Antipsychotic polypharmacy and augmentation strategies prior to clozapine initiation: a historical cohort study of 310 adults with treatment resistant schizophrenic disordersa

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Abstract

Rationale

Antipsychotic polypharmacy (APP) is commonly used in schizophrenia despite a lack of robust evidence for efficacy, as well as evidence of increased rates of adverse drug reactions (ADR's) and mortality.

Objectives

We sought to examine polypharmacy and use of other adjunctive medications in patients with treatment resistant schizophrenic disorders (ICD-10 diagnoses F20-29)schizophrenia immediately prior to clozapine initiation, and to investigate clinical and sociodemographic factors associated with polypharmacy use in this setting.

Methods

Analysis of case notes from 310 patients receiving their first course of clozapine at the South London and Maudsley NHS Trust (SLaM) was undertaken using the Clinical Record Interactive Search (CRIS) case register. Medication taken immediately prior to clozapine initiation was recorded, and global clinical severity was assessed at time points throughout the year prior to medication assessment using the Clinical Global Impression - Severity scale (CGI-S). Logistic regression was used to investigate factors associated with antipsychotic polypharmacy.

Results

The point prevalence of antipsychotic polypharmacy prior to clozapine initiation was 13.6% (n=42), with 32.6% of subjects prescribed adjuvant psychotropic medications. APP was associated with increasing number of adjuvant medications (odds ratio [OR] 1.97, 95% confidence interval [CI] 1.27 – 3.06), concurrent depot antipsychotic prescription (OR 2.64, CI 1.24 – 5.62), concurrent antidepressant prescription (OR 4.40, CI 1.82 – 10.63), and a

CGI-S over the previous year within the two middle quartiles (Quartile 2 vs. 1 OR 6.19, CI 1.81 – 21.10, Quartile 3 vs. 1 OR 4.45, CI 1.29 – 15.37 Quartile 4 vs. 1 OR 1.88, CI 0.45 – 7.13).

Conclusions

Antipsychotic polypharmacy and augmentation of antipsychotics with antidepressants, mood stabilisers, and benzodiazepines are being employed in treatment resistant schizophrenia prior to clozapine. -The conservative antipsychotic polypharmacy rate observed may have been influenced by an initiative within SLaM that reduced polypharmacy rates during the study window (Mace and Taylor, 2015). Efforts to reduce the use of poorly evidenced prescribing should focus on adjuvant medications as well as antipsychotic polypharmacy.

Key Words: schizophrenia, polypharmacy, antipsychotic, clozapine, treatment resistant, augmentation, adjunctive, antidepressant, mood stabiliser, benzodiazepine.

Abbreviations: ADR's – adverse drug reactions, APP – antipsychotic polypharmacy, CGI-S – Clinical Global Impression Severity scale CRIS – Clinical Record Interactive Search, GATE – general architecture for text engineering, MHA – Mental Health Act, NHS – National Health Service, NICE - National Institute for Health and Care Excellence, POMH – Prescribing Observatory for Mental Health, SLaM – South London and Maudsley NHS Trust, SMI – serious mental illness.

Antipsychotic polypharmacy, the concurrent use of two or more antipsychotics, remains common in the UK with 38% of all psychiatric inpatients and 16% of those with

schizophrenia living in the community prescribed multiple antipsychotics (Mace and Taylor, 2015; Patel et al. 2014). Analysis of the national Danish health registers demonstrated wide geographical variation in polypharmacy utilisation, and whilst its use decreased between 2006 and 2012, it remains more prevalent than in 1996 (Sneider et al., 2015).

A number of factors contribute to the use of APP. From the limited number of studies that examine antipsychotic polypharmacy in schizophrenia, individuals with treatment resistance .(the failure to respond to adequate courses of two different antipsychotics.) show much higher rates of APP (Schmidt-Kraepelin et al., 2013). Ineffectual control of symptoms may lead to clinicians prescribing multiple antipsychotics, and improvement during cross-titration between antipsychotics may lead to long-term prescribing of both drugs. Additional antipsychotics, sometimes used initially as 'as required' medication, may be introduced as regular medication for patients with aggression or short-term distress and agitation, leading to long-term use. Grech et al. (2014) found 39% of patients were prescribed long-term polypharmacy (> 6 months) after 0 or 1 monotherapy trials, and that less than half of those prescribed polypharmacy had been trialled on clozapine.

