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RESEARCH ARTICLE

The hidden magnitude of polypharmacy: using defined daily doses and maximum licensed daily doses to measure antipsychotic load

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Abstract

Background Antipsychotic polypharmacy ("polypharmacy") is the concurrent prescribing of more than one antipsychotic. It is widely practised, as reported in the literature, and is known to increase the risk of adverse outcomes for patients. *Objective* To quantify the prevalence and magnitude of polypharmacy in patients with schizophrenia or schizoaffective disorder and identify potential factors contributing to this practice. *Setting* Armadale Mental Health Service (a public inpatient and outpatient psychiatric facility in Perth, Western Australia). *Method* A retrospective, cross-sectional study was conducted, evaluating the medical records of adult (18–64 years old) patients fulfilling the established inclusion criteria in the period between August and December 2016. Data collected included the number and doses of antipsychotic(s) prescribed and documented rationale for polypharmacy. Defined daily doses and proportions of maximum licensed daily doses were calculated for all regularly prescribed antipsychotics and were evaluated as measures of antipsychotic load. *Main Outcome Measure* The percentage prevalence of antipsychotic polypharmacy; defined daily antipsychotic doses and proportions of maximum licensed daily doses. *Results* Seventy-seven patients were assessed, with a polypharmacy prevalence of 39.0%. Total defined daily doses ranged from 0.9 to 5.9 and maximum licensed daily doses from 0.4 to 2.3. Documented rationales for polypharmacy included poor symptom control, patient's preference, hesitancy to amend other prescribers' management plans, off-label antipsychotic indications and medication cross-titration. *Conclusion* Antipsychotic polypharmacy occurred in more than one-third of patients. Individual antipsychotics were typically prescribed at doses within the licensed range, however, the total proportion of combined maximum licensed doses and combined daily defined doses often exceeded 100%. Due to suboptimal documentation, prescribing rationale was unclear in the majority of cases. The magnitude of polypharmacy aims to foster a greater appreciation of the prescribed antipsychotic load, increasing clinician self-awareness of prescribing practices and facilitating future opportunities to optimise prescribing.

Keywords Antipsychotic load · Australia · Defined daily doses · Polypharmacy · Schizoaffective disorder · Schizophrenia

Impact on practice

- Combined defined daily doses and proportion of maximum licensed daily doses serve as useful measures of antipsychotic load. Quantifying these parameters will assist clinicians to recognise the overall burden of polypharmacy, especially when relatively low doses of multiple antipsychotics are used.
- An awareness of antipsychotic burden can facilitate opportunities for medication review and rationalisation of prescribing.
- Rationalising antipsychotic prescribing has the potential to improve patient compliance and outcomes overall.

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Introduction

Antipsychotics play an important role in the management of schizophrenia and schizoaffective disorder by fundamentally counteracting the hyperdopaminergic activity underlying psychosis [1–5]. Antipsychotic polypharmacy is frequently referred to as the simultaneous prescribing of more than one antipsychotic medication [6]. It is a controversial treatment strategy, with conflicting data regarding its relative benefits and risks [3, 7]. While some studies have suggested some antipsychotic polypharmacy regimens are associated with a reduction in negative symptoms [8] and, more recently, psychiatric rehospitalisation [7], the adverse consequences of combining antipsychotics include poor medication compliance, increased risk of adverse reactions and higher treatment costs [3, 9, 10]. The Royal Australian and New Zealand College of Psychiatrists (RANZCP) adopted a balanced approach in their 2016 guidelines, stating that antipsychotic monotherapy is ideal, however, on occasions polypharmacy may be justified, such as in patients who have demonstrated treatment resistance to monotherapy, for treatment augmentation, or during medication cross-titration [3]. Similar monotherapy treatment recommendations for schizophrenia are advocated in international guidelines, such as the National Institute for Health and Care Excellence (NICE) and World Federation of Societies of Biological Psychiatry guidelines [11]. Despite conflicting evidence to support antipsychotic polypharmacy, it continues to be widely practised in both Australian and overseas settings [3, 12, 13].

