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Check the effects: systematic assessment of antipsychotic side-effects in an inpatient cohort

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Abstract

Background: Antipsychotics are associated with a range of side-effects that can influence patients' subjective well-being negatively resulting in poor adherence. In order to limit the negative consequences of side-effects, they should be regularly systematically assessed. The aim of this study was to systematically assess antipsychotic side-effects in an inpatient cohort using validated rating scales.

Methods: Eligible individuals prescribed an antipsychotic for at least 2 weeks were invited to have their side-effects assessed systematically.

Results: A total of 208 individuals were assessed systematically for antipsychotic side-effects; 71.5% ($n = 138$) stated that they had not reported side-effects to their clinician prior to the assessment. The most commonly reported side-effects were daytime drowsiness (75%), dry mouth (58.2%) and weight gain (50.0%), while the most distressing side-effects reported were erectile dysfunction (35.0%), sexual dysfunction (26.3%) and amenorrhoea (26.3%). There was no evidence of an association between side-effect severity/number of side-effects reported/distress caused by those taking high dose/combination antipsychotics *versus* standard dose monotherapy.

Conclusion: Side-effects must be regularly and systematically assessed using a validated rating scale. As distress caused by side-effects plays a major role in non-adherence, assessment should examine distress and data on distressing side-effects should be available to those choosing an antipsychotic. Given the lack of correlation between high dose/combination antipsychotics and side-effects, treatment should be tailored to the individual based on response/tolerance and dose reduction/avoidance of polypharmacy should not be recommended to minimise side-effects.

Keywords: adverse effects, atypical antipsychotic agent, drug monitoring, questionnaire, checklist, adherence

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Introduction

Side-effects and adherence to antipsychotics

People diagnosed with a serious mental illness such as psychosis, schizophrenia, schizoaffective and bipolar disorders are frequently prescribed antipsychotic medicines. However, antipsychotics are associated with a varying range of potential side-effects, which can include extra pyramidal side-effects (EPSEs), sedation, weight gain, metabolic disturbance, sexual dysfunction, urinary effects, gastrointestinal effects and symptoms of prolactin elevation (e.g. menstrual irregularities, galactorrhoea).[1–3] These side-effects can impair quality of life, be associated with distress and stigma and lead to physical morbidity (and mortality in rare cases).[1,2] In addition, antipsychotic side-effects can influence patients' attitudes and subjective well-being negatively, resulting in poor adherence to treatment.[4,5] In fact, the prevalence of non-adherence to antipsychotics is high, with up to 80% of those prescribed antipsychotic

medicine stopping it prematurely.[4,5] The impact of non-adherence on patient outcome is marked and is reported to be one of the most powerful predictors of relapse resulting in rehospitalisation and longer hospital admission.[2,6–8] For those with schizophrenia, non-adherence results in a five-fold increase in relapse rates, while suicide rates are increased five-fold in those with bipolar disorder who do not take their medicine as agreed.[9,10]

Systematic assessment of side-effects

In order to limit the negative consequences of side-effects and optimise patient outcomes, clinicians should regularly monitor side-effects and offer appropriate interventions.[8] Patients may be reluctant to openly report certain side-effects, especially those of an intimate or embarrassing nature, such as sexual dysfunction, constipation and urinary frequency.[11] They may also under-report antipsychotic side-effects as a result of misattribution of symptoms or forgetfulness.[11] The number of side-effects elicited will be greater with a structured assessment tool compared with spontaneous reporting or open questioning about side-effects.[12,13] Thus, routine monitoring using systematic enquiry (ideally using a validated rating scale) is recommended by many international guidelines.[3,14–16] Among current validated scales, the Glasgow Antipsychotic Side-effects Scale (GASS) is one of the most practical for clinical use.[17] It is patient-completed, relatively short, global in its coverage, and rates both the frequency and distress of each item.[2,17] It is a 22-question self-rating scale for detecting second generation antipsychotic side-effects, validated in a community population against the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS).[17] The GASS for Clozapine (GASS-C) is a 16-question self-report side-effects scale for patients on clozapine therapy adapted from the GASS and validated in a community population against the original GASS.[18] The use of rating scales over time ensures that information about the same experiences is collected at each administration and helps avoid omission of key elements of information needed to guide treatment.[3]