Despite the widespread use of antipsychotic polypharmacy evidence regarding efficacy over monotherapy in treatment resistance is both limited and equivocal, particularly with regard tofor non-clozapine combinations of polypharmacy. Clozapine monotherapy has been demonstrated in individual studies and meta-analyses to reduce symptoms in treatment resistant patients, and is more efficacious than other second generation antipsychotics (Lewis et al, 2006; McEvoy et al., 2006; Wahlbeck et al., 1999). Small open-label trials have demonstrated varying levels of symptom improvement when non-clozapine combinations of APP were utilised (Lerner et al., 2000; Lerner et al., 2005; Potkin et al., 2002; Zink et al., 2004,). However, a meta-analysis of 19 polypharmacy trials by Correll et al (2009) suggested that publication bias may have been present, with larger studies showing smaller effects and

the greatest effect evident when clozapine was included in the polypharmacy regimen. In particular, a large scale randomised controlled trial with 323 subjects found no improvement in symptoms when adjunctive aripiprazole or placebo were used in combination with either risperidone or quetiapine (Kane et al., 2009). Meanwhile, some studies investigating augmentation of clozapine have demonstrated efficacy in positive symptom reduction (Muscatello et al., 2011; Josiassen et al, 2005), whilst others suggest the adjunctive use of aripiprazole can reduce metabolic side effects (Henderson et al, 2006). –In addition to questionable efficacy APP is associated with an increase in adverse drug reactions and hospitalisation (Centorrino et al., 2004), mortality (Waddington et al., 1998), and higher antipsychotic doses (Roh et al., 2014). At s such therepresent there is insufficient evidence to support the use of any particular combination of non-clozapine antipsychotics.

As such,In view of the lack of evidence for polypharmacy, Nnational efforts have been made to reduce polypharmacy in the UK since 2009 when the National Institute for Health and Care Excellence (NICE) issued guidance recommending the avoidance of polypharmacy except for the augmentation of clozapine in treatment resistance resistant patients who are unresponsive to clozapine alone. Despite this, existing research suggests that this guidance has not been fully incorporated into clinical practice (Grech and Taylor, 2012). A systematic review concluded that careful switching from polypharmacy to monotherapy is feasible for most patients (Tani et al, 2013)., with but a large scale quality improvement program in the UK demonstrating demonstrated little change in polypharmacy rates with a baseline rate of 43% amongst adult in-patients, and a re-audit rate of 39% (Paton et al., 2008). Additionally, Howes et al. (2012) reported the prescription of clozapine was preceded by a mean theoretical delay of 47.7 months from when patients were first eligible for clozapine therapy. with 36.2% of patients receiving antipsychotic polypharmacy during this time.

Evidence regarding the efficacy of adjunctive antidepressants or mood stabilisers is also inconclusive (Leucht et al., 2007; Rummel et al., 2006; Schwarz et al., 2008; Sepehry et al., 2007), whilst benzodiazepines have been found to have no effect beyond short term sedation. (Volz et al., 2007). In addition to concerns regarding efficacy there are not enough data regarding adverse effects and long-term safety to recommend any of these adjunctive strategies for routine clinical use.

It remains unclear how current evidence and guidance for antipsychotic polypharmacy in adults with treatment resistant schizophrenia are applied clinically. There are very few UK based naturalistic studies of APP in schizophrenia, and, as yet, no detailed examination of the sociodemographic and clinical predictors of non-clozapine antipsychotic polypharmacy in treatment resistant patients. Additionally, to date no studies have investigated the use of both APP and augmentation with other classes of psychotropic drugs concurrently.

So that psychopharmacological prescribing practices are better understood in treatment resistant schizophrenia we sought to investigate the use of antipsychotic polypharmacy and the use of antipsychotic augmentation with mood stabilisers, antidepressants, and benzodiazepines. Using a retrospective cohort design, in a sample of patients with treatment resistant schizophrenia, we examined the sociodemographic and clinical factors associated with polypharmacy prior to first-ever clozapine use.