Previous studies usually considered only the number of antipsychotics prescribed; few have considered how the combined doses of various antipsychotics and/or different dosage formulations impact on overall medication burden [9, 14]. The full magnitude of polypharmacy is difficult to recognise when there are numerous antipsychotics involved and prescribed at varying doses. The defined daily dose (DDD) is a useful instrument for quantifying antipsychotic load [15, 16]. It represents "the assumed average maintenance dose per day for a drug used for its main indication in adults" [15], but does not necessarily reflect its maximum licensed daily dose (MLDD). The MLDD represents the highest prescribed dose defined by the manufacturer, based on clinical trials assessing the drug's efficacy and safety. The relationship between antipsychotic polypharmacy, MLDD and DDD is under-explored and a need was identified to assess the influence of these factors in the context of polypharmacy [17].

Aim of the study

The primary objective was to quantify the prevalence and magnitude (medication load) of antipsychotic polypharmacy at the study site, utilising DDD as a measure of antipsychotic load, with a comparison to MLDD. The secondary objective was to identify factors contributing to antipsychotic polypharmacy; data that could inform future strategies for rationalising prescribing.

Ethics approval

Ethics approvals to conduct this study were granted by the South Metropolitan Health Service (REG number 2016-245) and Curtin University (approval number HRE2017-0061) Human Research Ethics Committees. A study site-specific assessment was completed and approval to commence the study was granted by the site's Executive Director, Drugs and Therapeutics Committee and Education/Training/Research Committee.

Method

Defining antipsychotic polypharmacy

There is no universally accepted definition for antipsychotic polypharmacy, but the consensus amongst researchers is the concurrent prescribing of at least two antipsychotic agents [9, 11, 13, 17]. For the purposes of this study, antipsychotic polypharmacy was defined as the simultaneous prescribing of two or more antipsychotics intended for regular, not "when required" administration; including the off-label prescribing of multiple dosage formulations of the same antipsychotic [i.e.: combining oral and depot dosage forms of the same drug outside the scope of its licensed use(s)] [18].

Study location

A retrospective, cross-sectional study was conducted at a public psychiatric facility in Western Australia that encompasses more than 40 inpatient beds, a discharge clinic and three outpatient clinics. The outpatient clinics include the

Assessment and Treatment Team (ATT), Clinical Treatment Team (CTT) and the Older Adult Mental Health Clinic (OAMHC). Patients requiring less than 10 weeks of follow-up care are referred to ATT, while chronic patients requiring ongoing follow-up are referred to CTT. All patients over the age of 65 years are referred to the OAMHC, regardless of follow-up duration.

Study population

A list of all adult (18 years and above) patients who presented to the study site between 1 August and 31 December 2016 (inclusive) was generated from the hospital's database. This list was screened for those with an International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnostic code of F20 or F25 varieties, signifying schizophrenic and schizoaffective illnesses, respectively [19]. Duplicated entries were removed. Where there had been multiple contacts with the health service, the patient's most recent presentation was considered. The medical records of these patients were further examined for study eligibility, with exclusion criteria being pregnancy, lactation and those under the care of the OAMHC (i.e.: 65 years and above). Patients who were "lost to follow-up" (i.e.: failure to attend scheduled appointment(s) during the studied period) were excluded due to insufficient data.

Data collection

Data collected included patient demographics, prescribed antipsychotic regimen (medication, route and dose) and documented rationale for polypharmacy. Additional data such as laboratory and physical investigation results were gathered to provide insight into possible factors contributing to polypharmacy. The practicality of the data collection tool was assessed in a pilot audit of 20 patients, with modifications made subsequent to this process and upon advice received from a statistician.

The health service's clinical database (iSoft), dispensing program (iPharmacy), discharge summary system (TEDS), and each patient's paper-based medical record were reviewed to gather the information required. The medication regimens prescribed on discharge (for inpatient admissions) or at the lattermost clinic appointment (for outpatients) were recorded. Data collected were entered into a Microsoft Excel spreadsheet.

Data synthesis and analysis

The World Health Organisation (WHO) has compiled DDD data for a range of drugs; the DDD of antipsychotics considered within this study are shown in "Appendix 1" [15]. This DDD index was consulted to calculate the proportion of the WHO DDD each antipsychotic represented at the doses prescribed. For example, the WHO DDD for oral olanzapine is 10 mg; at a prescribed dose of 10 mg twice daily, this equates to 2 DDD [15]. Being an additive parameter, the calculated DDD of individual antipsychotics was combined to compute the overall DDD [16]. A Student's *T* test was performed to compare the mean DDD values between the monotherapy and polypharmacy patient cohorts.

