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ORIGINAL RESEARCH ARTICLE

Disability and Adverse Effects of Oral Versus Long-Acting Injectable Antipsychotics in Schizophrenia-Spectrum and Bipolar Disorder: A Comparison Based on Data-Driven Taxonomy

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Abstract

Background Patients undergoing antipsychotic treatment for psychiatric disorders may experience challenges in functioning, either stemming from the severity of the illness or from the tolerability issues of prescribed medications.

Objectives The aims of this cross-sectional study are to investigate the impact of adverse effects of antipsychotic drugs on patients' daily life functioning, comparing oral and long-acting injectable (LAI) antipsychotics, and further dividing antipsychotics by receptor-binding profiles based on recently defined data-driven taxonomy.

Methods This study involved patients with schizophrenia and bipolar spectrum disorders taking oral or LAI antipsychotics. Disability and functioning levels were assessed using the World Health Organization Disability Assessment Schedule 2.0 (WHODAS), and the adverse effects of medications were evaluated using the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale and its subscales.

Results The total sample consisted of 126 participants with a diagnosis of schizophrenia-spectrum or bipolar disorder, and included 54 males and 72 females ranging from 18 to 78 years of age (mean 45.1, standard deviation 14); 78 patients were taking oral antipsychotics and 48 were taking LAI antipsychotics, with subcategories of muscarinic (31), adrenergic/low dopamine (25), serotonergic/dopaminergic (23), dopaminergic (1), LAI muscarinic (15), LAI adrenergic (6), and LAI serotonergic/dopaminergic (25). The UKU total score for adverse effects showed significant correlations with WHODAS total score ($\rho = 0.475$; $p < 0.001$). Compared with oral antipsychotics, LAIs showed significantly lower scores in psychological ($p = 0.014$), autonomic ($p = 0.008$), other ($p = 0.004$), and sexual adverse effects ($p = 0.008$), as well as the UKU total score ($p = 0.002$). The Kruskal–Wallis test showed a significant difference in adverse effects between LAI and oral muscarinic subgroups, with LAIs having lower scores compared with antipsychotics binding to muscarinic receptors ($p = 0.043$).

Conclusion These findings indicate clinically relevant differences in adverse effects among formulations, warranting further investigation for future observational studies.

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Key Points

Significant correlations between adverse effects and disability levels were found.

Long-acting injectable (LAI) antipsychotics showed fewer adverse effects across various domains compared with oral formulations.

LAI medications targeting muscarinic receptors exhibited significantly lower adverse effect scores, suggesting potential benefits in reducing adverse effects associated with this receptor subtype.

1 Introduction

The World Health Organization (WHO) recognizes disability as a complex construct that includes impairment, activity limitation, and participation restrictions [1]. The WHO adopted the International Classification of Functioning, Disability and Health (ICF) definition of disability, acknowledging it as a complex construct that considers the cultural context and varying living conditions across different environments [2]. Untreated severe psychiatric disorders or significant relapses may impact self-care and daily functioning in critical domains [3], thus necessitating a holistic rehabilitation approach [4]. Antipsychotics are essential for controlling psychiatric symptoms, maintaining an acceptable quality of life and preventing drug resistance after discontinuation; however, they often cause adverse effects that can further impair functioning already affected by the underlying pathology [5, 6]. While effective, more recent antipsychotics have distinct adverse effects such as metabolic disturbances, weight gain, and increased cardiovascular risk [7]. Adverse effects require vigilant monitoring through tools such as the UKU for a comprehensive assessment [8]. The impact of adverse effects on disability still warrants further investigation, since the scope and extension of this relationship remain unclear [9, 10]. Despite recognizing the impact of adverse effects on disability, research lacks specific data across diverse populations and domains [11–13], with limited differentiation of disability proportions attributable to adverse effects versus underlying illness or contextual factors [14]. This study explores the link between antipsychotic-induced adverse effects and functional impairments in daily life among psychiatric patients with a diagnosis of schizophrenia-spectrum or bipolar disorder using standardized tools. It examines variations in adverse effects and disabilities across different groups, identifying unique patterns. By connecting medication adverse effects to daily-life quality, this study aims to inform personalized treatment plans, considering intolerable adverse effects that cause distress and poor adherence, thus improving patient care.