Methods

Study setting

The cohort was identified within the South London and Maudsley (SLaM) Biomedical Research Council Case Register. SLaM is an NHS mental health trust that provides

secondary mental health services to a population of 1.2 million in the boroughs of Lambeth, Southwark, Lewisham and Croydon in South-East London, a population where age, gender, education, and levels of social deprivation are comparable to the wider population of London (Stewart et al., 2009). The Clinical Record Interactive Search (CRIS) system, described in detail elsewhere (Stewart et al., 2009), allows researchers to access de-identified copies of patient's electronic health records which have been in use across the trust since 2006. A general architecture for text engineering application within CRIS was used to identify patients who fulfilled the inclusion criteria for this study (Fig. 1). Eligibility was then manually confirmed by accessing full-text anonymised case notes in the user interface of CRIS.

310 patients were eligible for inclusion (Fig. 1). Individuals aged 18 – 65 with an ICD-10 F20-F29 diagnosis and who were prescribed clozapine for the first time between 1st January 2007 and 31st December 2011 were included. Patients Subjects were receiving care as either inpatients or outpatients under secondary mental health services provided by SLaM. National patients referred from out of area for clozapine initiation were excluded as they are not representative of the study population and frequently lacked data on prescribing prior to clozapine initiation.

Fig. 1 Cohort selection

[Insert Figure 1]

Outcome measures

The main outcome measure in this study was use of antipsychotic polypharmacy at a single time point immediately prior to clozapine initiation in those with an ICD-10 F20 - F29

diagnosis. Additionally, the use of adjunctive antidepressants, mood stabilisers, and benzodiazepines was assessed. A retrospective analysis of full-text anonymised case notes (inpatient and community notes, correspondence between clinicians and external agencies) was undertaken within the CRIS system, and medications prescribed were manually recorded, taken from the clinical entries closest in time to clozapine initiation that contained sufficient information. Antipsychotics, mood stabilisers, antidepressants and benzodiazepines prescribed for regular use were recorded along with route of administration. Antipsychotic polypharmacy was defined as the concurrent use of more than one regular antipsychotic drug. In subjects where no antipsychotic prescription prior to clozapine initiation was evident in the immediately preceding case notes, evaluation of the previous 6 months case notes were undertaken to confirm subjects were not receiving antipsychotics. 13 patients were prescribed both oral and depot risperidone, and these patients were not included in the polypharmacy group, since this practice is recommended during risperidone depot initiation.

Explanatory variables

The main factors of interest in this study were clinical severity, concurrent use of adjuvant psychoactive medications, and sociodemographic factors. In order to evaluate the relationship between polypharmacy use and clinical severity, manual analysis of case notes in the CRIS system was undertaken using the Clinical Global Impression Severity scale (CGI-S) to assess symptomatology and functioning immediately prior to clozapine initiation, as well as at 1, 3, 6, 9, and 12 months prior to clozapine therapy. Average CGI-S over the year prior to medication data collection was calculated for each patient. Case notes dated up to the midpoint between time points were used when assessing CGI-S to ensure an accurate reflection of psychopathology over the year was obtained. For example, entries from 4.5 months to 7.5 months were eligible for use in assessing the 6 month time point. A variety of

source material was used for each assessment to allow both symptoms and social functioning to be assessed, (ward round notes, nursing notes, community notes, correspondence) in addition to minimising potential bias from individual sources. Inter-rater reliability for CGI-S rating was calculated using two-way mixed effect model intra-class correlation coefficients. The absolute individual intra-class correlation coefficient for all four raters (JVT, JMC, SEL, JD) was 0.71, indicating substantial agreement. Data regarding the use of adjuvant psychoactive medications was collected at a single time point for each patient prior to clozapine initiation, as described above. Number of adjuvant medications was defined as the total number of antidepressants, mood stabilisers, and regular benzodiazepines prescribed to each patient in addition to antipsychotics.

Age, gender, ethnicity, ICD-10 diagnosis, and whether patients were detained under the mental health act (MHA) at clozapine initiation were extracted from structured fields within CRIS. Age was defined as age at start of clozapine treatment. Ethnicity was categorised into three groups – White British or other white background, African Caribbean or other black background, and other. Social deprivation was estimated using the 'Index of Multiple Deprivation', with area-level deprivation scores available in CRIS based on postal codes and data from the 2007 UK census, and was categorised into high, medium, and low levels of deprivation. The Index of Multiple Deprivation is calculated based upon employment, health, education, housing, crime, and environment. Polypharmacy point prevalence in SLaM inpatients was calculated from audit data supplied by SLaM pharmacy and the Prescribing Observatory for Mental Health (POMH) for 2007, 2008, 2009, and 2012 after exclusion of patients prescribed clozapine to aid comparability. Some categories of explanatory variables have been merged in line with confidentiality protocols required for use of the CRIS dataset.