Distress caused by side-effects

Once side-effects have been identified using the appropriate rating scale, they may be addressed accordingly. As it is the subjective impact, i.e., the distress caused by side-effects, rather than an objective rating of severity as assessed by a clinician that is particularly relevant to adherence, management of side effects is best decided in partnership with the patient and should prioritise those that are causing distress or discomfort.[2,4] Side-effects causing little distress may not warrant any change to treatment but ongoing monitoring would be appropriate. For distressing side-effects, interventions such as antipsychotic dose reduction, switching medications, implementing lifestyle interventions or commencing a treatment to counter the side-effect in question may be implemented.[2,8,15]

While regular, systematic and comprehensive assessment of antipsychotic side-effects is part of good clinical care, it is uncommon in practice.[2,15] A 2010 United Kingdom (UK) national audit of 6000 patients prescribed an antipsychotic depot found that 35% had no documented assessment of side-effects in the preceding 12 months.[15] This study set out to systematically assess antipsychotic side-effects in an inpatient cohort using the GASS or GASS-C.

Methods

Ethics statement

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the Saint John of God Hospitaller Services Ethics Committee (ID-627).

Study design

This was a prospective cohort study carried out at an independent (not-for-profit) acute psychiatric hospital in Dublin, Ireland that provides a range of both inpatient and outpatient specialist mental health services. Data were gathered over two time periods from October 2015 to January 2016 and again from September 2016 to January 2018.

Setting

The study took place among three inpatient mental health teams over two inpatient suites at an independent acute inpatient mental health facility.

Participants

The inclusion criteria were individuals over 18 years who were admitted to the inpatient setting for a community mental health service with a catchment area population of over 175,000 and prescribed a

regular antipsychotic medicine. The exclusion criteria were inpatients under the care of the community mental health service, who were not prescribed a regular antipsychotic medicine and those who declined to complete the side-effects assessment.

Eligible individuals were identified on a weekly basis following a medication chart and electronic patient record review. Those prescribed an antipsychotic medicine on a regular basis for at least 2 weeks were invited to have their antipsychotic side-effects assessed systematically. For those who declined to participate in the assessment, a note was made in their electronic patient record to this effect. Only those who agreed to participate in the assessment were included in the study and verbal consent to participate was witnessed and formally recorded. While the GASS and GASS-C are self-report scales, the principal investigator facilitated the completion of the scale to all participants to ensure timely (approximately 5 min to complete together) and appropriate completion and to provide information and support to participants as appropriate.

Assessments were carried out either in the inpatient suite where the participant was staying (in a private space) or in the consultation room in the pharmacy department, and took approximately 5 min to complete. On completion of the assessment, the side-effects reported were documented in the participant's electronic health record and interventions to minimise side-effect burden were provided to the treating clinicians as appropriate.

For those who reported distressing side-effects, a reassessment was carried out after 4 weeks to establish if side-effects had improved.

Statistical analysis

Statistical analyses were performed using SPSS for Windows version 25. The correlation between antipsychotic dose and side-effect severity was assessed using Spearman's correlation coefficient. The correlation between the severity of side-effects and the number of side-effects reported by those on high dose *versus* standard dose antipsychotics and combination antipsychotic *versus* monotherapy was assessed using Fisher's exact test. The correlation between distress caused by high dose *versus* standard dose antipsychotic and combination *versus* monotherapy was assessed using Pearson's chi-squared test.

Results

Demographic data

A total of 208 individuals were assessed systematically for antipsychotic side-effects using the GASS ($n = 185$) or GASS-C ($n = 23$). Participants had a primary diagnosis of schizophrenia, schizoaffective disorder, psychosis, bipolar disorder or major depressive disorder. The median age of participants was 42 years old (range 18–81 years; SD = 13.314); 56.3% ($n = 117$) participants were male and 43.7% (91) were female.