2 Materials and Methods

2.1 Patients and Methods

This retrospective study analyzed data collected between May 2023 and December 2023 at the Clinical Hospital 'Policlinico G. Rodolico' (Psychiatry Unit, University of Catania, Catania, Italy). Inclusion criteria involved being diagnosed with schizophrenia-spectrum or bipolar disorder in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), having been treated with antipsychotics for at least 1 month (either as a primary therapy for schizophrenia or as mood stabilizers for bipolar disorder), and being clinically stable based on clinician judgment. Exclusion criteria included intellectual disability, major neurocognitive disorder, acute psychotic relapse, poor understanding of the Italian language, and substance misuse at the time of the assessment. The study size was defined based on the available data for the time frame considered. Sociodemographic, clinical, and test data were extracted from psychiatric unit archives. Psychometric tests were routinely administered and recorded for pharmacovigilance purposes, and these records were subsequently obtained for the study. Antipsychotics were categorized by administration route. Additionally, they were divided into muscarinic, adrenergic/low dopaminergic, serotonergic/dopaminergic, and dopaminergic antagonist categories based on recent data-driven classification [15]. This taxonomy utilized an algorithm to cluster 27 antipsychotics into four groups, then employed a machine learning model to predict the most common adverse effects for each group. Accordingly, the muscarinic group is associated with metabolic and cholinergic adverse effects; the adrenergic group is associated with a low overall adverse effect profile; the serotonergic/dopaminergic group is associated with a moderate adverse effect burden; and the dopaminergic group is associated with extrapyramidal symptoms (EPS) and hyperprolactinemia. All subjects provided informed consent for their scores to be used for research, adhering to the Declaration of Helsinki. During the preparation of this work, the authors used GPT-4 by OpenAI© in order to refine sentence structures and linguistic style. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

2.2 Measures

2.2.1 Medication Treatment Adverse effects

The UKU Side Effect Rating Scale [8] was selected to evaluate the adverse effects of drug treatment for its reliability since it is regarded as a gold standard in the assessment of medication-induced adverse effects [16]. Administered by the clinician, the scale consists of 48 items, each rated by the clinician on a 4-point Likert scale ranging from 0 to 3, corresponding to the severity of the symptoms. These items are grouped into four main categories: psychic, neurological, autonomic, and other adverse effects. Additionally, genitosexual adverse effects from the 'other' subscale (considering UKU items 4.7–4.16) were extracted because this category is mixed and isolating these adverse effects can provide more detailed and valuable information. Both total scores and subscale scores are reported, with the scoring being done by summing the severity ratings from the Likert scale.

2.2.2 Disability and Functioning

Functional disability was evaluated using the Italian language-validated version of the World Health Organization Disability Assessment Schedule 2.0 (WHODAS) [17], which was developed to measure functioning and disability in accordance with the ICF. The clinician-assisted version of the scale was used, in which the researcher read each question aloud and the patient rated their difficulty in specific functional areas on a 5-point visual analog scale (VAS), ranging from 0 (no difficulty) to 4 (extreme difficulty). The scale comprises 36 items referring to the previous 30 days. These items are grouped into six life domains: cognition (understanding and communication), mobility (getting around), self-care (personal hygiene, dressing and eating, etc.), getting along (interacting with others), life activities (to carry out responsibilities), and participation in society (be able to attend a community of people, attending recreational activities) [18]. Final scores were computed using the scoring method outlined by the original authors of the scale, yielding a percentage score for each domain and an aggregate overall score; higher percentage scores correspond to a higher level of disability. The tool has shown high internal consistency (Cronbach's alpha [α] 0.86) and high test–retest reliability (intraclass correlation coefficient 0.98), and effect sizes ranged from 0.44 to 1.38 [18].