Statistical analysis

Crude analysis of factors associated with antipsychotic polypharmacy prior to clozapine

initiation was carried out using Pearson's χ^2 for categorical variables and logistic regression

for continuous variables. Logistic regression was used for multivariable analysis. The logistic

regression model was adjusted for all variables that appear within Table 2, with the exception

of 'increasing number of adjunctive medications' as this was highly correlated with mood

stabiliser, antidepressant, and benzodiazepine prescription. Likelihood ratio tests indicated

that it was appropriate to include average CGI-S over the year prior to medication review as

an ordered categorical variable (quartiles), and age as a continuous variable. Stata 13 was

used for all statistical analysis.

Ethical approval

Ethical approval for the use of CRIS as a research dataset was given by Oxfordshire Research

Ethics Committee C (08/H0606/71). Permission for this study was granted by the CRIS

oversight committee.

Results

64.5% of the cohort was male, and 91% of subjects had an ICD-10 diagnosis of

Schizophrenia (F2~~5~~0).   Black Africans and Caribbeans comprised 47.7% of the cohort

whilst White subjects comprised 40.0%.

Antipsychotic polypharmacy

13.6% of patients (n=42) were prescribed antipsychotic polypharmacy immediately prior to

clozapine initiation (Table 2), of whom 22 were prescribed two oral antipsychotics and 17

were prescribed concurrent oral and depot medication. Amisulpride combined with

quetiapine was the most commonly prescribed individual regimen of polypharmacy (n=6), with 28 different combinations of antipsychotics used across the 42 instances of APP.

Factors associated with antipsychotic polypharmacy

Increasing number of adjuvant medications (antidepressants, mood, stabilisers, benzodiazepines) was associated with polypharmacy (Table 2, odds ratio [OR] 1.97, 95% confidence interval [CI] 1.27 – 3.06). Multivariable analysis indicated that individuals with an average CGI-S within the two middle quartiles (4.33 – 5.17) over the year prior to clozapine initiation were more likely to be prescribed polypharmacy prior to clozapine initiation (Table 2, Quartile 2 vs. Q1 OR 6.19, CI 1.81 – 21.10, Q3 vs. Q1 OR 4.45, CI 1.29 – 15.37, Q4 vs. Q1 OR 1.88, CI 0.45 – 7.13). Additionally, the prescription of antidepressants (OR 4.40, CI 1.82 – 10.63), and depot preparations of antipsychotics (OR 2.64, CI 1.24 – 5.62) were associated with increased use of APP, whilst the prescription of mood stabilisers and benzodiazepines were not. Age, gender, ethnicity, diagnosis, detention under the MHA at clozapine initiation, and socioeconomic status were not significantly associated with polypharmacy. APP decreased year on year throughout the study window from 18.2% 2007 to 11.4% in 2011. These results are in line with the reduction in polypharmacy across the trust due to the quality improvement program implemented within SLaM between 2006 and 2012 which aimed to reduce antipsychotic polypharmacy and high dose prescribing (Fig. 2).

Adjuvant medication

32.6% of patients (n=101) were prescribed 1 or more adjuvant medications (mood stabilisers, antidepressants, benzodiazepines) in addition to antipsychotics (Table 1). Sodium valproate (n=27) and lithium (n=7) were the most frequently prescribed adjunctive mood stabilisers (11.9% of cohort, n=37), whilst citalopram (n=17) and mirtazapine (n=8) were the most commonly prescribed antidepressants (15.2% of cohort, n=47). Regular benzodiazepines

were prescribed to 11.6% (n=36), with clonazepam (n=23) used more frequently than diazepam (n=13).

Monotherapy

60.0% of patients were prescribed oral monotherapy, with olanzapine (n=68, 36.6% of oral monotherapy) and risperidone (n=44, 23.4% of oral monotherapy) the most commonly prescribed drugs. Depot monotherapy was prescribed to 18.7% of patients, with zuclopenthixol decanoate (n=19, 32.7% of all depot monotherapy) and risperidone depot (n=13, 22.4% of all depot monotherapy) most commonly utilised. Additionally, 4.2% of patients (n=13) were prescribed both depot and oral risperidone. Of 11 patients who were prescribed no antipsychotics prior to clozapine initiation, seven were taking no psychoactive medication at all whilst the remainder were prescribed either mood stabilisers or antidepressants.

