescribing of the combination was preceded by failure trials of monotherapy in hospital. Certain relevant variables were not directly recorded. We attempted to overcome this problem by examining related variables. Length of time from first hospitalization to most recent discharge was used to provide some indication of duration of illness or time in treatment, although we acknowledge that the patient may have been diagnosed with mental illness prior to first hospital admission. Number of previous admissions and length of stay were recorded as indicators of illness severity and possibly treatment resistance, although we realize that these are not direct substitute measures.

5 Conclusion

Our study suggests that current local practice deviates from standard local and international guidelines in that combination antipsychotic agents are prescribed for a number of patients with a range of psychiatric diagnoses without evidence for this practice, and at possible cost of increased adverse effects. Our findings indicate that antipsychotic prescription patterns reflect a complex interplay among patient, illness and treatment characteristics of our population. Additional research is needed examining the practice of APP across diagnoses, focusing on the multiple aspects affecting local practice and various contributing factors that could be targeted for intervention. This would be a positive step towards improving the quality of our service in order to advance mental health care practice and provide optimal patient management in a resource-limited setting.

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Declarations

List of abbreviations

AOR	Adjusted odds ratio
APM	Antipsychotic monotherapy
APP	Antipsychotic polypharmacy
FGA	First-generation antipsychotic
LAI	Long acting injectable
SGA	Second-generation antipsychotic

Ethics approval

Approved by the University Of Cape Town Faculty of Health Sciences Human Research Ethics Committee, HREC REF 399/2014

Consent for publication

Not applicable

Availability of data and materials

Data capture instrument and dataset of study presented in additional supporting file

Competing interests

This research was conducted in partial fulfilment of the principle researcher's requirements for the degree of Mmed in Psychiatry through the University of Cape Town. However, the University did not influence the course or outcome of the study in any way. No financial competing interests existed.

Funding

We made use of Valkenberg Hospital's electronic patient record database, *Clinicom*, to attain relevant data for our study. The principle researcher captured the data and her supervisor assisted with data analysis. No additional funding was required.

Authors' contributions

Dr Kerryn Armstrong was the principal researcher. She developed the study protocol, captured data for the study, interpreted results of data analysis and produced the research report.
Dr Henk Temmingh acted as research supervisor. He provided valuable input at all stages of the research project and assisted with data analysis.

Authors' information

Dr Kerryn Armstrong is a psychiatric registrar training through the University of Cape Town.
Dr Henk Temmingh is a specialist psychiatrist at Valkenberg Hospital, Department of Psychiatry, University of Cape Town.

Appendices

Appendix 1: Data capture instrument

Data capture instrument appended electronically in additional supporting file due to large size.

Appendix 2: Letter of study approval from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee

Ethics approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: lamees.emjedi@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

10 July 2014

HREC REF: 399/2014

Dr H Temmingh
Psychiatry
Education Centre
Valkenberg Hospital
Private Bag X
Observatory

Dear Dr Temmingh

PROJECT TITLE: PREVALENCE AND FACTORS ASSOCIATED WITH ANTIPSYCHOTIC POLYPHARMACY IN PATIENTS WITH SERIOUS MENTAL ILLNESS: FINDINGS FROM A CROSS-SECTIONAL STUDY OF PATIENTS DISCHARGED FROM A PSYCHIATRIC HOSPITAL IN CAPE TOWN, SOUTH AFRICA (MMed candidate-Dr K Armstrong)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th July 2015.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

We acknowledge that the* MMed Candidate Dr K Armstrong *will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC reference no in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

HREC 399/2014

Appendix 3: Letter of study approval from the acting director of Health Impact Assessment, Western Cape Department of Health

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
Tel: +27 21 483 6857; fax: +27 21 483 9895
5th Floor, Norton Rose House, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za

REFERENCE: RP099/2014
ENQUIRIES: Ms Charlene Roderick

Education Centre
Valkenberg Hospital
Private Bag X
Observatory 7935
Cape Town

For attention: **Dr Kerryn Armstrong, Dr Henk Temmingh, and Dr Janine Benson-Martin**

Re: The prevalence and factors associated with antipsychotic polypharmacy in patients with serious mental illness: Findings from a cross-sectional study of patients discharged from a psychiatric hospital in Cape Town, South Africa.

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.

Please contact the following people to assist you with any further enquiries in accessing the following sites:

Valkenberg Hospital	**C Dean**	**Contact No. 021 440 3260**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final report within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

3. The reference number above should be quoted in all future correspondence.

Yours sincerely

DR J EVANS
ACTING DIRECTOR: HEALTH IMPACT ASSESSMENT
DATE: 12/09/14
CC

Appendix 4: Instructions to authors of chosen journal, BioMed Central Psychiatry (BMC Psychiatry)

BMC Psychiatry, guidelines for research articles

1 Criteria

Research articles should report on original primary research, but may report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our editorial policies. Please note that non-commissioned pooled analyses of selected published research will not be considered.

