



# BMJ Open Prescribing pattern of antipsychotic medication for first-episode psychosis: a retrospective cohort study

Dolores Keating <sup>1,2</sup>, Stephen McWilliams,<sup>3,4</sup> Fiona Boland <sup>5</sup>, Roisin Doyle,<sup>6</sup> Caragh Behan,<sup>6</sup> Judith Strawbridge,<sup>2</sup> Mary Clarke<sup>4,6</sup>

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<sup>1</sup>Pharmacy Department, Saint John of God Hospital, Dublin, Ireland

<sup>2</sup>School of Pharmacy, Royal College of Surgeons in Ireland, Dublin, Ireland

<sup>3</sup>Department of Medicine, Saint John of God Hospital, Dublin, Ireland

<sup>4</sup>School of Medicine and Medical Sciences, University College Dublin, Dublin, Ireland

<sup>5</sup>Data Science Centre and HRB Centre for Primary Care Research, Royal College of Surgeons in Ireland, Dublin, Ireland

<sup>6</sup>Dublin and East Treatment and Early Care Team, Blackrock, Co Dublin, Ireland

## Correspondence to

Dolores Keating;  
[dolores.keating@sjog.ie](mailto:dolores.keating@sjog.ie)

## ABSTRACT

**Objective** Guidelines for antipsychotic use in first-episode psychosis (FEP) recommend that medication be chosen initially on the basis of side effect profile with doses at the lower end of the range. Our objective was to describe the pattern of antipsychotic use in FEP over a period of 21 years in the context of changing clinical guidelines and the development of specialist early intervention in psychosis (EIP) services.

**Setting** A community-based mental health service in South County Dublin (population 187 000) and a large private hospital.

**Participants** Participants included 465 patients with FEP (146 from an epidemiological study (1995–1999) and 319 from a specialist EIP service (2005–2016)). Treatment with antipsychotic medication did not exceed 30 days at study entry.

**Outcome measures** This is a descriptive study of prescribing practices in the context of service development and changing guidelines.

**Results** First-generation antipsychotics were prescribed for 65% of the early cohort compared with 4.3% of the EIP cohort. Olanzapine was initially prescribed for 79.7% of EIP patients. Initial doses of medication were frequently low ( $\leq 50\%$  British National Formulary (BNF) maximum) in both cohorts (71% and 78.6%). The demographic and clinical factors investigated did not influence the initial choice of antipsychotic medication significantly. Univariate logistic regression analysis suggested inpatient treatment setting was associated with a higher initial dose ( $> 50\%$  BNF maximum) of antipsychotic medication. Increasing dose requirements over the first month of engagement with an EIP service was associated with poorer global functioning at baseline, greater positive symptoms at baseline and the inpatient treatment setting. However, these associations were not seen in the multivariable model.

**Conclusions** Second-generation antipsychotic prescribing predominates, but guidelines are often overlooked when choosing olanzapine notwithstanding lower initial dosages. EIP services should include proactive support for optimising medicines in line with evidence-based guidelines.

## INTRODUCTION

Early intervention in psychosis (EIP) has been shown to reduce illness severity, reduce hospitalisation and improve aspects of social

## Strengths and limitations of this study

- This 21-year study describes antipsychotic prescribing practices for a naturalistic cohort of patients with first-episode psychosis during two discrete periods before and after the introduction of an early intervention in psychosis service.
- All 465 patients had an objectively rated diagnosis of first-episode psychosis using validated instruments.
- All participants had little or no antipsychotic exposure before the study.
- A limitation of the study is its retrospective nature, meaning some data were missing.
- Rates of adherence to international prescribing guidelines may reflect the fact that they were not specifically promoted in this study setting.

functioning such as involvement in school or work.<sup>1</sup> Benefits are sustained in the short term to medium term.<sup>2 3</sup> The components of an EIP service differ with regard to the specific interventions offered. Common themes, however, include use of medication, psychosocial interventions such as cognitive-behavioural therapy, family interventions, rehabilitative interventions and psychoeducation.<sup>1</sup> EIP models of care also vary with some services delivered by specialist stand-alone multidisciplinary teams and others by enhanced community mental health teams (CMHT) whereby staff within CMHTs care for people with EIP in addition to their usual roles. ‘Hub and spoke’ models involve a centralised specialist ‘hub’ which supports specialist staff or ‘spokes’ embedded in local CMHTs.<sup>4</sup> Despite the variations in how the EIP services are delivered, recent evidence suggests that the early intervention approach is likely to be cost-effective.<sup>5 6</sup>

Antipsychotic medications are a key component of care for those experiencing psychosis. Response to a first antipsychotic medication in first-episode psychosis (FEP) is high with up to 80% achieving a reduction

in symptoms.<sup>7</sup> Maintenance treatment with antipsychotic medications reduces hospitalisations, improves life expectancy and enhances functional outcomes.<sup>8–11</sup> Given the evidence that no one agent has shown significant superiority in terms of efficacy in this population,<sup>12</sup> international guidelines recommend that tolerability should be the main influence when it comes to the choice of medication.<sup>13</sup> Clozapine is generally reserved for those who have not adequately responded to antipsychotic treatment; however, lack of response should be identified early and clozapine initiated to improve outcomes.<sup>13 14</sup> Furthermore, doses of medication should also be lower in FEP than those used to treat later episodes of schizophrenia because people experiencing FEP are particularly sensitive to the effects and side effects of antipsychotic medication.