2.3 Data Analysis

Spearman's rank correlation coefficient was employed to evaluate the monotonic relationship between the WHODAS scale variables and the UKU variables. This non-parametric approach is suitable for assessing correlation between variables measured on continuous or ordinal scales, particularly when the distribution of the variables may not meet the assumptions of parametric tests. To account for potential confounders, partial correlations were computed after adjusting for pertinent sample characteristics, such as sex, age, smoking, history of substance misuse, antipsychotic administration, diagnosis, and other medical disease. The Mann–Whitney U test was performed to compare levels of disability and adverse effects across various groups, due to the likely non-normal distribution of data and the probable absence of homogeneity of variance. To avoid potential source of bias, the groups were differentiated by sociodemographic and clinical factors, including age, sex, diagnosis, smoking, class of drugs, antipsychotics administration, number of children, educational status, history of substance misuse, and family history of psychiatric disorder [19]. A conventional alpha threshold for significance was assumed for all analyses ($\alpha = 0.05$). Bonferroni correction was not applied because each correlation has been treated as an independent hypothesis with a single test, maintaining the nominal alpha level for each without inflating the risk of type II errors due to overcorrection; this approach is appropriate when hypotheses are independent and not subject to the compounding type I error risk associated with multiple related tests [20]. Cronbach's alpha and McDonald's omega were calculated for each of WHODAS domains to confirm internal reliability of the measures. Due to the non-normal distribution of the scores, the Kruskal–Wallis test was used to compare scores across groups of participants categorized based on the type of antipsychotic medication taken (long-acting injectables [LAI] and oral) and their respective pharmacodynamic profiles. This test was chosen for its ability to assess differences in central tendency across multiple independent groups without assuming a normal distribution. Following a significant Kruskal–Wallis test result, Dwass–Steel–Critchlow–Fligner pairwise comparisons were conducted as post hoc analyses to identify specific group differences. All statistical analyses were conducted using the open-source software 'Jamovi' [21].

3 Results

3.1 Sociodemographic Features of the Total Sample

The total sample comprised 126 participants, including 72 males and 54 females. The mean age was 45.1 (standard deviation [SD] 14), ranging from 18 to 78 years of age. Eighty-four patients were diagnosed with schizophrenia-spectrum disorders and 42 with bipolar disorders. Relevant

Table 1 Sample characteristics

Characteristics	Category	Value [*n* (%)]
Sex	Male	72 (57.1)
	Female	54 (42.9)
Age, years	Mean (SD) [Range]	45.1 (14) [18–78]
	Young (18–49 years)	71 (56.3)
	Mature (>50 years)	55 (43.7)
Occupation	No occupation	92 (73)
	Occupation	34 (27)
Education	Elementary school	10 (7.9)
	Middle school	45 (35.7)
	High school	56 (44.4)
	University degree	15 (11.9)
Marital status	Maiden/divorced	91 (72.2)
	Married	35 (27.8)
Parental status	Has children	51 (40.5)
	No children	75 (59.5)
Smoking	Yes	66 (52.4)
	No	60 (47.6)
Diagnosis	Schizophrenia-spectrum disorder	84 (66.7)
	Bipolar disorder	42 (33.3)
History of substance misuse	Yes	18 (14.3)
	No	108 (85.7)
Family history of psychiatric disorders	Yes	45 (35.7)
	No	81 (64.3)
Antipsychotic administration	Oral	78 (61.9)
	LAI	48 (38.1)
Antipsychotic group	LAI muscarinic	15 (11.9)
	LAI adrenergic	6 (4.8)
	LAI serotonergic/dopaminergic	25 (19.8)
	Muscarinic	31 (24.6)
	Adrenergic	25 (19.8)
	Serotonergic/dopaminergic	23 (18.3)
	Dopaminergic	1 (0.8)
Antipsychotic dosage[a]	Target (LAI)	46 (36.5)
	Target (oral)	61 (48.4)
	Low (oral)	19 (15.1)

LAI long-acting injectable, *SD* standard deviation

[a]Antipsychotics were divided into target and low, according to the dosage range recommended in recent literature [22]

characteristics of the sample are reported in Table 1, while antipsychotic distribution is reported in Table 2.

The mean and SD of the Scales are reported in Table 3. The alpha and omegas of the WHODAS scale were found to be very high, affirming the reliability of this data collection (see Table 4).

3.2 Correlations and Partial Correlations

3.2.1 Group Comparisons

Tables 5 and 6 show comparisons between groups conducted using the Mann–Whitney U test. History of substance misuse and smoking did not show significant differences; however, sex did show significant differences, with women reporting higher adverse effects in the UKU global

Table 2 Antipsychotic distribution

Antipsychotic medication	Oral [*n* (%)]	LAI [*n* (%)]
Muscarinic		
Olanzapine	10 (7.9)	15 (11.9)
Clozapine	6 (4.8)	–
Quetiapine	13 (10.3)	–
Levomepromazine	1 (0.8)	–
Promazine	1 (0.8)	–
Adrenergic/low DA		
Aripiprazole	16 (12.7)	6 (4.8)
Lurasidone	5 (4)	–
Cariprazine	2 (1.6)	–
Brexpiprazole	2 (1.6)	–
Serotonergic/dopaminergic		
Paliperidone	6 (4.8)	22 (17.5)
Risperidone	11 (8.7)	22 (17.5)
Zuclopenthixol	4 (3.2)	–
Haloperidol	2 (1.6)	–
Dopaminergic		
Amisulpride	1 (0.8)	–