Of those who completed the side-effects assessment, only 28.5% ($n = 55$) stated that they had already reported side-effects to their clinician, whereas 71.5% ($n = 138$) stated that this was their first time discussing side-effects.

Antipsychotics prescribed

A total of 15 different antipsychotics were prescribed to the 208 participants. The most commonly prescribed antipsychotic was olanzapine, with nearly half of all participants prescribed this antipsychotic (46.6%). This was followed by quetiapine (21.2%) and then haloperidol (12.0%). Clozapine, paliperidone, risperidone were prescribed for 11.1% ($n = 23$), 10.1% ($n = 21$) and 10.1% ($n = 21$) of participants, respectively, whereas aripiprazole [8.7% ($n = 18$)], amisulpride [4.8% ($n = 10$)], zuclopenthixol [3.4% ($n = 7$)], sulpiride [2.4% ($n = 5$)], chlorpromazine [1.9% ($n = 4$)], asenapine [1.4% ($n = 3$)], pipothiazine [1.0% ($n = 2$)], flupenthixol [0.5% ($n = 1$)] and perphenazine [0.5% ($n = 1$)] were each prescribed to less than 10% of participants.

Concomitant medicines

Of the 208 participants, 14.4% ($n = 30$) were prescribed antipsychotic therapy only and 85.6% ($n = 178$) were also taking other mental and physical health medicines. Lorazepam was the most commonly prescribed concomitant medicine with 26.9% ($n = 56$) of participants taking it, followed by zopiclone [24.0% ($n = 50$)] and valproate [14.9% ($n = 31$)]. Other concomitant medicines included clonazepam [12.5% ($n = 26$)], lithium [12.5% ($n = 26$)], venlafaxine [12.5% ($n = 26$)], zolpidem [9.6% ($n = 20$)], promethazine [9.1% ($n = 19$)], atorvastatin [8.7% ($n = 18$)] and lamotrigine [7.7% ($n = 16$)].

Side-effects reported

The most commonly reported side-effects were daytime drowsiness (75%), dry mouth (58.2%), weight gain (50.0%), polydypsia/polyuria (48.1%) and akathisia (45.7%) (Table 1).

Table 1. Most commonly reported side-effects.

Side-effect	Frequency
Daytime drowsiness	75.0% ($n=156$)
Dry mouth	58.2% ($n=121$)
Weight gain	50.0% ($n=104$)
Polydypsia/polyuria	48.1% ($n=100$)
Akathisia	45.7% ($n=95$)
Sedation	44.7% ($n=93$)
Dizziness/hypotension	40.9% ($n=85$)
Bradykinesia	39.9% ($n=83$)
Tremor	34.6% ($n=72$)
Tachycardia	29.3% ($n=61$)
Hypersalivation	29.3% ($n=61$)
Blurred vision	27.4% ($n=57$)
Dystonia	26.9% ($n=56$)
Nausea/vomiting	26.0% ($n=54$)
Urinary retention	15.9% ($n=33$)
Nocturnal enuresis	11.1% ($n=23$)
Tardive dyskinesia	10.6% ($n=22$)
Erectile dysfunction	9.6% ($n=20$)
Sexual dysfunction	9.1% ($n=19$)
Amenorrhoea	9.1% ($n=19$)
Hyperprolactinaemia	7.7% ($n=16$)
Polydypsia	6.7% ($n=14$)
Constipation	6.3% ($n=13$)
Myoclonus	4.3% ($n=9$)
Reflux/Heartburn	3.8% ($n=8$)
Polyuria	3.8% ($n=8$)
Galactorrhoea	1.9% ($n=4$)

Of those prescribed antipsychotic monotherapy, only those on olanzapine had enough data to identify the most commonly reported side-effects. Daytime drowsiness [66.7% ($n=44$)], dry mouth [66.7% ($n=44$)], polyuria/polydypsia [59.1% ($n=37$)], weight gain [48.5% ($n=32$)] and akathisia [47.0% ($n=31$)] were the most commonly reported side-effects of olanzapine.