2 Preparing your manuscript

2.1 Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
    - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"
    - or for non-clinical or non-research studies a description of what the article reports
- list the full names, institutional addresses and email addresses for all authors
    - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the "Acknowledgements" section in accordance with the instructions below
- indicate the corresponding author

2.2 Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications
- **Trial registration:** If your article is a systematic review or reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be in stated in this section. See our editorial policies for more information on trial registration

2.3 Keywords

Three to ten keywords representing the main content of the article.

2.4 Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

2.5 Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

2.6 Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

2.7 Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

2.8 Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

2.9 Declarations

2.9.1 List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

2.9.2 Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

- include a statement on ethics approval and consent (even where the need for approval was waived)
- include the name of the ethics committee that approved the study and the committee's reference number if appropriate

Studies involving animals must include a statement on ethics approval.

See our editorial policies for more information.

If your manuscript does not report on or involve the use of any animal or human data or tissue, this section is not applicable to your submission. Please state "Not applicable" in this section.

2.9.3 Consent for publication

If your manuscript contains any individual person's data in any form (including individual details, images or videos), consent to publish must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent to publish. You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage (including after publication).

See our editorial policies for more information on consent for publication.

If your manuscript does not contain any individual persons data, please state "Not applicable" in this section.

2.9.4 Availability of data and materials

For all journals, BioMed Central strongly encourages all datasets on which the conclusions of the manuscript rely to be either deposited in publicly available repositories (where available and appropriate) or presented in the main paper or additional supporting files, in machine-readable format (such as spreadsheets rather than PDFs) whenever possible. Please see the list of recommended repositories in our editorial policies.

For some journals, deposition of the data on which the conclusions of the manuscript rely is an absolute requirement. Please check the Criteria section for this article type (located at the top of this page) for journal specific policies.

For all journals, authors must include an "Availability of data and materials" section in their article detailing where the data supporting their findings can be found. If you do not wish to share your data, please state that data will not be shared, and state the reason.

For information on how to cite your data and format this section see preparing your manuscript.

2.9.5 Competing interests

All financial and non-financial competing interests must be declared in this section. See our editorial policies for a full explanation of competing interests. If you are unsure whether you or any of your co-authors have a competing interest please contact the editorial office.

2.9.6 Funding

All sources of funding for the research reported should be declared. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

2.9.7 Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section. Guidance and criteria for authorship can be found in our editorial policies.

2.9.8 Acknowledgements

Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials.

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

See our editorial policies for a full explanation of acknowledgements and authorship criteria.

Group authorship: if you would like the names of the individual members of a collaboration Group to be searchable through their individual PubMed records, please ensure that the title of the collaboration Group is included on the title page and in the submission system and also include collaborating author names as the last paragraph of the "Acknowledgements" section. Please add authors in the format First Name, Middle initial(s) (optional), Last Name. You can add institution or country information for each author if you wish, but this should be consistent across all authors.

Please note that individual names may not be present in the PubMed record at the time a published article is initially included in PubMed as it takes PubMed additional time to code this information.

2.9.9 Authors' information

You may choose to use this section to include any relevant information about the author(s) that may aid the reader's interpretation of the article, and understand the standpoint of the author(s). This may include details about the authors' qualifications, current positions they hold at institutions or societies, or any other relevant background information. Please refer to authors using their initials. Note this section should not be used to describe any competing interests.

2.10 Endnotes

Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

3 General formatting information

Manuscripts must be written in concise English. For help on scientific writing, or preparing your manuscript in English, please see Springer's Author Academy.

Quick points:

- Use double line spacing
- Include line and page numbering
- Use SI units: Please ensure that all special characters used are embedded in the text, otherwise they will be lost during conversion to PDF

- Do not use page breaks in your manuscript

3.1 File formats

The following word processor file formats are acceptable for the main manuscript document:

- Microsoft word (DOC, DOCX)
- Rich text format (RTF)
- TeX/LaTeX (use BioMed Central's TeX template)

Please note: editable files are required for processing in production. If your manuscript contains any non-editable files (such as PDFs) you will be required to re-submit an editable file if your manuscript is accepted.

Note that figures must be submitted as separate image files, not as part of the submitted manuscript file.