The MLDDs of antipsychotics were extracted from their approved Australian product information; those pertaining to this study are shown in "Appendix 2" [18]. For each patient prescribed multiple antipsychotics, the dose of each were calculated as a proportion of the MLDD, and then summated. For example, the MLDD of oral olanzapine is 20 mg each day; the MLDD of haloperidol depot is 300 mg every 4 weeks [20]. For patients prescribed oral olanzapine 10 mg twice daily and haloperidol depot 150 mg every 4 weeks, this equates to 100% MLDD of olanzapine and 50% MLDD of haloperidol; in total, this equates to 150% of the combined MLDDs.

The documented rationales for polypharmacy were assessed against the RANZCP Clinical Practice Guidelines [3]. Treatment resistance, antipsychotic augmentation and medication cross-titration were regarded as clinically "appropriate" reasons for polypharmacy. Other rationales or the absence of any documented rationale were considered clinically "inappropriate".

Results

Frequency and magnitude of antipsychotic polypharmacy prescribing

Of the 88 patients initially identified as suitable for inclusion in this study, 11 were excluded for reasons such as

Table 1 Patient demographic data (n = 77)

Patient demographics	
Median age (years) [range]	34 [21–62]
Male gender	56 (72.7%)
Diagnoses n (%)	
Schizophrenic illness (ICD-10 F20 codes)	67 (87.0)
Schizoaffective illness (ICD-10 F25 codes)	10 (13.0)
Treatment setting n (%)	
Inpatients	
Inpatient wards	15 (19.5)
Outpatients	
Clinical Treatment Team (CTT)	47 (61.0)
Assessment and Treatment Team (ATT)	12 (15.6)
Discharge clinic	3 (3.9)
Total	77 (100.0)

their diagnosis not fulfilling the ICD-10 F20 or F25 criteria (n = 7), failure to attend scheduled appointments (n = 3) or contact with the health service occurring outside of the studied period (n = 1). The median age of the 77 eligible patients was 34 years, and more than two-thirds were male (Table 1). The majority of diagnoses were schizophrenic illness, and approximately 20% of patients were assessed at the point of discharge from inpatient treatment.

Thirty patients (39.0%) were prescribed antipsychotic polypharmacy. Of these, one patient was in the process of being weaned off medication (i.e.: polypharmacy being rationalised to monotherapy). Of the 77 patients, seven were also prescribed an antipsychotic for "when required" use, in addition to their regularly prescribed antipsychotic(s). Figure 1 is a schematic overview of these study findings. Table 2 outlines the antipsychotics prescribed for each of the 30 patients with polypharmacy, as well as the DDD and MLDD results.

Of the polypharmacy cohort, 15/30 (50.0%) were prescribed a regimen containing one or more antipsychotics at a dose equivalent to less than 1 DDD. Most (29/30, 96.7%) patients who were prescribed antipsychotic polypharmacy had a combined DDD in excess of 1, with a value of 5.9 observed in one case. The mean ± standard deviation DDDs of the polypharmacy and monotherapy cohorts were 2.8 ± 1.1 and 1.3 ± 0.7, respectively. The difference between these mean DDDs were considered statistically and clinically significant (t = 7.34, $p < 0.00001$). Taking into consideration the MLDDs of these individual antipsychotics, 29 patients (96.7%) were prescribed one or more antipsychotics at a dose less than the maximum defined by the manufacturer. When the entire antipsychotic regimen of each of these patients was assessed, 24 patients (80%) totalled more than 100% of MLDDs combined. In comparison, there was one patient in the monotherapy cohort who was prescribed an off-label dose of an antipsychotic (olanzapine) that exceeded the MLDD.

Documented rationale for antipsychotic polypharmacy

Of the 30 patients prescribed polypharmacy, a rationale for combining antipsychotics was documented in 11 medical records. The documented justification for initiating or continuing polypharmacy included poor control of psychotic symptoms (5), patient's preference (3), concerns about interfering with treatment if the patient was usually under the care of another treating team or health service (1), unlicensed (off-label) indications for antipsychotic use—such as insomnia (1), and medication cross-titration (1).