DA dopamine antagonist, *LAI* long-acting injectable

score ($p = 0.002$), psychological ($p = 0.001$), neurological ($p = 0.020$), autonomic ($p = 0.013$) and other adverse effects ($p = 0.047$). Younger patients (18–49 years of age) reported higher adverse effects in the other subgroup ($p = 0.025$) and sexual adverse effects ($p = 0.049$) compared with older patients (>50 years of age). Educational status showed a significant difference in neurological adverse effects, showing higher scores in participants with no education ($p = 0.004$). Married participants reported higher scores in UKU total ($p = 0.039$), other adverse effects ($p = 0.018$), sexual adverse effects ($p = 0.029$), and self-care ($p = 0.012$). Parental status showed significant differences in neurological adverse effects ($p = 0.048$), with higher scores reported by patients with children. Occupational status showed a significant difference in global disability ($p = 0.043$), mobility ($p = 0.021$), and neurological adverse effects ($p = 0.040$), with subjects without employment showing higher scores. Comparison based on diagnosis revealed significant differences in WHODAS global score ($p = 0.004$), as well as in mobility ($p = 0.017$), life activities ($p = 0.009$), and participation ($p = 0.008$). In each of these domains, patients with schizophrenia exhibited lower scores compared with those with bipolar disorder. Antipsychotic administration (LAIs vs. orals) showed a significant difference in the UKU total score ($p = 0.002$), psychological ($p = 0.014$), autonomic ($p = 0.008$), other ($p = 0.004$), and sexual subgroups ($p = 0.008$) with LAIs resulting in lower scores in life activities and adverse effects. Considering the results shown by the comparison of orals versus LAIs, further investigations were carried out. Patients treated with LAIs reported significantly lower scores in inner unrest ($p = 0.012$), reduced duration of sleep ($p = 0.029$), constipation ($p = 0.014$), and itching ($p = 0.046$).

3.3 Group Comparison Based on Data-Driven Taxonomy for Antipsychotics

The Kruskal–Wallis test comparing multiple administration routes and the antipsychotic receptor-binding profile revealed significant differences in UKU total score ($p = 0.013$) and autonomic adverse effects ($p = 0.037$), as reported in Table 7. Dwass–Steel–Critchlow–Fligner pairwise comparisons (Table 8) revealed significant differences

Table 3 Scale measures

Scale/subscale	Sample [mean (SD)]	Median	IQR	Internal reliability	*N*
WHODAS total	2.43 (0.85)	0.310	0.310	$\alpha = 0.951$ $\omega = 0.953$	126
Cognition	2.32 (1.03)	0.292	0.375	$\alpha = 0.884$ $\omega = 0.885$	126
Mobility	1.99 (0.992)	0.175	0.388	$\alpha = 0.813$ $\omega = 0.828$	126
Self-care	1.73 (0.89)	0.125	0.297	$\alpha = 0.755$ $\omega = 0.799$	126
Getting along	2.44 (1.24)	0.350	0.600	$\alpha = 0.887$ $\omega = 0.897$	126
Life activities	2.77 (1.29)	0.438	0.469	$\alpha = 0.932$ $\omega = 0.933$	126
Participation in society	2.81 (0.893)	0.422	0.281	$\alpha = 0.803$ $\omega = 0.808$	126

IQR interquartile range, *SD* standard deviation, *WHODAS* World Health Organization Disability Assessment Schedule 2.0

Table 4 Correlation and partial correlation matrix[a]