Distress caused by antipsychotic side-effects

A total of 28.8% ($n=60$) of participants reported distressing side-effects (Table 2). The most distressing side-effect reported by participants was erectile dysfunction (35.0%), sexual dysfunction (26.3%), amenorrhoea (26.3%), galactorrhoea (25.0%) and sedation (21.5%).

The most distressing side-effects reported by those taking olanzapine were sexual dysfunction [66.7% ($n=4$)], erectile dysfunction [50.0% ($n=4$)], weight gain [25.0% ($n=8$)], amenorrhoea [16.7% ($n=1$)] and sedation [15.4% ($n=4$)].

Relationship between antipsychotic dose and side-effect severity

There was no correlation between antipsychotic dose (expressed as a percentage of the maximum licensed dose according to the manufacturers' summary of product characteristics) and side-effect severity (expressed as a percentage of total side-effect score) with Spearman's correlation coefficient = 0.081 ($p<0.001$) (0.00–0.19 = very weak correlation) (Figure 1).

High dose and combination antipsychotics

A total of 68.8% ($n=143$) of participants were prescribed a single regular antipsychotic, whereas 26.9% ($n=56$) were prescribed two antipsychotics and 4.3% ($n=9$) were prescribed three antipsychotics. A total of 20.2% ($n=42$) of participants were prescribed high dose antipsychotic therapy, 19.2% ($n=40$) of which were as a result of a combination of more than one antipsychotic. A total of 31.3% ($n=65$) participants were prescribed combination antipsychotic therapy.

High dose and combination antipsychotics and side-effect severity

There was no evidence of an association between the severity of side-effects reported by those taking

Table 2. Most distressing side-effects reported.

	% reporting distress
Erectile dysfunction	35.0% ($n=7$)
Sexual dysfunction	26.3% ($n=5$)
Amenorrhoea	26.3% ($n=5$)
Galactorrhoea	25.0% ($n=1$)
Sedation	21.5% ($n=20$)
Urinary retention	21.2% ($n=7$)
Constipation (Clozapine only)	15.4% ($n=2$)
Dystonia	14.3% ($n=8$)
Blurred vision	14.0% ($n=8$)
Weight gain	13.5% ($n=14$)
Tachycardia	13.1% ($n=8$)
Nocturnal enuresis	13.0% ($n=3$)
Akathisia	12.6% ($n=12$)
Dizziness/hypotension	11.8% ($n=10$)
Nausea/vomiting	11.3% ($n=6$)
Daytime drowsiness	10.9% ($n=17$)
Dry mouth	10.7% ($n=13$)
Tremor	9.7% ($n=7$)
Polydypsia/polyuria	9.0% ($n=9$)
Hyperprolactinaemia	6.3% ($n=1$)
Bradykinesia	6.0% ($n=5$)
Hypersalivation	4.9% ($n=3$)
Tardive dyskinesia	4.5% ($n=1$)

high dose antipsychotic therapy (mild, moderate or severe) and those taking a standard antipsychotic dose with the Pearson's chi-square = 0.455 ($p < 0.001$) (weak correlation) (Table 3). There was also no evidence of an association between the severity of side-effects reported by those taking combination antipsychotic therapy (mild, moderate or severe) and those taking a monotherapy