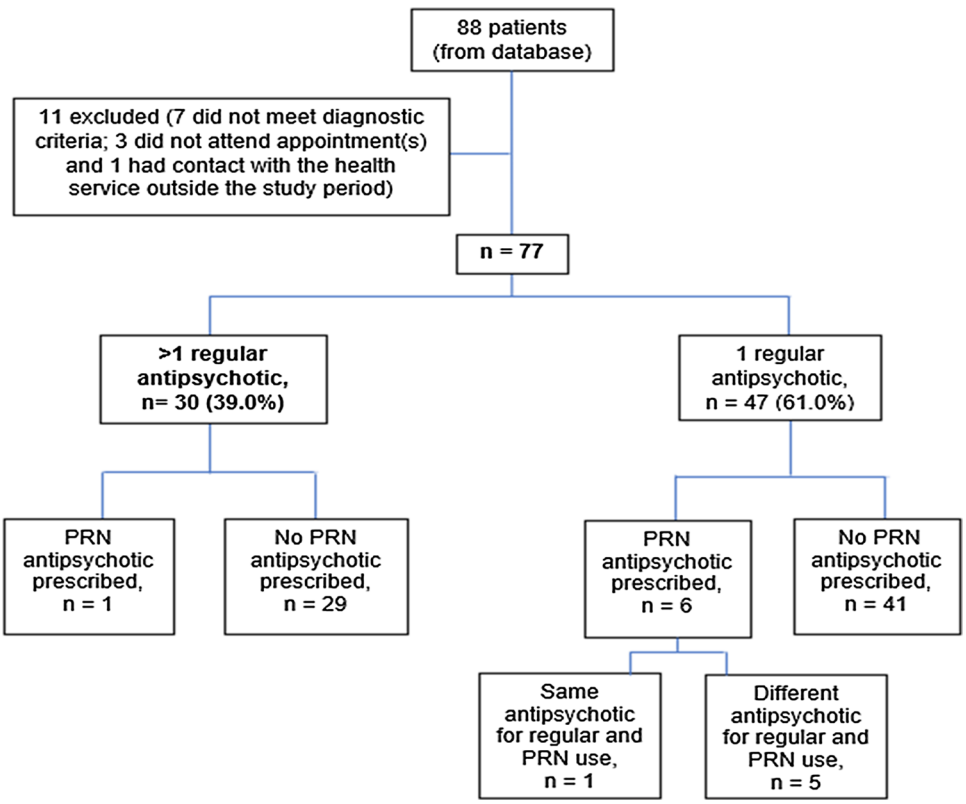

Fig. 1 Schematic overview of antipsychotic prescribing (PRN = "when required")

Table 2 Antipsychotic polypharmacy combinations and associated defined daily dose (DDD) and maximum licensed daily dose (MLDD) [15, 18]