	UKU total	Psychological AEs	Neurological AEs	Autonomic AEs	Other AEs	Sexual AEs	1.1 Concentration difficulties	1.6 Tension/inner unrest
WHODAS Total	$\rho = 0.475$*** Moderate $\rho c = 0.456$*** Moderate	$\rho = 0.484$*** Moderate $\rho c = 0.488$*** Moderate	$\rho = 0.282$** Weak $\rho c = 0.185$* Weak	$\rho = 0.201$* Weak	$\rho = 0.241$** Weak $\rho c = 0.249$** Weak	$\rho = 0.265$** Weak $\rho c = 0.315$*** Weak		$\rho = 0.440$*** Moderate $\rho c = 0.452$*** Moderate
Cognition	$\rho = 0.386$*** Weak $\rho c = 0.376$*** Weak	$\rho = 0.435$*** Moderate $\rho c = 0.443$*** Moderate	$\rho = 0.277$** Weak $\rho c = 0.232$* Weak	$\rho = 0.211$* Weak		$\rho c = 0.184$* Weak	$\rho = 0.436$*** Moderate $\rho c = 0.470$*** Moderate	
Mobility	$\rho = 0.281$** Weak $\rho c = 0.233$* Weak	$\rho = 0.266$** Weak $\rho c = 0.247$** Weak	$\rho = 0.266$** Weak	$\rho = 0.188$* Weak				
Self-care	$\rho = 0.275$** Weak $\rho c = 0.255$** Weak	$\rho = 0.194$* Weak	$\rho = 0.236$** Weak		$\rho c = 0.207$* Weak			
Getting along	$\rho = 0.364$** Weak $\rho c = 0.368$*** Weak	$\rho = 0.394$*** Weak $\rho c = 0.421$*** Moderate			ρ=0.285** weak ρc=0.277** weak	ρ=0.307*** weak ρc=0.317*** weak		
Life activities	ρ=0.389*** weak ρc=0.345*** weak	$\rho = 0.421$*** Moderate $\rho c = 0.405$*** Moderate	$\rho = 0.215$* Weak		$\rho = 0.186$* Weak	$\rho = 0.208$* Weak $\rho c = 0.202$** Weak		$\rho = 0.425$*** Moderate $\rho c = 0.420$*** Moderate
Participation	$\rho = 0.479$*** Moderate $\rho c = 0.437$*** Moderate	$\rho = 0.491$*** Moderate $\rho c = 0.458$*** Moderate	$\rho = 0.215$* Weak		$\rho = 0.296$*** Weak $\rho c = 0.258$** Weak	$\rho = 0.361$** Weak $\rho c = 0.356$*** Weak		$\rho = 0.462$*** Moderate $\rho c = 0.433$*** Moderate

AEs adverse effects, *UKU* Udvalg for Kliniske Undersogelser, *WHODAS* World Health Organization Disability Assessment Schedule 2.0, ρ Spearman's rho for correlation matrix, ρc Spearman's rho for partial correlation

[a]Partial correlations are controlled for 'sex', 'age', 'smoking', 'history of substance misuse', 'antipsychotic administration', 'diagnosis', 'children', 'educational status', 'group of drugs', and 'family history'. For the UKU total score and its subscales, only significant correlations are reported. For UKU specific items, only those showing a moderate to strong correlation are reported. The complete table is available in the electronic supplementary material (Table A and Table B). It was assumed that a ρ-value of $\geq$0.80 indicates a very strong relationship; values between 0.60 and 0.79 suggest a strong relationship; values between 0.40 and 0.59 indicate a moderate relationship; values between 0.20 and 0.39 indicate a weak relationship; and values below 0.20 indicate a very weak or negligible relationship [23] *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. In the correlation analysis, all 126 participants were considered

between LAIs that bind to muscarinic receptors and oral muscarinic drugs ($p = 0.043$) in autonomic adverse effects.

The LAI muscarinic subgroup revealed significantly lower scores (mean 2.33, SD 2.23) when compared with the oral muscarinic subgroup (mean 5.00, SD 2.79) for autonomic adverse effects.

3.4 Group Comparison Based on Dosage

The Kruskal–Wallis test was used to compare the doses of antipsychotics (orals and LAIs). As shown in Table 9, significant differences emerged in the UKU total score ($p = 0.013$), autonomic adverse effects ($p = 0.034$), and other adverse effects ($p = 0.014$). Dwass–Steel–Critchlow–Fligner pairwise comparisons (Table 10) revealed significant differences in the UKU total score ($p = 0.015$) and other adverse effects ($p = 0.017$) between LAIs at target dosages and low dosages of oral antipsychotics.