Pharmacological treatment guidelines have evolved over the lifetime of early intervention services with a notable change being the role of second-generation antipsychotics (SGA).<sup>15–17</sup> The National Institute for Health and Care Excellence (NICE), for example, recommended SGAs as initial treatment in the early 2000s. Emerging evidence regarding the relative risks of SGAs, particularly metabolic risks, led to a change in the 2009 update of the NICE guidelines with initial choice being driven by side effect profile rather than classification of antipsychotics.<sup>17</sup> The Patient Outcome Research Team (PORT) guidelines, also updated in 2009, specifically excluded olanzapine as a first-line treatment option<sup>16</sup> and other guideline development groups have followed suit.<sup>15 18</sup> EIP services vary in their approach to medication with limited published information on prescriber training, treatment goals, algorithms or guidelines and delivery of treatment.<sup>19</sup> This is perhaps surprising given the evidence of suboptimal use of antipsychotic medication in clinical practice.<sup>20 21</sup>

In this study, we describe the pattern of antipsychotic medication use in two cohorts of patients with FEP in the context of evolving clinical practice guidelines and the introduction of specialised EIP services. Our objectives were to determine (1) the adherence to international guideline recommendations on the initial choice and dose of antipsychotic medication, (2) whether a specific range of clinical or demographic factors at baseline were associated with the choice of medication or the initial dose of medication for patients supported by an EIP service.

## METHODS

### Study design

The study is a retrospective examination of the medication prescribed for two cohorts of patients with FEP before and after the introduction of EIP services. Data were gathered from clinical records, the EIP study database and electronic prescribing records. This article was written using the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting cohort studies.<sup>22</sup>

### Study setting

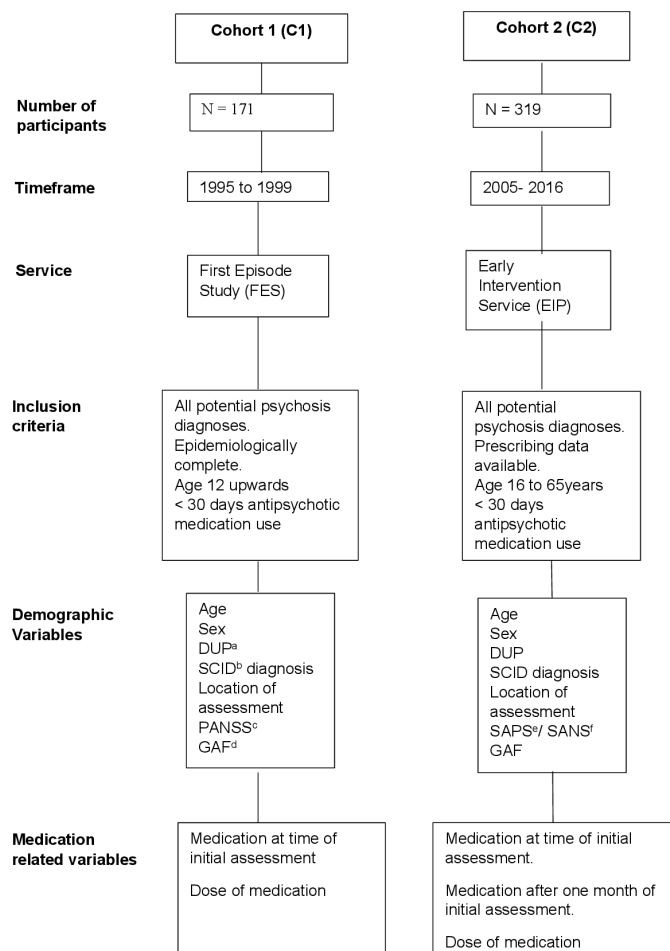
Data were extracted from a community-based mental health service located in an urban area of South County Dublin with a current population of approximately 187 000. A large private hospital, located within the catchment area, also participated in the study. EIP services were preceded by an epidemiological First Episode Study (FES) between 1995 and 1999.<sup>23</sup> Evidence from this study was used to secure funding for the Dublin and East Treatment and Early Care Team (DETECT). The specialist DETECT team offers rapid assessment leading to phase-specific psychological and family interventions. Antipsychotic medication use is managed by the patient's usual psychiatrist.

### Participants and inclusion criteria

The FES cohort (C1) was an epidemiologically complete sample recruiting all patients presenting in the catchment area with a first lifetime episode of psychosis between 1995 and 1999. Patients were included if they were aged 12 or over, gave consent to participate and had received less than 30 days of antipsychotic treatment. Cases included in the DETECT cohort (C2) were assessed by the EIP service between 2005 and 2016 and gave consent to participate in the study. Participants were aged between 16 and 65 and had received fewer than 30 days of antipsychotic treatment before the EIP service assessment. At the time of assessment, informed consent was given by parents or guardians for all participants aged under 18 years in line with the study protocol and the requirements of the ethics committee. The cohorts are described in [figure 1](#).

