Gender differences in clinician-recorded side effects among people with first episode psychosis: real-world evidence from electronic health record data

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Objectives

Previous research has demonstrated gender differences in the clinical presentation of first episode psychosis.[1] However, less is known about gender differences related to the tolerability of antipsychotics used to treat psychotic disorders.[2] We sought to investigate the associations of gender with clinician-recorded side effects by analysing real-world data assembled from electronic health records (EHRs).

Methods

De-identified EHR data were analysed from adults who received care from **Early Intervention Services for psychosis** in the **South London and Maudsley (SLaM) NHS Foundation Trust, UK**.[3] Data were assembled using the **Clinical Record Interactive Search tool (CRIS)** and analysed using **R v4.1.0**. The presence or absence of clinician-recorded side effects (**extrapyramidal; hyperprolactinemia; sedation; sexual; weight gain**) were ascertained through manual review of free text clinical records. Patients aged over 16 years presenting to SLaM Early Intervention Services between April-01-2008 and March-31-2019 with ≥2 years of follow-up data were included. Patients without first episode psychosis or with incomplete clinical records were excluded (Figure 1). The associations of side effects with discontinuation of the first-prescribed antipsychotic and antipsychotics prescribed at any point during the follow-up period were investigated using **multivariable Cox regression** with age, gender, ethnicity, and prescription setting (inpatient vs community) as covariates. The index date was the date of accepted referral to Early Intervention Services.

Figure 1 – Study attrition chart

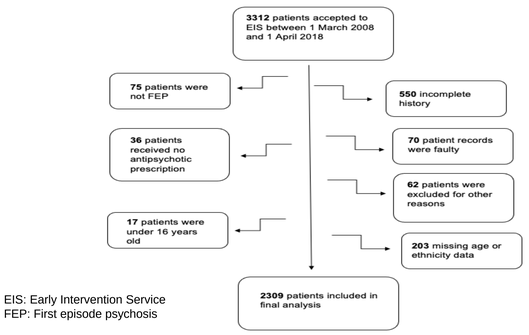
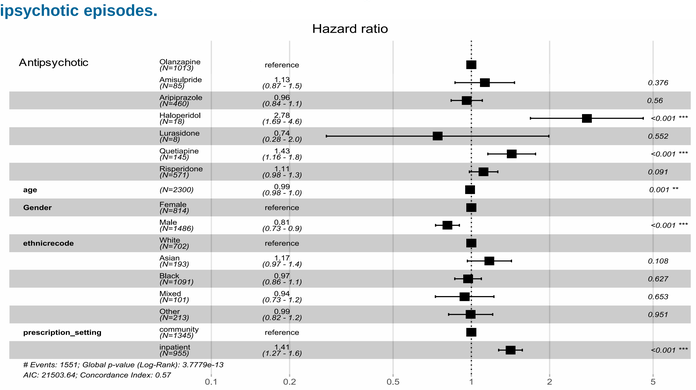


Figure 2 – Cox regression analysis comparing the rate of discontinuation between first antipsychotic episodes.