The comparison between the group taking the target dose of the LAI formulation and the low-dose oral group revealed significant differences in both the UKU total score ($p = 0.015$) and other adverse effects ($p = 0.017$). The group taking the target dose of the LAI formulation had lower scores, with a UKU total mean of 12.6 (SD 9.36) and a mean of 3.24 (SD 3.14) for other adverse effects, compared with the low-dose oral group, which had a UKU total mean

Table 5 Group comparisons

Variable	Total AEs	Psychological AEs	Neurological AEs	Autonomic AEs	Other AEs	Sexual AEs	WHODAS total	Cognition	Mobility	Self-care	Getting along	Life activities	Participation
Sex	0.331 ($p = 0.002$)	0.330 ($p = 0.001$)	0.236 ($p = 0.020$)	0.257 ($p = 0.013$)	0.206 ($p = 0.047$)								
Female	Mean 17.667 (SD 10.095)	Mean 6.593 (SD 5.268)	Mean 2.074 (SD 1.941)	Mean 4.630 (SD 3.252)	Mean 4.370 (SD 2.980)								
Male	Mean 12.361 (SD 7.249)	Mean 3.847 (SD 3.266)	Mean 1.264 (SD 1.463)	Mean 3.292 (SD 2.537)	Mean 3.472 (SD 3.076)								
Age, years					0.231 ($p = 0.025$)	0.196 ($p = 0.049$)							
18–49					Mean 4.366 (SD 3.181)	Mean 2.549 (SD 3.215)							
< 50					Mean 3.200 (SD 2.778)	Mean 1.655 (SD 2.696)							
Educational status			0.289 ($p = 0.004$)										
No education			Mean 2.109 (SD 1.863)										
Education <8 years			Mean 1.225 (SD 1.514)										
Marital status	0.238 ($p = 0.039$)				0.272 ($p = 0.018$)	0.240 ($p = 0.029$)				0.281 ($p = 0.012$)			
Maiden/ divorced	Mean 13.549 (SD 8.391)				Mean 3.462 (SD 2.889)	Mean 1.890 (SD 2.964)				Mean 0.233 (SD 0.205)			
Married	Mean 17.457 (SD 9.820)				Mean 4.886 (SD 3.252)	Mean 2.857 (SD 3.098)				Mean 0.350 (SD 0.245)			
Parental status			0.201 ($p = 0.048$)										
No children			Mean 1.293 (SD 1.422										
Children			Mean 2.078 (SD 2.018)										
Occupational status			0.231 ($p = 0.040$)				0.236 ($p = 0.043$)		0.267 ($p = 0.021$)				

Table 5 (continued)

Variable	Total AEs	Psychological AEs	Neurological AEs	Autonomic AEs	Other AEs	Sexual AEs	WHODAS total	Cognition	Mobility	Self-care	Getting along	Life activities	Participation
Unemployed			Mean 1.815 (SD 1.821)				Mean 0.382 (SD 0.187)		Mean 0.386 (SD 0.278)				
Employed			Mean 1.059 (SD 1.301)				Mean 0.316 (SD 0.195)		Mean 0.251 (SD 0.187)				
Diagnosis							0.312 ($p = 0.004$)		0.259 ($p = 0.017$)			0.285 ($p = 0.009$)	0.291 ($p = 0.008$)
Schizophrenia-spectrum							Mean 0.330 (SD 0.177)		Mean 0.312 (SD 0.261)			Mean 0.354 (SD 0.241)	Mean 0.419 (SD 0.215)
Bipolar disorder							Mean 0.431 (SD 0.201)		Mean 0.425 (SD 0.252)			Mean 0.498 (SD 0.288)	Mean 0.531 (SD 0.227)
Antipsychotic administration	0.331 ($p = 0.002$)	0.259 ($p = 0.014$)		0.279 ($p = 0.008$)	0.304 ($p = 0.004$)	0.272 ($p = 0.008$)							
Oral	Mean 16.436 (SD 9.176)	Mean 5.564 (SD 4.335)		Mean 4.397 (SD 3.042)	Mean 4.410 (SD 3.085)	Mean 2.487 (SD 3.145)							
LAI	Mean 11.708 (SD 7.792)	Mean 4.146 (SD 4.505)		Mean 3.000 (SD 2.535)	Mean 2.958 (SD 2.813)	Mean 1.625 (SD 2.757)							

AEs adverse effects, *LAI* long-acting injectable, *SD* standard deviation, *WHODAS* World Health Organization Disability Assessment Schedule 2.0

Table 6 Comparison of orals versus LAIs in specific adverse effects[a]