### Assessments

Participants were included if they had a diagnosis of FEP based on the Structured Clinical Interview for DSM-IV Axis I Disorders.<sup>24</sup> The Global Assessment of Functioning (GAF) scale was used to rate subjectively social, occupational and psychological functions. Scores range from 100 (extremely high functioning) to 1 (severe impairment).<sup>25</sup> For C1, psychological symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS).<sup>26</sup> The PANSS is scored by summation of individual items to produce positive symptom and negative symptom domain scores in a range of 7–49 and a composite general psychopathology score in the range of 16–112. The Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS), well-established rating scales used in clinical research, were used to assess symptoms in C2.<sup>27</sup> SANS measures negative symptoms on a 25-item, 6-point scale. Items are listed under the five domains of affective blunting, avolition/apathy, anhedonia/asociality and attention. SAPS measures positive symptoms on a 34-item, 6-point scale. Items are listed under hallucinations, delusions, bizarre behaviour and positive formal thought disorder. All scales were administered by trained clinicians who participated with inter-rater reliability. Duration of untreated psychosis (DUP) was defined as the interval between first



**Figure 1** Description of cohorts of patients presenting to an early intervention service, time frame of presentation, inclusion criteria, demographic and medication-related variables. <sup>a</sup>Duration of untreated psychosis. <sup>b</sup>Structured Clinical Interview for DSM-IV Axis I Disorders. <sup>c</sup>Positive and Negative Syndrome Scale. <sup>d</sup>Global Assessment of Functioning. <sup>e</sup>Scale for the Assessment of Positive Symptoms. <sup>f</sup>Scale for the Assessment of Negative Symptoms. EIP, early intervention in psychosis.

experience of psychotic symptom(s) and presentation to the psychiatric services for initiation of treatment; first manic symptom(s) were used for bipolar disorder.<sup>28</sup>

### Antipsychotic prescribing data

Prescribing data pertaining to C1 were compiled from paper charts. For the EIP cohort (C2), prescribing data at the time of clinical assessment (T1) were collected as part of a larger study of outcomes in FEP following the introduction of an EIP service. Medication at the time of initial assessment was recorded in the study database by the clinician carrying out the assessment. Data missing from the database and prescribing information following 1 month of engagement with the services (T2) were collected using hospital dispensing records and outpatient electronic prescribing records. Reports with details of prescription records were generated from the electronic health record separately using Discover Plus, a business intelligence software. It was taken that prescriptions

generated within 1 week of the specified time points were the current medications. Cases for which no medication data were available were excluded.

Regular antipsychotic medications were included. Antipsychotics used for short periods on a 'pro re nata' basis or for rapid tranquilisation were excluded. Where medications were being switched, we considered this to be appropriate polypharmacy and included the new antipsychotic as the choice assuming that the switch would be completed.

Doses of antipsychotic medication were categorised into 'low', <50% of the current British National Formulary (BNF) maximum dose; medium, >51% to <100% of current BNF maximum dose; and 'high' dose, >100% of current BNF maximum dose. The rationale for this approach was based on pharmacological treatment guidelines which recommend doses at the lower end of the therapeutic dose range.<sup>13</sup> An exception to this was risperidone for which <6 mg was categorised as a 'low' dose in FEP based on guideline recommendations.<sup>16</sup> The current BNF dosing standards for haloperidol were applied but it should be noted that the BNF maximum dose has reduced over the lifetime of this study.

### Statistical methods

Initially, descriptive statistics were used to describe baseline characteristics and general prescribing patterns in both cohorts. Means and SDs are reported for continuous variables and frequencies and percentages for categorical variables. For continuous scales which show evidence of or are expected to show some skew, a median and IQR is also presented. Scatterplots were used to display trends in olanzapine prescribing over time and an indicator included at 2009 when guidelines were first published advising against the use of olanzapine as an initial medication in FEP. Univariate and multivariable logistic regression analyses were used to explore potential demographic and clinical associations with olanzapine use (yes/no), dose initiated (medium/high vs low) and also change in dose (increased vs the same or decreased). Demographic and clinical variables included in the models were age, gender, DUP, GAF, SAPS, diagnosis and agitation symptoms. Statistical analysis was conducted using SPSS V.24 and Stata V.13.

### Patient and public involvement

Patients and the public were not involved in this study.