Table 1 – Sample characteristics

Variables	Number of individuals (%)
Total	310 (100)
Demographic variables	
Gender	
Male	200 (64.5)
Female	110 (35.5)
Age	
<20	10 (3.2)

20-29	104 (33.6)
30-39	77 (24.8)
40-49	82 (26.5)
50-59	28 (9.0)
60-65	9 (2.9)
Ethnicity	
White	124 (40.0)
Black African / Caribbean	148 (47.7)
Other	38 (12.3)
Diagnosis	
Schizophrenia (F20)	282 (91.0)
Schizoaffective disorder (F25)	18 (5.8)
Other F20-29 diagnosis	10 (3.2)
Detained under MHA at clozapine initiation	
Detained	156 (50.3)
Not Detained	154 (49.7)
Social deprivation index	
Low	82 (26.5)
Medium	110 (35.5)
High	98 (31.5)
Unknown	20 (6.5)

Medication prescribed immediately prior to clozapine initiation	
Antipsychotic use	
Polypharmacy	42 (13.5)
Monotherapy	257 (83.0)
No antipsychotic	11 (3.5)
Antidepressant use	
Antidepressant(s)	47 (15.2)
No antidepressant	263 (84.8)
Mood stabiliser use	
Mood stabiliser(s)	37 (11.9)
No mood stabiliser	273 (88.1)
Benzodiazepine use	
Benzodiazepine(s)	36 (11.6)
No benzodiazepine	274 (88.4)
Number of adjunctive[a] medications prescribed	
0	209 (67.4)
1	81 (26.1)
2 or more	20 (6.5)
Average CGI-S[b] in the year prior to clozapine initiation (quartiles)	
Q1 (2.00 – 4.33)	76 (24.5)
Q2 (4.33 – 4.71)	79 (25.5)
Q3 (4.71 – 5.17)	69 (22.3)
Q4 (5.17 – 6.33)	86 (27.7)

[a]Adjunctive medications defined as any anti-depressant, mood stabiliser, or benzodiazepine.

[b]Increasing CGI-S denotes worsening global clinical severity.

Table 2 – Crude analysis (χ^2) and multivariate analysis (logistic regression) of factors associated with antipsychotic polypharmacy immediately prior to clozapine initiation

Variable		Crude OR (95% CI)	Fully adjusted OR[a] (95% CI)
Age		1.01 (0.98 – 1.04)	1.02 (0.98 – 1.05)
Gender	Male	reference	reference
	Female	1.01 (0.51 – 1.99)	0.91 (0.41 – 2.00)
Ethnicity	White	reference	reference
	Black	1.18 (0.59 – 2.36)	1.47 (0.63 – 3.47)
	Other	0.79 (0.25 – 2.54)	1.17 (0.32 – 4.47)
Diagnosis	Schizophrenia	reference	reference
	Schizoaffective disorder	1.28 (0.35 – 4.65)	1.52 (0.68 – 3.50)
	Other F20-29 diagnosis	0.71 (0.09 – 5.80)	0.76 (0.08 – 7.80)
Detained under MHA at clozapine initiation	Not detained	reference	reference
	Detained	1.10 (0.57 – 2.11)	1.54 (0.67 – 3.50)

Social deprivation index	Low	reference	reference
	Medium	1.13 (0.53 – 2.44)	1.24 (0.52 – 2.95)
	High	0.62 (0.26 – 1.50)	0.55 (0.21 – 1.45)
Average CGI-S over year prior to medication review	Quartile 1 (least severe)	reference	reference
	Quartile 2	4.94 (1.58 – 15.45)	6.19 (1.81 – 21.10)
	Quartile 3	4.18 (1.29 – 13.51)	4.45 (1.29 – 15.37)
	Quartile 4 (most severe)	1.85 (0.53 – 6.39)	1.88 (0.45 – 7.13)
Mood stabiliser prescribed		1.59 (0.65 – 3.89)	1.37 (0.49 – 3.85)
Antidepressant prescribed		3.09 (1.46 – 6.51)	4.40 (1.82 – 10.63)
Benzodiazepine prescribed		2.01 (0.85 – 4.78)	2.47 (0.92 – 6.66)
Depot antipsychotic prescribed		2.12 (1.09 – 4.14)	2.64 (1.24 – 5.62)
Number of adjunctive[b] medications		1.97 (1.27 – 3.06)	

[a]Adjusted for all variables that appear within the table with the exception of number of adjunctive medications which was highly correlated with mood stabiliser, antidepressant, and benzodiazepine prescription.