Results

- **2,309 adults with first episode psychosis** were included in the study with a mean follow-up duration of 34.2 months and a **total study follow-up of 6,830.8 person years**.
- The mean age of patients was **26.7 years**. **1,492 (64.6%) were male** and **817 (35.4%) were female**.
- **Olanzapine (n=1,013)**, **risperidone (n=571)** and **aripiprazole (n=460)** were the most frequently first-prescribed antipsychotics. The first prescribed antipsychotic choice varied between male and female patients (Table 1) with female patients less likely to be prescribed risperidone (22.2%) than male patients (26.1%).
- First prescribed antipsychotics were discontinued earlier when commenced in **inpatient settings than in community settings (HR=1.41, 95%CI=1.27-1.60)**. **Haloperidol (HR=2.78, 95%CI=1.69-4.60)** and **quetiapine (HR=1.43, 95%CI=1.16-1.80)** were discontinued significantly sooner compared to olanzapine (Figure 2).
- **Female patients discontinued their first-prescribed antipsychotic significantly earlier than male patients (hazard ratio (HR)=1.23, 95%CI=1.11-1.37)**.
- Among antipsychotics prescribed at any point during the follow-up period, **clozapine (HR=0.55, 95%CI=0.41-0.73)** and **paliperidone once-monthly long-acting injectable (LAI)/PP1M (HR=0.80, 95%CI=0.68-0.94)** were discontinued significantly later compared to olanzapine while **aripiprazole (HR=1.09, 95%CI=1.01-1.19)** and **lurasidone (HR=1.40, 95%CI=1.10-1.78)** were discontinued significantly sooner (Figure 3).
- **Extrapyramidal (n=125, HR=1.33, 95%CI=1.08-1.64)** and **sexual side effects (n=24, HR=1.59, 95%CI=1.03-2.46)** were associated with significantly faster treatment discontinuation of first prescribed antipsychotics (Figure 4).
- Among antipsychotics prescribed at any point during the follow-up period, **sedation (n=898, HR=0.89, 95%CI=0.81-0.97)**, **weight gain (n=374, HR=0.73, 95%CI=0.64-0.83)**, or **multiple side effects (n=873, HR=0.83, 95%CI=0.76-0.90)** were associated with significantly delayed treatment discontinuation (Figure 5).
- 709 male (47.5%) and 427 female (52.3%) patients had at least one clinician-recorded side effect ($\chi2$=4.8, p=0.03).
- Male patients had similar rates of sedation, extrapyramidal side effects and sexual side effects but **lower rates of weight gain (16.7% vs. 22.2%, $\chi2$=10.4, p=0.001)** and **hyperprolactinaemia (3.2% vs. 7.2%, $\chi2$=19.2, p<0.001)** compared to female patients (Table 2).

Table 1 – Frequency of first-prescribed antipsychotics by gender

	Amisulpride	Aripiprazole	Haloperidol	Lurasidone	Olanzapine	Quetiapine	Risperidone	Other	Total
Male	61	300	12	6	645	72	390	6	1492
Female	24	160	6	2	368	73	181	3	817
Total	85	460	18	8	1013	145	571	9	2309
Row percentages									
Male	4.1%	20.1%	0.8%	0.4%	43.2%	4.8%	26.1%	0.4%	100.0%
Female	2.9%	19.6%	0.7%	0.2%	45.0%	8.9%	22.2%	0.4%	100.0%
Column percentages									
Male	71.8%	65.2%	66.7%	75.0%	63.7%	49.7%	68.3%	66.7%	64.6%
Female	28.2%	34.8%	33.3%	25.0%	36.3%	50.3%	31.7%	33.3%	35.4%

$\chi2$: 20.4, p=0.004

Table 2 – Frequency of clinician-recorded side effects by gender

	Sedation n (%)	Weight gain n (%)	EPSE n (%)	Sexual side effects n (%)	Hyperprolactinaemia n (%)
Male yes	476 (31.9%)	249 (16.7%)	136 (9.1%)	56 (3.8%)	48 (3.2%)
Male no	1016 (68.1%)	1243 (83.3%)	1356 (90.9%)	1436 (96.2%)	1444 (96.8%)
Female yes	265 (32.4%)	181 (22.2%)	60 (7.3%)	42 (5.1%)	59 (7.2%)
Female no	552 (67.6%)	636 (77.8%)	757 (92.7%)	775 (94.9%)	758 (92.8%)
Test statistic	$\chi2$: 0.07, p=0.79	$\chi2$: 10.4, p=0.001	$\chi2$: 2.1, p=0.14	$\chi2$: 2.5, p=0.11	$\chi2$: 19.2, p<0.001

EPSE: Extrapyramidal side effect

Figure 3 – Cox regression analysis comparing the risk of discontinuation between antipsychotics prescribed at any time point.