## RESULTS

### Demographic and clinical characteristics

Demographic and clinical baseline data from the FES (C1) are described in [table 1](#) and have previously been reported.<sup>28</sup> This was an epidemiologically complete sample and all people presenting with FEP consented to participate. Demographic and clinical characteristics for the EIP service (C2) were included for those who consented to participate in the study and for whom prescribing data

**Table 1** Baseline description of demographic and clinical characteristics of two cohorts of patients presenting between 1995–1999 and 2005–2016 for assessment of first-episode psychosis prior to (C1) and after (C2) the introduction of an EIP service

	C1 (1995–1999) n=171	C2 (2005–2016) n=319		
Gender, n (%)				
Male	99 (58)			189 (59.2)
Female	72 (42)			130 (40.8)
Age, mean (SD)	28.5 (11.1)			32.5 (11.3)
Inpatient on assessment, n (%)	144 (84.2)			216 (67.7)
Initial diagnosis*, n (%)				
Schizophrenia spectrum	101 (59.1)			124 (39.2)
Substance-induced psychosis	12 (7)			45 (14.2)
Major depressive disorder	11 (6.4)			36 (11.4)
Bipolar disorder	25 (14.6)			35 (11.1)
Delusional disorder	13 (7.6)			35 (11.1)
Brief psychotic disorder	0			22 (7)
All other psychotic diagnoses	4 (5.2)			19 (6)
	<b>Mean</b>	<b>Median</b>	<b>Range</b>	<b>Median (IQR)</b>
DUP (months)†	17.9	5	0.25–240	3 (0.63–13)
GAF‡	22.9			35 (30–48.5)
PANSS-Total	74.4			
PANSS-Negative	15.7			
PANSS-Positive	21.3			
SAPS-Total§				18 (10–31)
SANS-Total¶				12 (3–22)

\*3 missing C2.

†5 missing C1; 156 missing C2.

‡6 missing C2.

§11 missing C2.

¶14 missing C2.

DUP, estimated duration of untreated psychosis; EIP, early intervention in psychosis; GAF, Global Assessment of Functioning; PANSS-Negative, Positive and Negative Syndrome Scale negative symptom score; PANSS-Positive, Positive and Negative Syndrome Scale positive symptom score; PANSS-Total, Positive and Negative Syndrome Scale total symptom score; SAPS-Total, Scale for the Assessment of Positive Symptoms total score; SANS-Total, Scale for the Assessment of Negative Symptoms total score.

were available (table 1). Participants in both time periods were predominantly male with an average age of 28.5 (SD 11.1) years in the early cohort and 32.5 (SD 11.3) years in the EIP cohort. For both cohorts, the majority were assessed in the inpatient setting and schizophrenia spectrum was the most common initial diagnosis (table 1).

### Choice of antipsychotic medication

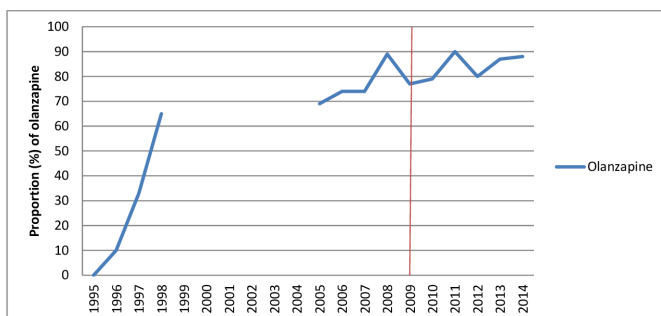
Prescribing data for a total of 465 patients were included, 146 in C1 and 319 in C2. Cases were excluded if prescribing data were not available for C1 (n=25) or if there were no prescribing data at the time of initial assessment or 1-month follow-up for C2. Prescribing patterns of antipsychotic medications are described in table 2. The proportion of SGAs increased from 32.2% in C1 to over 90% in C2. First-generation antipsychotic (FGA)

use predominated in C1 (65.1%), of which the most frequently chosen was sulpiride (19.2%), followed by thioridazine (11%) and haloperidol (10.3%). Olanzapine was the most frequently prescribed SGA throughout the time of the study and the prescribing frequency increased per year as represented in figure 2. Guidelines published in 2009 advising against the use of olanzapine as an initial medication in FEP and widening the choice to first or second-generation medicines did not appear to have an impact on prescribing patterns. Using C2 data, logistic regression analysis was used to explore demographic and clinical associations with olanzapine use (table 3). Univariate analysis showed evidence of an association with GAF scale, in that for every unit increase in GAF scale, the odds of being on olanzapine, compared with no olanzapine,

**Table 2** Antipsychotic prescribing patterns among two cohorts of patients presenting for assessment of first-episode psychosis before and after the introduction of an early intervention in psychosis service

	Cohort 1		Cohort 2	
	n=146		T1 (n=305)	
	n (%)	n (%)	n (%)	n (%)
<b>Second generation</b>				
Olanzapine	36 (24.7)	243 (79.7)	210 (71.7)	
Risperidone (oral)	8 (5.5)	25 (8.2)	22 (7.5)	
Amisulpride	2 (1.4)	7 (2.3)	11 (3.3)	
Quetiapine	1 (0.7)	6 (2.0)	9 (2.7)	
Aripiprazole		1 (0.3)	4 (1.4)	
Risperidone LAI			3 (0.9)	
Paliperidone (oral)			1 (0.3)	
Paliperidone LAI			5 (1.5)	
<i>Second generation total</i>	47 (32.2)	282 (92.4)	265 (90.4)	
<b>First generation</b>				
Sulpiride	28 (19.2)	1 (0.3)	1 (0.3)	
Thioridazine	16 (11)	4 (1.3)		
Haloperidol	15 (10.3)		4 (1.4)	
Chlorpromazine	13 (8.9)	3 (1)	1 (0.3)	
Trifluoperazine	9 (6.2)	2 (0.7)	2 (0.6)	
Flupenthixol depot	4 (2.7)		1 (0.3)	
Pimozide	4 (2.7)		1 (0.3)	
Zuclopenthixol depot	1 (0.7)		5 (1.5)	
Zuclopenthixol oral	1 (0.7)	1 (0.3)		
Flupenthixol (oral)	1 (0.7)	2 (0.7)	1 (0.4)	
Fluphenazine	1 (0.7)			
Pipotiazine	1 (0.7)			
Perphenazine	1 (0.7)			
<i>First generation total</i>	95 (65.1)	13 (4.3)	16 (5.5)	
No antipsychotic	4 (2.7)	10 (3.3)	12 (3.6)	