Antipsychotic combination[a]	Proportion of WHO DDD	Total DDD	Percentage of MLDD (%)	Percentage of MLDD (%) (combined)
Clozapine oral 350 mg nocte	1.2	5.9	39	114
Haloperidol oral 10 mg mane, 5 mg noon, 10 mg nocte	3.1		25	
Haloperidol depot 150 mg every 4 weeks	1.6		50	
Aripiprazole depot 400 mg every 4 weeks	1.1	4.5	100	225
Chlorpromazine oral 50 mg mane, 50 mg noon, 100 mg nocte	0.7		25	
Lurasidone oral 160 mg nocte	2.7		100	
Olanzapine oral 20 mg mane	2.0	4.1	100	200
Paliperidone depot 150 mg every 4 weeks	2.1		100	
Aripiprazole oral 30 mg mane	2.0	4.0	100	167
Clozapine oral 600 mg nocte	2.0		67	
Clozapine oral 500 mg nocte	1.7	3.9	56	123
Haloperidol depot 150 mg every 3 weeks	2.2		67	
Haloperidol depot 200 mg every 3 weeks	2.9	3.9	89	139
Olanzapine oral 10 mg nocte	1.0		50	
Lurasidone oral 160 mg nocte	2.7	3.8	100	150
Paliperidone depot 75 mg every 4 weeks (maintenance)	1.1		50	
Haloperidol depot 150 mg every 4 weeks	1.6	3.6	50	150
Olanzapine oral 10 mg BD	2.0		100	
Aripiprazole depot 300 mg every 4 weeks	0.8	3.5	75	175
Lurasidone oral 160 mg nocte	2.7		100	
Aripiprazole oral 20 mg mane	1.3	3.5	67	139
Clozapine 100 mg mane, 550 mg nocte	2.2		72	
Olanzapine oral 5 mg mane, 10 mg nocte	1.5	3.4	75	175
Zuclopenthixol depot 400 mg every 2 weeks	1.9		100	
Aripiprazole oral 30 mg mane	2.0	3.3	100	150
Lurasidone oral 80 mg nocte	1.3		50	
Flupenthixol depot 20 mg every 2 weeks	0.4	3.1	20	120
Lurasidone oral 160 mg nocte	2.7		100	
Olanzapine oral 10 mg BD	2.0	3.0	100	150
Paliperidone oral 6 mg mane	1.0		50	
Olanzapine oral 5 mg mane, 10 mg nocte	1.5	2.9	75	142
Paliperidone depot 100 mg every 4 weeks	1.4		67	
Quetiapine oral (XR) 400 mg nocte	1.0	2.9	50	150
Zuclopenthixol depot 400 mg every 2 weeks	1.9		100	
Paliperidone depot 150 mg every 4 weeks	2.1	2.6	100	125
Quetiapine oral (IR) 100 mg BD	0.5		25	
Aripiprazole depot 400 mg every 4 weeks	1.1	2.2	100	136
Clozapine oral 325 mg nocte	1.1		36	
Paliperidone oral 6 mg BD	2.0	2.1	100	103
Quetiapine oral (IR) 25 mg nocte	0.1		3	
Aripiprazole oral 10 mg mane	0.7	2.1	33	146
Aripiprazole depot 400 mg every 4 weeks	1.1		100	
Olanzapine oral 2.5 mg nocte	0.3		13	
Olanzapine oral 5 mg BD	1.0	2.0	50	100
Paliperidone oral 6 mg nocte	1.0		50	
Paliperidone depot 100 mg every 4 weeks	1.4	1.9	67	92
Quetiapine oral (IR) 100 mg BD	0.5		25	

Table 2 (continued)

Antipsychotic combination[a]	Proportion of WHO DDD	Total DDD	Percentage of MLDD (%)	Percentage of MLDD (%) (combined)
Amisulpride oral 200 mg mane, 100 mg noon, 400 mg nocte	1.8	1.9	58	64
Quetiapine oral (IR) 50 mg nocte	0.1		6	
Aripiprazole depot 400 mg every 4 weeks	1.1	1.8	100	125
Lurasidone oral 40 mg nocte	0.7		25	
Aripiprazole 400 mg every 4 weeks	1.1	1.8	100	125
Chlorpromazine oral 200 mg nocte	0.7		25	
Quetiapine oral (IR) 50 mg mane	0.1	1.8	6	125
Quetiapine oral (XR) 150 mg nocte	0.4		19	
Risperidone depot 50 mg every 2 weeks	1.3		100	
Amisulpride oral 50 mg mane, 100 mg nocte	0.4	1.7	13	113
Risperidone depot 50 mg every 2 weeks	1.3		100	
Aripiprazole depot 400 mg every 4 weeks	1.1	1.6	100	125
Quetiapine oral (IR) 200 mg nocte	0.5		25	
Haloperidol oral 2.5 mg nocte (weaning)	0.3	1.4	3	53
Paliperidone depot 75 mg every 4 weeks	1.1		50	
Amisulpride oral 100 mg BD	0.5	0.9	17	37
Flupenthixol depot 40 mg every 4 weeks	0.4		20	

[a]Nocte, each night; mane, each morning; BD, twice each day; XR, extended release; IR, immediate release

Discussion

Antipsychotic polypharmacy was prescribed for 39.0% of patients with schizophrenic and schizoaffective illnesses in this study. Of these, 96.7% were prescribed antipsychotic regimens amounting to a combined DDD greater than one, and 80% were prescribed antipsychotic regimens in excess of 100% of MLDDs when combined. Previous studies have evaluated the frequency of antipsychotic polypharmacy in Australia and overseas; notably the study by John et al. in 2010 at another Australian public psychiatric facility and the multi-centred quality improvement initiative led by the UK Prescribing Observatory for Mental Health (POMH-UK) in 2006 [12, 13]. The frequency of antipsychotic polypharmacy was approximately 43% in both studies, though larger sample sizes, amongst other differences in study design were noted [12, 13]. These results are overall consistent with the findings from this study, reinforcing that antipsychotic polypharmacy continues to be practised by prescribers across multiple institutions and geographical locations [12, 13].