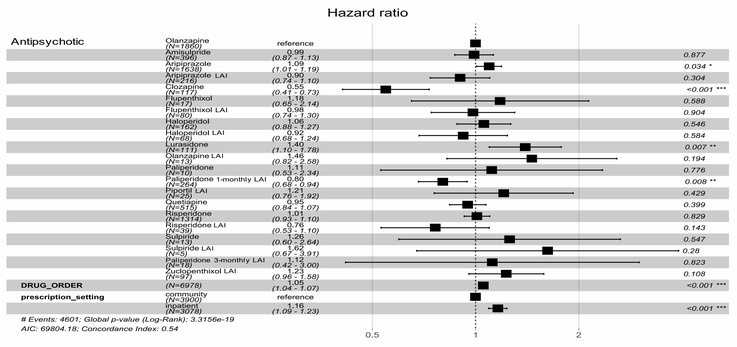


Figure 4 – Kaplan-Meier survival curve comparing time to discontinuation of first prescribed antipsychotic with clinician-recorded side effects.

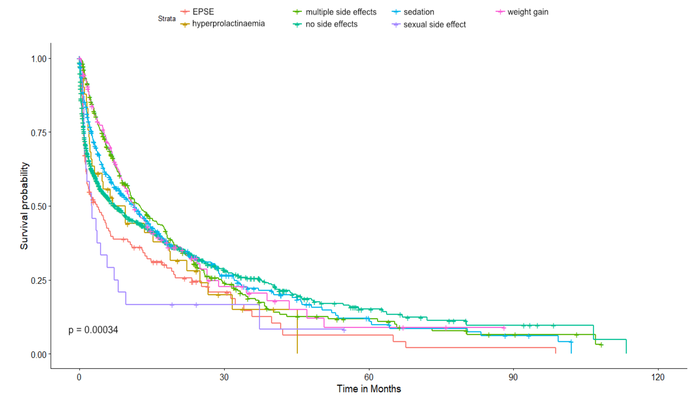
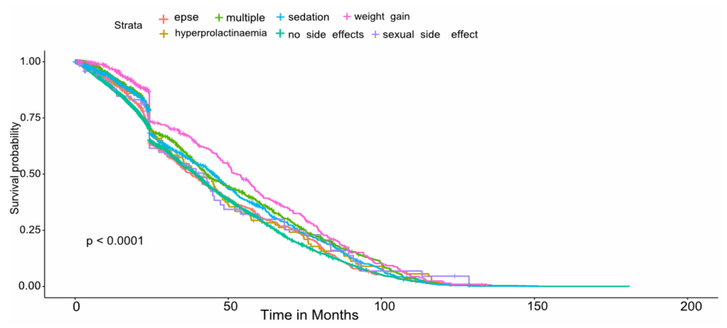


Figure 5 – Kaplan-Meier survival curve comparing time to discontinuation of antipsychotics prescribed at any time point with clinician-recorded side effects.



Conclusions

Extrapyramidal and sexual side effects were associated with faster treatment discontinuation among first-prescribed antipsychotics. This may reflect the relatively fast onset of these side effects leading to earlier treatment discontinuation. In contrast, sedation, weight gain and multiple side effects were associated with slower treatment discontinuation. This could reflect the propensity for antipsychotics with relatively high efficacy to be associated with these side effects. Frequent monitoring and enhanced clinical support are likely to contribute to the lower discontinuation rate of clozapine. The lower discontinuation rate of PP1M suggests that LAI antipsychotics may support treatment adherence in FEP.

Female patients were more likely to have weight gain or hyperprolactinaemia recorded in EHR data whereas sedation, extrapyramidal side effects, and sexual side effects were similar compared to male patients. These differences, along with other potentially confounding variables, may explain the greater rate of antipsychotic discontinuation among female patients and highlight a need to tailor treatment options for first episode psychosis accordingly.

References:

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2. Ther Adv Psychopharmacol 2023, Vol. 13: 1–14. doi: 10.1177/20451253231211575
3. BMJ Open 2016, doi: 10.1136/bmjopen-2015-008721

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Conflict of Interest disclosure:

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