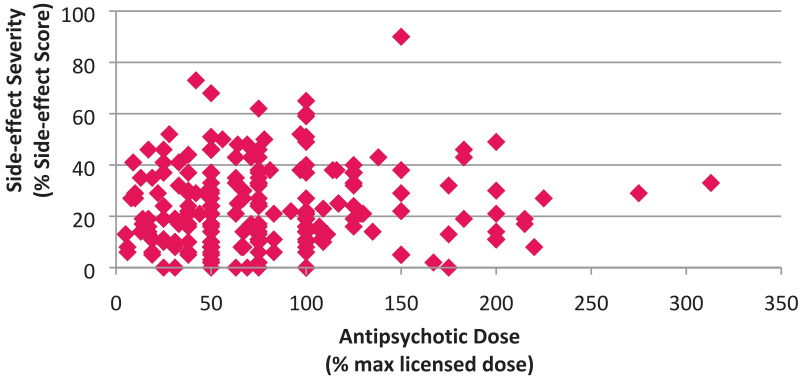

Figure 1. Side-effect severity *versus* antipsychotic dose.

with the Pearson's chi-square = 0.244 ($p < 0.001$) (weak correlation).

High dose and combination antipsychotics and number of side-effects reported

There was no evidence of an association between the number of side-effects reported by those taking high dose antipsychotic therapy (0–10, 11–20) and those taking a standard antipsychotic dose with Pearson's chi-square = 0.301 ($p < 0.001$) (weak correlation) (Table 4). There was also no evidence of an association between the number of side-effects reported by those on combination antipsychotic therapy and those on monotherapy with the Pearson's chi-square = 0.278 ($p < 0.001$) (weak correlation).

High dose and combination antipsychotics and distress

There was no evidence of an association between the distress caused by side-effects reported by those taking high dose antipsychotic therapy and those taking a standard antipsychotic dose with Pearson's chi-square = 0.002 ($p < 0.001$) (no correlation). A total of 28.5% ($n = 12$) of those prescribed high dose antipsychotic therapy reported distressing side-effects *versus* 28.9% ($n = 48$) of those prescribed a standard dose. Similarly, there was no evidence of an association between the distress caused by side-effects reported by those prescribed combination antipsychotic therapy *versus* those prescribed monotherapy with Pearson's chi-square = 0.170 ($p < 0.001$) (weak correlation); 30.8% ($n = 20$) of those prescribed combination antipsychotic therapy reported distressing side-effects *versus* 28.0% ($n = 40$) of those prescribed monotherapy.

Table 3. Side-effect severity for high dose *versus* standard dose antipsychotics and combination *versus* monotherapy.

Severity of side-effects	High dose antipsychotics *n* (%)	Standard dose *n* (%)	Combination Antipsychotics *n* (%)	Monotherapy *n* (%)	Total *n* (%)
Mild (0–33)	*n* = 33 (78.6%)	*n* = 122 (73.5%)	*n* = 47 (72.3%)	*n* = 108 (75.5%)	*n* = 155 (74.5%)
Moderate/severe (34–67/68–100)	*n* = 9 (21.4%)	*n* = 44 (26.5%)	*n* = 18 (27.7%)	*n* = 35 (24.5%)	*n* = 53 (25.5%)
Total	*n* = 42 (100%)	*n* = 166 (100%)	*n* = 65 (100%)	*n* = 143 (100%)	*n* = 208 (100%)

Table 4. Number of side-effects for high dose *versus* standard dose antipsychotics and combination *versus* monotherapy.

Number of side-effects	High dose antipsychotics *n* (%)	Standard dose *n* (%)	Combination antipsychotics (*n* %)	Monotherapy *n* (%)	Total *n* (%)
0–10	*n* = 25 (59.5%)	*n* = 91 (54.8%)	*n* = 38 (58.4%)	*n* = 78 (54.5%)	*n* = 116 (55.7%)
11–20	*n* = 17 (40.5%)	*n* = 75 (45.2%)	*n* = 27 (41.6%)	*n* = 65 (45.5%)	*n* = 92 (44.3%)
Total	*n* = 42 (100%)	*n* = 166 (100%)	*n* = 65 (100%)	*n* = 143 (100%)	*n* = 208 (100%)

Distress following reassessment

Of the 60 participants who reported distressing side-effects on initial assessment, only 26.7% ($n = 16$) completed the reassessment. A total of 67.7% ($n = 43$) participants were discharged from hospital before the reassessment could be carried out and 1.7% ($n = 1$) participant declined reassessment. Just over 4% (4.3%, $n = 9$) of those who reported distress on initial assessment did not report distress on reassessment whereas just over 3% (3.4%, $n = 7$) reported distressing side-effects on reassessment.