These previous studies however, only explored the frequency but not the magnitude of antipsychotic polypharmacy. The DDD is a useful tool for quantifying antipsychotic load; a measurable parameter that considers the various antipsychotics prescribed in a standardised manner. Almost all patients (96.7%) in this study who were prescribed antipsychotic polypharmacy had a combined DDD greater than one, with half of this cohort being prescribed individual antipsychotics at a dose below one DDD. Whilst the DDD does not necessarily reflect the MLDD of a drug, it is indicative of the dose needed to elicit a therapeutic response [15]. The MLDD has been quantified in the same way as DDD, but occurs near the upper end of the dose response curve where higher doses may add less therapeutically, but more in terms of toxicity. However, with one-third of the polypharmacy cohort being prescribed individual antipsychotics at doses below the MLDD, the findings from this study raise the question of whether the doses of individual antipsychotics were optimised before the decision was made to prescribe an additional antipsychotic [15].

These findings also indicate that none of these 30 patients was prescribed antipsychotics at individual doses that exceeded their MLDD. However, when the overall regimen was considered, 80% of these patients had an antipsychotic load that exceeded the 100% MLDD value when combined. This may indicate a lack of prescriber awareness or consideration of the additive nature of antipsychotic polypharmacy. Alternatively, the decision to prescribe polypharmacy over high dose monotherapy may reflect the medicolegal concerns of prescribers with overstepping licensed use. Registered product information includes well defined MLDDs based on research conducted by the manufacturer, while clinical practice guidelines are non-mandated, being best practice recommendations only. This is further supported by results from the monotherapy cohort, which indicated that only one patient was prescribed an antipsychotic in a dose that exceeded its MLDD.

Approximately one-third of patients prescribed polypharmacy had a defined rationale for combining antipsychotics documented in their medical record. The RANZCP, amongst other global organisations, recognises that polypharmacy may be clinically indicated "if an adequate response is not achieved after monotherapy treatment trials of two antipsychotic agents given separately at therapeutic doses" [3]. It is unclear whether the cited incidences of poor symptom control in this study were appropriate reasons for prescribing polypharmacy, as this study did not explore the prescribing origins of individual antipsychotics to establish if monotherapy was adequately trialled or optimised before combining treatment. There may be valid reasons for not prescribing higher doses, such as dose-limiting adverse effects; a factor that remains unclear as it was not documented or reported in approximately half of the medical records examined. In contrast, the combining of antipsychotics at less than maximum recommended doses may have been a deliberate strategy by prescribers to overcome the need to utilise high doses of individual agents. Prescribers may be of the mindset that lower doses are associated with less adverse effects, not recognising the underlying toxicity (burden) of polypharmacy, as evidenced by the overall DDD or combined MLDD values. Recently, a lower risk of rehospitalisation has been reported with the specific combination of clozapine plus aripiprazole [7]. This combination was only prescribed for two of the patients in this study. It will take some time for this to be considered for prescribing guidelines in Australia or internationally.

Communication gaps impacting on continuity of care were identified in this study. This is largely related to the fact that different medical staff are treating patients in the inpatient and outpatient settings. Even within the same setting, the periodic rotation of medical staff between sites also contributes to patients being reviewed by different medical officers on each encounter. As evidenced in this study, unclear documentation of management plans (such as the proposed future weaning of polypharmacy) can be easily overlooked when a new medical officer, who is less familiar with the patient's history, takes over care.

Whilst not documented, there may be other factors contributing to polypharmacy, such as the impact of drug interactions, particularly those involving the cytochrome (CYP) P450 system [1]. Tobacco smoking, as an inducer of CYP1A2, can reduce the efficacy of CYP1A2 substrates, such as olanzapine and clozapine [1]. The perceived suboptimal response to monotherapy may trigger additional antipsychotic prescribing, thus polypharmacy. It is unknown how many patients in this study were smokers, as this was not consistently documented in medical records. A 2012 survey by Cooper et al. however, predicted smoking prevalence to be 71% and 59% in males and females with schizophrenia, respectively, suggesting that smoking may contribute to polypharmacy in a notable percentage of this population [3, 20].