[b]Adjunctive medications defined as any anti-depressant, mood stabiliser, or regular benzodiazepine.

Fig. 2 Antipsychotic polypharmacy rate by year in cohort vs. SLaM inpatients

[Insert Figure 2]

Discussion

Summary of main findings

The point prevalence of antipsychotic polypharmacy prior to clozapine initiation was 13.5% within our cohort of treatment resistant adults, with 28 different combinations of polypharmacy prescribed. The use of antidepressants, mood stabilisers, and regular benzodiazepines was common with 32.6% of patients prescribed at least one of these medications, and antipsychotic polypharmacy was associated with increasing number of adjuvant medications prescribed. Specifically, the prescription of antidepressants and depot antipsychotics were strongly associated with antipsychotic polypharmacy, whilst no association was evident between APP and the prescription of benzodiazepines or mood stabilisers. Subjects whose average CGI-S was within the two middle quartiles were much more likely to be prescribed polypharmacy than subjects whose CGI-S was within either the least or more severe quartile. No association was found between antipsychotic polypharmacy and any sociodemographic factors investigated.

Comparison to other studies

Our findings add to previous evidence that polypharmacy is being used inappropriately prior to clozapine, delaying use of this gold standard medication. Whilst we report a point prevalence of polypharmacy prior to clozapine initiation, prescription surveys undertaken in SLaM during 2003 and 2012 note lifetime prevalence rates of antipsychotic polypharmacy prior to clozapine initiation of 65% and 32.6% respectively (Taylor et al., 2003; Howes et al., 2012), with Howes et al. reporting that this contributed to a mean theoretical delay to clozapine initiation of 47.7 months in their cohort. Higher antipsychotic polypharmacy point

prevalence has been demonstrated amongst inpatients within SLaM, with rates falling during this study's period of observation from 37% in 2007 to 16% in 2012 (Mace and Taylor, 2015). In contrast to higher levels of inpatient polypharmacy, a large study of both community and inpatient subjects within SLaM with serious mental illness (SMI) diagnoses (schizophrenia, bipolar affective disorder, schizoaffective disorder) estimated that 4.7% were prescribed long-term antipsychotic polypharmacy for at least six months (Kadra et al., 2015).

No other studies to date have reported the prevalence of antidepressant, mood stabiliser, and benzodiazepine prescribing in addition to polypharmacy prior to clozapine initiation, despite the recognised lack of evidence for their use in addition to antipsychotics. Studies in the wider population with schizophrenia identified greater use of adjuvant psychotropic medications; antidepressants were prescribed to 38% of patients, anxiolytics to 22%, and mood stabilisers to 19% in a large study carried out in the USA (Chakos et al, 2006). An Austrian study further demonstrated high rates of adjuvant psychotropic medication use, but noted large variation in use between different clinics (Ritmannsberger et al, 1999).

Previous research has recognised severity of schizophrenia as a predictor of polypharmacy (Connolly and Taylor, 2014). Our results partially support this, suggesting polypharmacy is less common in those with milder symptoms, but also less common in those with the most severe symptoms. This finding could indicate a possible lowering of average CGI-S due to the use of polypharmacy.

We identified six patients who were prescribed a combination of quetiapine and amisulpride, representing 14.3% of polypharmacy. The evidence underlying this strategy is limited - one case series of six patients partially responsive to quetiapine monotherapy who exhibited a reduction in psychotic symptoms with the addition of amisulpride [Englisch et al., 2010]. However, subjects within this series gained an average of 6kg and prolactin levels increased

four-fold with the introduction of amisulpride, highlighting the potential for increased ADRs with polypharmacy.