Discussion

Key results

This study describes the systematic assessment of antipsychotic side-effects in an inpatient cohort. While antipsychotic medicines are effective at managing symptoms of a range of serious mental illnesses, their use is limited by high rates of non-adherence.[4,5,19] Antipsychotic side-effects (especially those that lead to distress) impact adherence negatively but are underreported. The data in this study highlight the importance of using systematic assessment when eliciting antipsychotic side-effects given that current *ad hoc* methods are missing over 70% of side-effects experienced. The data also describes the importance of distress caused by antipsychotic side-effects in addition to side-effect frequency considering the impact of distressing side-effects on adherence. Finally, the relationship between antipsychotic dose/antipsychotic polypharmacy and side-effect severity/number of side-effects reported/distress caused were also examined in this study and found to have no correlation. This highlights the need for effective strategies to reduce antipsychotic side-effect burden as simply reducing the dose or avoiding polypharmacy may not work given the lack of dose-response demonstrated.

Systematic side-effects assessment

Antipsychotic medicines are associated with a range of subjectively unpleasant side-effects that can impact negatively on the patient's experience of taking these medicines. This negative experience can shape their relationship with antipsychotic medicine for the duration of their treatment, which, for a chronic and enduring mental illness such as schizophrenia, schizoaffective or bipolar disorders, may be life-long. Those presenting with antipsychotic side-effects and those with past experience of side-effects have significantly more negative general attitude toward antipsychotics, which has a durable impact on adherence.[5] Intervening in the early stages of antipsychotic treatment to address and minimise antipsychotic side-effects is therefore a clinical priority in order to reduce the risk of a negative antipsychotic experience.

Antipsychotic side-effects cannot be addressed and minimised if they are not recognised.[13] There are varying methods of eliciting side-effects

including spontaneous reporting by patients, open questioning by clinicians and systematic assessment using a validated rating scale. Patients may be reluctant to spontaneously report intimate or embarrassing side-effects.[11] In addition, side-effects may go underreported as a result of misattribution of symptoms to the antipsychotic medicine or forgetfulness.[11] Spontaneous reporting of side-effects is therefore not a reliable resource on which to establish the experience of side-effects. Open questioning by clinicians also falls short in this regard as there is a difference in perception of side-effects between patients and clinicians.[20,21] Clinicians may not enquire about all of the relevant side-effects, as a key source of information with regard to side-effects is their own clinical experience of those identified in their patients and their shared experience of their peers.[22] However, such information may be skewed by selective patient reporting.[22] Systematic assessment using a validated rating scale is considered the gold standard when identifying the experience of antipsychotic side-effects. It is reported to elicit significantly more side-effects compared with open questioning (649 *versus* 61) and is recommended by international guidelines.[3,13–16]

The importance of systematic assessment is clearly demonstrated in this study where nearly three quarters of participants (71% $n=138$) stated that the systematic side-effects assessment administered to them was their first time reporting side-effects of their antipsychotic medicine. Using a validated rating scale such as the GASS or GASS-C after 2 weeks of regular antipsychotic treatment as occurred in this study, ensures a reliable picture of side-effect experience early in treatment for those newly commenced on the medicine. It also ensures those continuing with existing antipsychotic treatment in the inpatient setting have access to ongoing side-effect monitoring. This facilitates the implementation of interventions to reduce or minimise side-effects thus improving the antipsychotic experience at the earliest possible interval (for those newly commenced on treatment) and reducing the risk of a negative attitude towards medicine developing. In addition, while the GASS and GASS-C are both self-report scales, administration by a healthcare professional (in this case a specialist mental health pharmacist), ensured that all questions on the scales were appropriately understood and that information, support and reassurance were provided when distressing side-effects were reported.