3.2 Additional information for TeX/LaTeX users

Please use a recommended TeX template and BibTeX stylefile if you use TeX format. When submitting TeX submissions, please submit your TeX file as the main manuscript file and your bib/bbl file as a dependent file. Please also convert your TeX file into a PDF and submit this PDF as an additional file with the name 'Reference PDF'. This PDF will be used by our production team as a reference point to check the layout of the article as the author intended. Please also note that all figures must be coded at the end of the TeX file and not inline.

All relevant editable source files must be uploaded during the submission process. Failing to submit these source files will cause unnecessary delays in the production process.

TeX templates:

- BioMedCentral_article (ZIP format) - preferred template
- Springer article svjour3 (ZIP format) - preferred template
- birkjour (Birkhäuser, ZIP format)
- article (part of the standard TeX distribution)
- amsart (part of the standard TeX distribution)

3.3 Style and language

Manuscripts submitted to most journals do not undergo copyediting for style and language. Please check individual journal ‘About’ pages to confirm whether accepted manuscripts will undergo copyediting for style and language.

You can use a professional language editing service of your choice if you want to. Such services include:

- Edanz Language Editing. BioMed Central authors can obtain a 10% discount to the fee charged by Edanz if they choose to use this service.
- Nature Publishing Group Language Editing. Authors can use this coupon code to claim a 10% discount: LE_BM15

Contact the service providers directly to make arrangements for editing, and for pricing and payment details. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication.

3.4 Data and materials

For all journals, BioMed Central strongly encourages all datasets on which the conclusions of the manuscript rely to be either deposited in publicly available repositories (where available and appropriate) or presented in the main paper or additional supporting files, in machine-readable format (such as spread sheets rather than PDFs) whenever possible. Please see the list of recommended repositories in our editorial policies.

For some journals, deposition of the data on which the conclusions of the manuscript rely is an absolute requirement. Please check the Instructions for Authors for the relevant journal and article type for journal specific policies.

For all manuscripts, information about data availability should be detailed in an 'Availability of data and materials' section. For more information on the content of this section, please see the Declarations section of the relevant journal's Instruction for Authors. For more information on BioMed Central's policies on data availability, please see our editorial policies.

3.4.1 Formatting the 'Availability of data and materials' section of your manuscript

The following format for the 'Availability of data and materials section of your manuscript should be used:

"The dataset(s) supporting the conclusions of this article is(are) available in the [repository name] repository, [unique persistent identifier and hyperlink to dataset(s) in http:// format]."

The following format is required when data are included as additional files:

"The dataset(s) supporting the conclusions of this article is(are) included within the article (and its additional file(s))."

For databases, this section should state the web/ftp address at which the database is available and any restrictions to its use by non-academics.

For software, this section should include:

- Project name: e.g. My bioinformatics project
- Project home page: e.g. http://sourceforge.net/projects/mged
- Archived version: DOI or unique identifier of archived software or code in repository (e.g. enodo)
- Operating system(s): e.g. Platform independent
- Programming language: e.g. Java
- Other requirements: e.g. Java 1.3.1 or higher, Tomcat 4.0 or higher
- License: e.g. GNU GPL, FreeBSD etc.
- Any restrictions to use by non-academics: e.g. licence needed

Information on available repositories for other types of scientific data, including clinical data, can be found in our editorial policies.

3.5 References

See our editorial policies for author guidance on good citation practice.

3.5.1 What should be cited?

Only articles, clinical trial registration records and abstracts that have been published or are in press, or are available through public e-print/preprint servers, may be cited.

Unpublished abstracts, unpublished data and personal communications should not be included in the reference list, but may be included in the text and referred to as "unpublished observations" or "personal communications" giving the names of the involved researchers. Obtaining permission to quote personal communications and unpublished data from the cited colleagues is the responsibility of the author. Footnotes are not allowed, but endnotes are permitted. Journal abbreviations follow Index Medicus/MEDLINE.

Any in press articles cited within the references and necessary for the reviewers' assessment of the manuscript should be made available if requested by the editorial office.

3.6 Web links and URLs: All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, as well as the date the site was accessed, in the following format: The Mouse Tumor Biology Database. http://tumor.informatics.jax.org/mtbwi/index.do. Accessed 20 May 2013. If an author or group of authors can clearly be associated with a web link, such as for weblogs, then they should be included in the reference.

Authors may wish to make use of reference management software to ensure that reference lists are correctly formatted. An example of such software is Papers, which is part of Springer Science+Business Media.

4 Preparing figures

When preparing figures, please follow the formatting instructions below.

- Figures should be provided as separate files, not embedded in the main manuscript file.
- Each figure of a manuscript should be submitted as a single file that fits on a single page in portrait format.
- Tables should NOT be submitted as figures but should be included in the main manuscript file.
- Multi-panel figures (those with parts a, b, c, d etc.) should be submitted as a single composite file that contains all parts of the figure.
- Figures should be numbered in the order they are first mentioned in the text, and uploaded in this order.
- Figures should be uploaded in the correct orientation.
- Figure titles (max 15 words) and legends (max 300 words) should be provided in the main manuscript, not in the graphic file.