LAI, long-acting injection; T1, time of initial assessment; T2, 1-month following initial assessment.



**Figure 2** Proportion of olanzapine (%) prescribed per year for patients presenting for assessment of first-episode psychosis. Guidelines published in 2009 advising against the use of olanzapine as an initial medication in first-episode psychosis (FEP) and widening the choice to first or second-generation antipsychotics (orange line).

decreased (OR 0.97; 95% CI 0.95 to 0.99). However, there was no further evidence of associations with any other variables in univariate or multivariable analysis.

Data were available for C2 showing that 10 (3.3%) patients at T1 and 11 (3.9%) patients at T2 were not prescribed antipsychotic medications. At initial assessment, those who did not receive an antipsychotic medication had the following initial diagnoses: 'all other psychotic diagnosis' (n=4), substance-induced psychosis, major depressive disorder (n=2), brief psychotic episode (n=2) and delusional disorder. However, these data were only identifiable for patients who received prescriptions for other medication on the electronic database and may be an underestimate.

Five patients were prescribed long-acting injection (LAI) or depot formulation of antipsychotic medication in C1. While no patient was initiated on an LAI at initial

**Table 3** Regression analysis describing the odds of olanzapine use with reference to clinical and demographic characteristics for patients presenting to an EIP service

	Univariate analysis			Multivariable analysis (n=142)	
	n	OR (95% CI)	P value	OR (95% CI)	P value
Age	295	1.02 (0.99 to 1.05)	0.14	1.04 (1.00 to 1.08)	0.06
DUP (months)	167	0.99 (0.97 to 1.01)	0.22	0.99 (0.97 to 1.01)	0.43
GAF	291	0.97 (0.95 to 0.99)	0.02	0.98 (0.94 to 1.01)	0.18
SAPS	289	1.06 (0.97 to 1.16)	0.18	1.00 (0.86 to 1.17)	0.97
Sex	295				
Male		1.00		1.00	
Female		0.82 (0.45 to 1.51)	0.53	0.68 (0.28 to 1.63)	0.39
Treatment	295				
Outpatient		1.00		1.00	
Inpatient		1.34 (0.72 to 2.51)	0.36	1.66 (0.66 to 4.19)	0.28
Diagnosis	292				
Affective		1.00		1.00	
Schizophreniform		0.54 (0.25 to 1.18)	0.12	1.04 (0.36 to 3.05)	0.94
All other diagnoses		5.64 (0.69 to 46.39)	0.11	5.25 (0.53 to 52.08)	0.16
Agitation symptoms	295				
Present*		1.00		1.00	
Not present†		1.25 (0.66 to 2.39)	0.50	0.86 (0.35 to 2.10)	0.74

\*Score of 2=mild, 3=moderate, 4=marked or 5=severe on the SAPS excitatory/agitation score.

†Score of 0=none or 1=questionable on the SAPS excitatory/agitation score.

DUP, estimated duration of untreated psychosis; EIP, early intervention in psychosis; GAF, Global Assessment of Functioning; SAPS, Scale for the Assessment of Positive Symptoms.

presentation for C2, 14 (4.8%) had commenced an LAI by 1 month of treatment. Of the 319 cases in C2, data on both the medication used at initial assessment and at 1 month are available for 280 cases. Of these, 35 (12.5%) patients required a switch of antipsychotic medication within 1 month. Risperidone (n=6, 17.1%) was the most frequently used second-choice antipsychotic followed by amisulpride (n=4, 11.4%) and quetiapine (n=3, 8.6%).

### Dose of antipsychotic medication

Doses of medication at initial assessment were generally low in both cohorts (C1, 71% and C2, 78.6%). In this study, logistic regression was used to explore potential demographic and clinical associations with the odds of medium/high dose, compared with low dose (table 4). Univariate analysis showed that the odds of medium/high dose, compared with low dose, was significantly higher for an inpatient compared with an outpatient (OR 2.36; 95% CI 1.09 to 5.11). No further evidence of associations with any other variables in univariate or multivariable analysis was seen.

After 1 month of treatment the proportion of people in C2 requiring medium or high doses of medication increased from 17.9% to 42.7%. Of these, 4 (1.2%) patients were treated with doses above the BNF maximum, all of which were olanzapine at doses of 22.5–30 mg/day.