Strengths

As a provider of secondary mental health services within the UK National Health Service (NHS), SLaM has close to a 100% monopoly in providing care for those with schizophrenia with a catchment area containing 1.2 million people, leading to minimal selection bias. The procedure to detect medication use used data from pharmacy dispensing, structured medication fields, as well as Natural Language processing (using the GATE application) to extract medications data from free-text including clinical notes, and correspondence between clinicians and other agencies. The use of multiple sources of information allows for both high recall and precision, and additionally, the medication application has been validated against manual search methods. Manual screening for eligibility was subsequently undertaken to ensure all subjects met the inclusion criteria for the study. The GATE medication application was utilised for identifying subjects due to its high level of recall, whilst analysis of case notes was undertaken manually to allow for both high recall and precision. Studies investigating antipsychotic polypharmacy often fail to identify subjects who are undergoing cross-titration between antipsychotics, for whom polypharmacy is required in the short term to ensure adequate plasma levels of medication. As subjects in our study were being 'worked up' for clozapine initiation, it is unlikely that many of them were undergoing cross-titration between other antipsychotics, minimising the effect of cross-titration on the reported prevalence.

Limitations

Our study window coincided with the implementation of a quality improvement program within the trust that aimed to reduce polypharmacy and high dose prescribing, and the

effectiveness of this program means that results may not be generalizable to other trusts or regions (Mace and Taylor., 2015). Prescribed medications were assessed only at a single time point due to the labour intensive nature of assessing full-text case notes. Therefore, wWe report a point prevalence of polypharmacy prior to clozapine initiation, so and are unable to identify how many patients have beenwere prescribed polypharmacy on a long term those subjects who had been prescribed polypharmacy historically, but are currentlywere monotherapy immediately prior to clozapine initiation were not identified. Additionally, the

Polypharmacy was associated only with those subjects whose average CGI-S was within the two middle quartiles, and not with those subjects whose average CGI-S fell into the uppermost quartile, representing those with the most severe psychopathology. Whilst this finding could indicate a possible lowering of average CGI-S due to the use of polypharmacy, it must be interpreted with caution due to the uncertain temporal relationship between polypharmacy prescription and symptom severity as it is not known for how long subjects were prescribed polypharmacy.

The inclusion of patients with a diagnosis of schizoaffective disorder may have increasedexplain the prevalencesome cases of mood stabiliser and antidepressant use prior to clozapine initiation, although the prevalence of antidepressant and mood stabiliser prescription were around two and threefold greater than the rates of schizoaffective diagnoses. Finally, Ccase notes were often unclear as to whether benzodiazepines were prescribed on a regular or as required basis, and as such their use may be under-reported.

Implications

Our findings have important implications for prescribers and future guidelines. Our resultsWe show found that whilst the prevalence of polypharmacy in treatment resistant adults prior to clozapine therapy is was relatively low, the use of other poorly evidenced

adjunctive medications ~~is~~ was both common, and also more frequently observed, in those prescribed antipsychotic polypharmacy. This observation suggests that some prescribers are seeking to overcome treatment resistance through the addition of further drugs to already ~~unevidenced~~ ~~weakly~~poorly evidenced regimens. Of particular note is the marked association between antidepressant use and polypharmacy. Further research is required to better understand ~~whether~~ the extent to which this relationship is ~~due to~~driven by an increased incidence of comorbid depression in treatment resistant individuals, misdiagnosis of affective disorders with psychotic features, or a failure of antipsychotics to adequately treat the negative symptoms of schizophrenia.

The large number of different antipsychotic combinations prescribed suggests that what little evidence is available rarely factors in to clinical decision making when polypharmacy is used. There are many factors that influence clinician's decisions to implement polypharmacy or other augmentation strategies in preference to clozapine. Both clinician's own preferences and views held by patients regarding clozapine are ~~heavily~~ influenced by concerns surrounding adverse effects, adherence and required monitoring protocols, as well as a persisting lack of knowledge regarding clozapine's superior efficacy (Patel., 2012). Polypharmacy use, whilst modest in our cohort, contributes to delay in treatment with clozapine. (Howes et al., 2012) . Longer duration of inadequately treated psychosis is associated with poorer outcomes, both in terms of symptoms and overall functioning (Perkins et al., 2005). Whilst clinicians and patients may have negative perceptions of clozapine, it ~~is, for the time being at least,~~remains a better evidenced treatment than antipsychotic polypharmacy in terms of efficacy and safety.~~must be considered as both a more efficacious and probably safer option than polypharmacy~~.

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