Identifying distressing side-effects

Data on the incidence and frequency of antipsychotic side-effects is available from a range of sources, including randomised controlled trials (RCTs), naturalistic studies and post-marketing surveillance.[23] While each data source has its own strengths and weaknesses, there is inconsistent reporting of side-effects across studies and it can be difficult to establish the relative propensity of individual antipsychotics to cause specific side-effects.[22,23] In addition, individuals may have wide variation in their susceptibility to develop particular side-effects.[1] As a result, it may be difficult to predict in advance of treatment with a particular antipsychotic, the individual risk of side-effects. This may impact antipsychotic choice as there is a consensus that the most important consideration when helping a person make a decision about antipsychotic treatment is the side-effect profile of the medicine.[24]

In addition to these inconsistencies in side-effect reporting and frequency data, the impact of side-effects on those taking antipsychotics has not been sufficiently studied which further blurs the side-effect picture.[23] While antipsychotic side-effects are known to impact antipsychotic medicines adherence negatively, it is in fact the distress caused by side-effects rather than an objective measure of severity that is most relevant for adherence and quality of life.[2]

In this study, the most commonly reported side-effects of olanzapine (monotherapy) were daytime drowsiness, dry mouth, polydypsia/polyuria, weight gain and akathisia, whereas the most distressing side-effects were sexual dysfunction, erectile dysfunction, weight gain, amenorrhoea and sedation. These results are in line with other data reporting that, subjectively, sexual dysfunction is rated as one of the most distressing of the antipsychotic side-effects.[5] If an individual were to choose olanzapine using only the frequency data (i.e. the list of side-effects detailed on the patient information leaflet), their decision may be quite different than if they were also provided with the data on the most distressing side-effects reported with olanzapine. For example, those who see that drowsiness is likely to occur with olanzapine may opt for an alternative unless they are made aware that this side-effect is not reported to cause distress in others taking the medicine. While distress is clearly a subjective measure and will therefore vary from individual to individual, in order to provide a broader picture of the experience of taking an antipsychotic to those choosing their medicine,

information on both frequency and distress would be beneficial. In addition, once the antipsychotic has been commenced, treatment should be accompanied by regular systematic assessment – eliciting both frequency of and distress caused by side-effects – to ensure distressing side-effects are identified and managed early on, thus minimising their impact on adherence and quality of life.

High dose and combination antipsychotic prescribing

High dose antipsychotic treatment (HDAT) is defined as the prescription of either a single antipsychotic at a dose above the upper limit or two or more antipsychotics concomitantly that when expressed as a percentage of their respective maximum dose, and, added together, result in a cumulative dose of more than 100% (excluding clozapine).[25] Prescribing a 'high dose' is likely to exceed the acceptable risk-benefit ratio for the medicine(s) and constitutes off-label use.[25] While there is no firm evidence that the prescription of HDAT is more effective than standard doses, approximately 25–33% of hospital inpatients and 10% of community-based patients have been reported to be prescribed a high dose.[25–27] The HDAT prescribing rates reported in this study are therefore slightly below international rates at 20.2%. In spite of the lack of evidence for HDAT, from a pharmacological perspective, there may be a clinical rationale for higher doses of antipsychotics in certain circumstances due to individual patient differences in pharmacokinetics and pharmacodynamics.[25]

Combination antipsychotic therapy or antipsychotic polypharmacy results from the prescription of two or more antipsychotic medicines. The combination may or may not exceed the upper limit, i.e. it may or may not qualify as HDAT. Antipsychotic polypharmacy is currently discouraged by many international guidelines.[14,16] However, recent evidence demonstrates that in general, polypharmacy was associated with an approximately 10% lower relative risk of rehospitalisation compared with antipsychotic monotherapy.[28] Lower mortality rates have also been reported with combination antipsychotic therapy compared with monotherapy.[28–31]