Data on the dose of medication at both time points in C2 were available for 268 patients. Of these, 72 (26.8%) required an increase in dose over the first month of engagement with the early intervention service (table 5). All of those who required an increase in dose had received an initial low dose of medication which was increased to a medium dose for 71 patients and a high dose for one patient. The dose of medication decreased for 10 (3.7%) people between initial assessment and following 1 month of engagement with the service. All 10 had been started on a medium dose of antipsychotic and the dose was reduced to a low dose over the first month. Medication was discontinued for one person who initially started on a low dose of medication. The dose for 186 people (69.4%) remained unchanged over the first month of engagement with the EIP service.

Univariate logistic regression analysis showed evidence that the odds of increasing a dose, compared with no increase (or a decrease), was significantly higher for an inpatient compared with an outpatient (OR 2.10; 95% CI 1.09 to 4.05, table 5). Additionally, there was evidence of associations with GAF and SAPS. For every unit increase in GAF scale, the odds of an increase, compared with no increase, decreased (OR 0.97; 95% CI 0.94 to 0.99), and for every unit increase in SAPS the odds of an increase, compared with no increase, was 1.13 (95% CI 1.05 to

**Table 4** Regression analysis exploring the odds of medium or high-dose antipsychotic use with reference to clinical and demographic characteristics for patients presenting to an EIP service

	Univariate analysis			Multivariable analysis (n=142)	
	n	OR (95% CI)	P value	OR (95% CI)	P value
Age	280	0.98 (0.95 to 1.01)	0.11	0.97 (0.93 to 1.01)	0.18
DUP (months)	154	0.97 (0.93 to 1.01)	0.09	0.98 (0.94 to 1.02)	0.23
GAF	276	1.00 (0.98 to 1.02)	0.81	0.99 (0.95 to 1.03)	0.50
SAPS	274	1.05 (0.96 to 1.14)	0.28	0.97 (0.82 to 1.15)	0.73
Sex	280				
Male		1.00		1.00	
Female		0.84 (0.45 to 1.57)	0.58	0.78 (0.28 to 2.14)	0.63
Treatment	280				
Outpatient		1.00		1.00	
Inpatient		2.36 (1.09 to 5.11)	0.03	2.83 (0.79 to 10.15)	0.11
Diagnosis	274				
Affective		1.00		1.00	
Schizophreniform		0.82 (0.39 to 1.73)	0.60	0.92 (0.29 to 2.98)	0.89
All other diagnoses		1.83 (0.71 to 4.71)	0.21	2.17 (0.4 to 11.89)	0.37
Agitation symptoms	290				
Present*		1.00		1.00	
Not present†		0.94 (0.49 to 1.78)	0.83	0.75 (0.26 to 2.17)	0.59

\*Score of 2=mild, 3=moderate, 4=marked or 5=severe on the SAPS excitatory/agitation score.

†Score of 0=none or 1=questionable on the SAPS excitatory/agitation score.

DUP, estimated duration of untreated psychosis; EIP, early intervention in psychosis; GAF, Global Assessment of Functioning; SAPS, Scale for the Assessment of Positive Symptoms.

1.23). However, they did not remain significant in the multivariable analysis. There was no further evidence of associations with any other variables in univariate or multivariable analysis (table 5).

## DISCUSSION

### Summary of findings

This study describes the pattern of antipsychotic prescribing for a naturalistic cohort of patients presenting for assessment of FEP in a geographically defined catchment over a 21-year period. The data demonstrate the changes over time in the choice of antipsychotic medication, the move towards predominantly SGA use and the prevalence of olanzapine as a first-choice medication. Guidelines issued in both Europe and America widening the choice of antipsychotic medication or specifically not recommending olanzapine as an initial choice of agent do not appear to have had an impact on prescribing patterns. Additional indicators of good practice such as the use of low doses of antipsychotic medication for the initial treatment of FEP and the avoidance of high doses and antipsychotic polypharmacy are demonstrated. The demographic and clinical factors investigated did not appear to significantly influence the initial choice of antipsychotic medication. There was some evidence that inpatient treatment setting was associated with a higher

initial dose of antipsychotic medication (>50% BNF maximum). Increasing dose requirements over the first month of engagement with an EIP service was associated with poorer global functioning at baseline, greater positive symptoms at baseline and the inpatient treatment setting. However, these associations were not seen in the multivariable model.

### Comparison with previous literature and clinical implications

EIP services aim to provide timely access to comprehensive assessment and programmes of care including medical, psychological, occupational and social support.<sup>29</sup> A positive first experience of using antipsychotic medicines is likely to have an impact on future engagement with services and outcomes.<sup>30 31</sup> Careful consideration of the first antipsychotic medication involves balancing side effects with expected benefits and incorporating the patient perspective through a shared decision-making approach. Managing side effects is a significant challenge with the risks of metabolic abnormalities, sexual problems and movement disorders among the many potential disadvantages of using these medications. Given the variety of antipsychotic medication available, the lack of evidence for relative efficacy benefits in FEP in the context of significant differences in side effect profiles,<sup>12</sup> it is useful to examine what medications are actually used in practice with clinical implications for the services'