- Figure keys should be incorporated into the graphic, not into the legend of the figure.
- Each figure should be closely cropped to minimize the amount of white space surrounding the illustration. Cropping figures improves accuracy when placing the figure in combination with other elements when the accepted manuscript is prepared for publication on our site. For more information on individual figure file formats, see our detailed instructions.
- Individual figure files should not exceed 10 MB. If a suitable format is chosen, this file size is adequate for extremely high quality figures.
- **Please note that it is the responsibility of the author(s) to obtain permission from the copyright holder to reproduce figures (or tables) that have previously been published elsewhere.** In order for all figures to be open access, authors must have permission from the rights holder if they wish to include images that have been published elsewhere in non open access journals. Permission should be indicated in the figure legend, and the original source included in the reference list.

4.1 Figure file types

We accept the following file formats for figures:

- EPS (suitable for diagrams and/or images)
- PDF (suitable for diagrams and/or images)
- Microsoft Word (suitable for diagrams and/or images, figures must be a single page)
- PowerPoint (suitable for diagrams and/or images, figures must be a single page)
- TIFF (suitable for images)
- JPEG (suitable for photographic images, less suitable for graphical images)
- PNG (suitable for images)
- BMP (suitable for images)
- CDX (ChemDraw - suitable for molecular structures)

4.2 Figure size and resolution

Figures are resized during publication of the final full text and PDF versions to conform to the BioMed Central standard dimensions, which are detailed below.

Figures on the web:

- width of 600 pixels (standard), 1200 pixels (high resolution).

Figures in the final PDF version:

- width of 85 mm for half page width figure
- width of 170 mm for full page width figure
- maximum height of 225 mm for figure and legend
- image resolution of approximately 300 dpi (dots per inch) at the final size

Figures should be designed such that all information, including text, is legible at these dimensions. All lines should be wider than 0.25 pt when constrained to standard figure widths. All fonts must be embedded.

4.2.1 Figure file compression

Vector figures should if possible be submitted as PDF files, which are usually more compact than EPS files.

- TIFF files should be saved with LZW compression, which is lossless (decreases file size without decreasing quality) in order to minimize upload time.
- JPEG files should be saved at maximum quality.
- Conversion of images between file types (especially lossy formats such as JPEG) should be kept to a minimum to avoid degradation of quality.

If you have any questions or are experiencing a problem with figures, please contact the customer service team at info@biomedcentral.com.

5 Preparing tables

When preparing tables, please follow the formatting instructions below.

- Tables should be numbered and cited in the text in sequence using Arabic numerals (i.e. Table 1, Table 2 etc.).
- Tables less than one A4 or Letter page in length can be placed in the appropriate location within the manuscript.
- Tables larger than one A4 or Letter page in length can be placed at the end of the document text file. Please cite and indicate where the table should appear at the relevant location in the text file so that the table can be added in the correct place during production.
- Larger datasets, or tables too wide for A4 or Letter landscape page can be uploaded as additional files. Please see [below] for more information.
- Tabular data provided as additional files can be uploaded as an Excel spreadsheet (.xls) or comma separated values (.csv). Please use the standard file extensions.
- Table titles (max 15 words) should be included above the table, and legends (max 300 words) should be included underneath the table.
- Tables should not be embedded as figures or spreadsheet files, but should be formatted using 'Table object' function in your word processing program.
- Color and shading may not be used. Parts of the table can be highlighted using superscript, numbering, lettering, symbols or bold text, the meaning of which should be explained in a table legend.
- Commas should not be used to indicate numerical values.

If you have any questions or are experiencing a problem with tables, please contact the customer service team at info@biomedcentral.com.

6 Preparing additional files

As the length and quantity of data is not restricted for many article types, authors can provide datasets, tables, movies, or other information as additional files.

All Additional files will be published along with the accepted article. Do not include files such as patient consent forms, certificates of language editing, or revised versions of the main manuscript document with tracked changes. Such files, if requested, should be sent by email to the journal's editorial email address, quoting the manuscript reference number.

Results that would otherwise be indicated as "data not shown" should be included as additional files. Since many web links and URLs rapidly become broken, BioMed Central requires that supporting data are included as additional files, or deposited in a recognized repository. Please do not link to data on a personal/departmental website. Do not include any individual participant details. The maximum file size for additional files is 20 MB each, and files will be virus-scanned on submission. Each additional file should be cited in sequence within the main body of text.