Although not routinely recommended, the use of antipsychotics at high doses or in combination with another antipsychotic is sometimes required to treat people who have had an inadequate response to standard doses of a single antipsychotic.[32] While there is clearly some rationale for these prescriptions, they are not without risk. As the majority of antipsychotic side-effects such as drowsiness, sedation, cardiovascular side-effects, EPSEs and anticholinergic effects are dose-related, HDAT is reported to be associated with an increased risk of side-effects.[1,32] In addition, with the varying receptor profiles of different antipsychotics, the use of combination therapy is associated with an increased range and exacerbation of side-effects.[33] However, the opposite was demonstrated in this study. Those prescribed high dose and/or combination antipsychotics did not report more severe side-effects compared with those on standard doses and/or monotherapy. They also did not report an increased number of side-effects compared with their standard dose/monotherapy counterparts or more distressing side-effects. This demonstrates that it may not be possible to predict antipsychotic tolerance based on the dose or the number of antipsychotics prescribed. Treatment should therefore be tailored to individual need and side-effects should be routinely assessed systematically to establish the risk-benefit ratio between tolerance and response. In addition, the management of antipsychotic side-effects should incorporate strategies outside of dose reduction and avoidance of polypharmacy (which are common first line recommendations).[19] The lack of dose-response suggested in this study means that reducing the antipsychotic dose or prescribing antipsychotic monotherapy may not decrease the side-effect burden and other strategies should therefore be employed.

Study limitations

The GASS and GASS-C were administered to inpatients at an acute phase of their mental illness after 2 weeks of continued antipsychotic treatment. Only those who agreed to have their side-effects assessed were included in the study. Those that declined to participate ($n = 24$) (through completion of the GASS or GASS-C) were therefore excluded. As a result, the data gathered does not represent all of those prescribed antipsychotic medicine at the time of completion of the study, which is a limitation of the results.

As over 85% of participants were prescribed concomitant mental and physical health medicines

along with their antipsychotic, it is possible that side-effects reported may not be solely attributable to the antipsychotic in question. In addition, some participants may have also been receiving electroconvulsive therapy (ECT), details of which were not gathered. While each participant was made aware that the checklist referred to the side-effects of their antipsychotic medicine only, side-effects reported and the associated severity and distress may have been confounded by concomitant medicines and/or ECT, which is a limitation of the study results.

The GASS and GASS-C are both self-report side-effects scales. However, to facilitate appropriate completion and provide support and information to participants on side-effects reported, they were administered to participants by a specialist mental health pharmacist. Side-effects reported may therefore not accurately reflect the complete patient experience, as participants may have been reluctant to report embarrassing side-effects directly to the specialist mental health pharmacist. Of note, side-effects such as urinary retention, erectile dysfunction, sexual dysfunction, amenorrhoea, constipation and galactohorrea – embarrassing side-effects - were all reported less commonly than dry mouth, weight gain, dizziness, tachycardia and blurred vision.

Conclusion

Antipsychotic side-effects impact adherence to treatment and the relationship with antipsychotic medicine negatively, which leads to poorer long-term outcomes. In order to improve antipsychotic experience and ensure long-term positive outcomes, side-effects must be regularly systematically assessed using a validated rating scale commencing at an early stage in care. While both the GASS and GASS-C were developed and validated originally in English they have been translated into a number of other languages (GASS – Arabic, Indian, Danish, American, Spanish, Kenyan; GASS-C – Japanese, Dutch, Chinese, Serbian, Arabic, Greek) and, as such, may be used globally. As distress caused by side-effects plays a major role in non-adherence, the side-effects assessment should examine both how often each side-effect occurs along with the distress caused. In addition, data on distressing side-effects along with side-effect frequency should be made available to those choosing an antipsychotic to provide a broader picture of antipsychotic experience. Finally, given the lack of correlation between high dose/combination antipsychotics and side-effects experienced, antipsychotic treatment should be tailored to the individual based on their response and tolerance and dose reduction and/or avoidance of polypharmacy should no longer be recommended or employed first line as side-effect management strategies.

Conflict of interest statement

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