**Table 5** Regression analysis exploring the odds of an increase in dose (compared with no increase—stay the same or decreased) with reference to clinical and demographic characteristics for patients presenting to an EIP service

	Univariate analysis			Multivariable analysis (n=142)	
	n	OR (95% CI)	P value	OR (95% CI)	P value
Age	268	0.98 (0.96 to 1.00)	0.11	0.99 (0.95 to 1.03)	0.51
DUP (months)	147	0.99 (0.97 to 1.01)	0.37	1.00 (0.97 to 1.02)	0.76
GAF	263	0.97 (0.94 to 0.99)	<0.01	0.97 (0.93 to 1.01)	0.10
SAPS	262	1.13 (1.05 to 1.23)	<0.01	1.04 (0.89 to 1.21)	0.61
Sex	268				
Male		1.00		1.00	
Female		0.8 (0.46 to 1.40)	0.44	1.37 (0.57 to 3.29)	0.48
Treatment	268				
Outpatient		1.00		1.00	
Inpatient		2.10 (1.09 to 4.05)	0.03	1.76 (0.61 to 5.06)	0.30
Diagnosis	265				
Affective		1.00		1.00	
Schizophreniform		0.83 (0.43 to 1.61)	0.58	0.68 (0.23 to 2.01)	0.48
All other diagnoses		1.13 (0.46 to 2.81)	0.79	1.43 (0.29 to 7.12)	0.67
Agitation symptoms	263				
Present*		1.00		1.00	
Not present†		1.66 (0.95 to 2.91)	0.07	1.23 (0.5 to 3.06)	0.65

\*Score of 2=mild, 3=moderate, 4=marked or 5=severe on the SAPS excitatory/agitation score.

†Score of 0=none or 1=questionable on the SAPS excitatory/agitation score.

.DUP, estimated duration of untreated psychosis; EIP, early intervention in psychosis; GAF, Global Assessment of Functioning; SAPS, Scale for the Assessment of Positive Symptoms.

approach to managing physical health complications of antipsychotic use.

The trend towards SGA use over time in our study reflects the early optimism for medications with reduced propensity to cause anticholinergic side effects and long-term movement disorders. While the preference for olanzapine as a first-choice antipsychotic has been previously reported in the literature,<sup>32–35</sup> the prescribing rate in this cohort is high by comparison. For example, a Spanish study of prescribing practices for FEP found that 22.7% were prescribed olanzapine and a UK study described a prescribing rate of 35%. In the USA, where the PORT guidelines specifically exclude olanzapine as a first-choice medication, the prescribing rate was 31.2% in the Recovery After an Initial Schizophrenia Episode-Early Treatment Programme (RAISE-ETP) study.<sup>20</sup> Although this study did not explore the reasons for clinicians' choice of antipsychotic medication, olanzapine may be perceived to be more effective<sup>36</sup> and reduce the need for additional prescribing, for example, a benzodiazepine or hypnotic.

Olanzapine has a higher risk of inducing weight gain and metabolic abnormalities in comparison to other antipsychotics that could potentially be used as an initial treatment option in FEP.<sup>37,38</sup> Antipsychotic-induced weight gain causes considerable patient distress, has serious general health implications and leads to early discontinuation of

medication.<sup>39</sup> Over time the characteristics of the population changed with more people provisionally diagnosed with substance use disorder in comparison to the early cohort. This likely reflects the achievements of the EIP service in reducing DUP and the diagnostic criteria for schizophrenia requiring presence of symptoms for 6 months or more. Olanzapine is a sedative medicine and may be a reasonable choice if the patient were agitated, a presentation commonly associated with substance misuse. However, univariate and multivariate regressions did not find an association with symptoms of agitation. While a reduction in the proportion of patients with FEP using olanzapine as an initial treatment could be beneficial, strategies to prevent and manage weight gain should form part of an EIP programme where olanzapine continues to be used as a first-line agent. Lifestyle interventions,<sup>40</sup> metformin<sup>41</sup> and liraglutide<sup>42</sup> are potential options.

Historically, LAI and depot formulations were recommended if adherence to oral medication was poor<sup>13</sup> or, in more recent times, as first-line agents if the patient expressed a preference for the formulation.<sup>43</sup> The advantages may include reduced hospitalisation, more stable therapeutic blood levels with no additional side effect burden and convenience for the patient.<sup>43,44</sup> Confirming adherence through the use of LAIs may lead to better treatment decisions and earlier recognition of treatment resistance. However, barriers to the use of these



formulations include a reluctance on the part of some patients to engage in their use and a view that there may be a coercive nature to injecting medication.<sup>45</sup> In this study, the prevalence of LAI use is low, with some historical use of the FGAs described in our first cohort. The preference for SGAs may have had an impact on the use of LAIs until the development of the first second-generation LAI formulation of risperidone.