Strengths and limitations

Despite its relatively small sample size, the strengths of this study lie in the process of comprehensive medical record review to explore the prevalence and reasons for antipsychotic polypharmacy, and the novel approach of using both DDD and MLDD to define the associated burden. The prevalence may have been underestimated as the medical records typically contained only details of medications prescribed at the study site. Patients may consult more than one doctor, where duplication in antipsychotic prescribing may unknowingly occur. Polypharmacy may have been further underestimated as "when required" antipsychotic use was not considered, due to the unreliable documentation of actual usage frequency in outpatients. If patients were utilising "when required" antipsychotics

on a daily basis, this would not differ from prescribing two (sometimes more) antipsychotics as maintenance therapy. Furthermore, this study only evaluated medications prescribed and did not assess compliance, as this was not routinely reported in the medical record, nor were patients directly questioned by the authors. Prescribers were not questioned about the factors contributing to polypharmacy, therefore limiting findings about prescribing rationale. Unlike DDD, where it is well established that values are additive, combining the proportions of MLDDs has not been validated. The purpose of performing that analysis was to identify if additional insight regarding prescribing could be elicited from its use, to help better inform prescribing practices.

Conclusion

The prevalence of antipsychotic polypharmacy at the study site was 39%. Consideration of DDD and combined MLDDs suggested a reluctance among prescribers to prescribe any antipsychotic at a dose exceeding its MLDD, not recognising that the burden of multiple antipsychotics (potentially at relatively low doses each) is cumulative. With suboptimal documentation of prescribing rationale, it was challenging to assess what proportion of polypharmacy was justified. Future research will employ other methodologies to further understand why and how antipsychotic polypharmacy occurs. "Quantifying" polypharmacy with DDD data and combined MLDDs, as opposed to simply reporting that it occurs, may evoke greater recognition amongst prescribers, prompting them to consider their practices and the hidden burden of multiple antipsychotic prescribing. These findings will be presented in focus group discussions, where the aim is to collaborate with mental health stakeholders to collectively formulate strategies to address polypharmacy; ensuring that when polypharmacy occurs, it conforms to best-practice guidelines.

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Conflicts of interest The authors declare that there is no conflict of interest.

Appendices

Appendix 1

See Table 3.

Table 3 DDD values of the antipsychotics evaluated [15]

Antipsychotic	Dosage formulation/ route of administration	WHO DDD
Amisulpride	Oral	0.4 g
Aripiprazole	Oral	15 mg
	Depot	13.3 mg
Chlorpromazine	Oral	0.3 g
Clozapine	Oral	0.3 g
Flupenthixol	Depot	4 mg
Haloperidol	Oral	8 mg
	Depot	3.3 mg
Lurasidone hydrochloride	Oral	60 mg
Olanzapine	Oral	10 mg
Paliperidone	Oral	6 mg
	Depot	2.5 mg
Quetiapine	Oral	0.4 g
Risperidone	Oral	5 mg
	Depot	2.7 mg
Zuclopenthixol	Oral	30 mg
	Depot	15 mg

Extracted from World Health Organisation (WHO). ATC/DDD Index 2017 Norway: WHO; 2016 [cited 2017 Apr 6]. Available from: https://www.whocc.no/atc_ddd_index

Appendix 2

See Table 4.

Table 4 MLDD values of antipsychotics evaluated [18]

Antipsychotic	Route/formulation	MLDD
Aripiprazole	Oral	30 mg each day
Aripiprazole	Depot	400 mg every 4 weeks
Chlorpromazine	Oral	800 mg each day
Clozapine	Oral	900 mg each day
Flupenthixol	Depot	100 mg every 2 weeks
Haloperidol	Oral	100 mg each day
Haloperidol	Depot	300 mg every 4 weeks (10.7 mg per day)
Lurasidone	Oral	160 mg each day
Olanzapine	Oral	20 mg each day
Paliperidone	Oral	12 mg each day
Paliperidone	Depot (4 weekly formulation)	150 mg every 4 weeks
Quetiapine	Oral	800 mg each day
Risperidone	Depot	50 mg every 2 weeks
Zuclopenthixol	Depot	400 mg every 2 weeks

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