Clozapine is generally reserved for patients whose symptoms have not responded to adequate trials of two antipsychotic medications at the maximum tolerable dose.<sup>13 46</sup> When compared with chlorpromazine as an initial treatment for FEP, clozapine was no more effective.<sup>47</sup> However, early use of clozapine for those considered treatment resistant has been recognised as increasingly important. For example, early use of clozapine was effective for 75% of those with treatment resistance included in an observational study by Agid *et al.*<sup>14</sup> Furthermore, Yoshimura *et al* report that early use of clozapine was associated with a response rate of 80% compared with a response rate of 30% if clozapine initiation was delayed by 2.8 years or more.<sup>48</sup> In our study, none of the patients were treated with clozapine and this is likely due to the inclusion of patients in the very early stages of treatment with up to 30 days of antipsychotic exposure at study entry. Additional research has demonstrated that the time to clozapine treatment for those with treatment-resistant illness in our study cohorts is reducing with an average time to clozapine treatment of 6.7 years in the FEP study<sup>49</sup> compared with 2.1 years for those engaged in the EIP service.<sup>50</sup>

Guidelines recommend commencing antipsychotic medication at the lower half of the dose range in FEP.<sup>16 17</sup> We therefore took a pragmatic approach to describing the pattern of antipsychotic doses by expressing dose as a percentage of the BNF maximum. Guideline recommendations were generally adhered to with 78.6% of patients prescribed lower doses at initial presentation and the use of high-dose medication regimens was negligible at both initial assessment and after 1 month of treatment. Bioque *et al* reported that 8.9% of patients received higher doses of medication, by comparison.<sup>34</sup> Our description of antipsychotic use in the very early stages of treatment for FEP may explain the low rates of antipsychotic polypharmacy and high-dose treatment strategies in comparison to other studies.<sup>34 51</sup>

Clinical practice guidelines in psychiatry are often difficult to implement.<sup>21 52</sup> In the RAISE-ETP study, for example, Robinson *et al* found that, at the point of engagement with an EIP service, medication review would be beneficial for 39.4% of the 404 patients enrolled in their study. The reasons for medication review included the use of olanzapine (31.2%) and the use of high-dose regimens (8.8%) or combinations of antipsychotic medications (23.3%).<sup>51</sup> Proactive support for prescribing practice can be an effective means of improving the quality of medication use in FEP.<sup>19 48 53</sup> Observational studies by Yoshimura *et al* and Yeisen *et al* demonstrated that the initial choice of antipsychotic can be influenced by locally implemented

algorithms.<sup>48 53</sup> Robinson *et al* developed the NAVIGATE prescribing principals and the COMPASS decision-making tool which was designed to facilitate communication between the patient and the prescriber in the RAISE trial.<sup>19</sup> Training was provided for prescribers and they were given ongoing support throughout the study. Over a 2-year period, study participants (n=223) had more medication visits, were more likely to use a medication that conformed to the NAVIGATE guidelines, experienced fewer side effects and gained less weight than those who had received usual community care (n=181). Adherence estimator scores also improved in the NAVIGATE group but not in the community group. The models of care for EIP internationally give varying attention to supporting medicines optimisation.<sup>1</sup> This evidence and the results of our study suggest that EIP services and patients could benefit from proactive support for prescribing practice.

### Strengths, limitations and future research

We report prescribing data from a naturalistic cohort with inclusion criteria reflecting the age range and diagnoses presenting to an EIP service. The longitudinal data allow a view of the pattern of prescribing practice over a 21-year period during the development and implementation of an EIP service. We were also able to describe the clinical use of the medications in terms of dose changes and the need to switch medication or formulation over the first month of engagement with the EIP service. In studies regarding antipsychotic use in an FEP population, patients were often treated with antipsychotic medication for a number of months before assessment by an EIP service and therefore may not accurately reflect the first choice of antipsychotic or initial dose.<sup>32 34 35 51</sup> In our study, participants had less than 30 days of antipsychotic exposure.

Patient-related factors other than those assessed, such as patient preference sociodemographic factors or clinical metabolic parameters, may have had an influence on the choice or dose of antipsychotic medication. While we were able to describe the choice of antipsychotic when switching medication, we did not have the data to explore the reasons for switching medication. The retrospective nature of this study led to some missing data in both cohorts. The pattern of prescribing in the interim period between the FES and the EIP studies could not be described. International prescribing guidelines are not specifically promoted in Ireland and there are no local antipsychotic prescribing guidelines for FEP in the Irish mental health services. Their influence may, therefore, be expected to be poor. It would be useful to examine the topic prospectively to include shared decision-making processes and clinician-related factors and investigate the impact on patient outcomes including physical health. Future local or national guidelines may influence prescribing practice and include decision support tools and proactive management protocols to mitigate the potential side effects of antipsychotic medication.

## CONCLUSION

There is clearly a move towards the use of SGAs as initial treatment for FEP. Guidelines which recommend avoiding olanzapine as an initial choice based on its side effect profile do not appear to have had an influence on prescribing practice. Antipsychotics are generally initiated at low doses. Given the importance of early experiences with medication, consideration should be given to including a proactive approach to medicines optimisation within the EIP model of care. This could include locally agreed guidelines, decision support tools for both patients and clinicians and active management of side effects.

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## ORCID iDs

Dolores Keating <http://orcid.org/0000-0001-7507-2680>

Fiona Boland <http://orcid.org/0000-0003-3228-0046>

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