	1.6 Inner unrest	1.8 Reduced duration of sleep	3.6 Constipation	4.2 Itching
Antipsychotic administration	0.248; $p = 0.012$	0.164; $p = 0.029$	0.202; $p = 0.014$	0.140; $p = 0.046$
Oral	Mean 0.974 SD 0.897	Mean 0.436 SD 0.815	Mean 0.487 SD 0.752	Mean 0.269 SD 0.527
LAI	Mean 0.583 SD 0.739	Mean 0.167 SD 0.519	Mean 0.208 SD 0.582	Mean 0.146 SD 0.545

LAIs long-acting injectables, *SD* standard deviation, *UKU* Udvalg for Kliniske Undersogelser

[a]Only significant differences concerning individual UKU items are reported

Table 7 Kruskal–Wallis tests

Kruskal–Wallis				
	χ^2	*df*	*p*-value	ε^2
UKU total	16.07	6	0.013	0.1285
Psychological AEs	9.35	6	0.155	0.0748
Neurological AEs	2.41	6	0.878	0.0193
Autonomic AEs	13.43	6	0.037	0.1074
Other AEs	11.86	6	0.065	0.0949
Sexual AEs	7.63	6	0.266	0.0610
WHODAS total	6.95	6	0.325	0.0556
Cognition	4.78	6	0.573	0.0382
Mobility	4.41	6	0.622	0.0353
Self-care	5.92	6	0.432	0.0474
Getting along	5.62	6	0.467	0.0450
Life activities	7.51	6	0.276	0.0601
Participation	7.23	6	0.300	0.0578

UKU Udvalg for Kliniske Undersogelser, *WHODAS* World Health Organization Disability Assessment Schedule 2.0, *AEs* adverse effects

of 19.3 (SD 10.7) and a mean of 5.21 (SD 2.76) for other adverse effects.

4 Discussion

4.1 Findings and Interpretation of Results

The aim of this retrospective study was to investigate the impact of adverse effects on patient functioning, distinguishing antipsychotics by treatment route and binding profile. Data suggest a potential role of psychological adverse effects on global disability, cognition, life activities, and participation. Specific adverse effects that have an impact on functioning include concentration difficulties and inner unrest. Concentration difficulties were moderately correlated with abnormal cognitive functioning. These results suggest that pharmacological treatment may compromise patients' cognition when those treatments affect concentration, consistent with other reports suggesting that antipsychotic drugs may impair cognition [24]. Inner unrest exhibited strong correlations with WHODAS global score, life activities, and participation. Neurological adverse effects showed correlations with disability and each subdomain except for the subdomain on social interactions, which might suggest that interpersonal relations remained relatively unaffected despite other impairments. Autonomic adverse effects showed weak correlations with WHODAS global score, cognition, and mobility. The impact of antipsychotics on the autonomic nervous system may be responsible for the cardiovascular problems observed in some patients with schizophrenia, although further studies are needed in this area [5]. Other adverse effect subgroups showed weak correlations with global disability, getting along, life activities, and participation. This subgroup includes a wide range of items, including gynecological and dermatological symptoms, and also weight changes, which are often associated with psychiatric therapy [7]. Increased attention should be given to sexual dysfunctions as they may profoundly affect patient quality of life [25]; for this reason, adverse effects on sexuality have been extracted from the respective subgroup and treated independently. Sexual adverse effects, common in patients treated with psychotropic medications [26], emerged as significant in getting along, life activities, participation, and global disability, thus highlighting the significant effect that drug therapy might have on the relational aspect of the patient's life. Patients with schizophrenia-spectrum disorders showed lower levels of disability compared with those with bipolar disorder. These findings differ from recent literature, which has not shown significant differences between the two diagnoses in terms of disability [27]. Additionally, patients treated with LAIs developed fewer adverse effects overall, including fewer psychological, autonomic, other, and sexual adverse effects. Results from this study provide additional information about the potential differences between oral and LAI medications in terms of adverse effects [28]. Although the literature has already shown robust results regarding the superiority of LAIs in reducing the risks of hospitalization and non-compliance, data are not always consistent when comparing adverse effects [29, 30]. Patients treated with muscarinic LAIs had fewer autonomic adverse effects than those taking oral muscarinic medications. M1 receptors, considered the most prevalent muscarinic receptors in the

Table 8 Dwass–Steel–Critchlow–Fligner pairwise comparison based on autonomic adverse effects

		W	*p*-value
Oral muscarinic	Oral adrenergic	− 2.644	0.501
Oral muscarinic	Oral serotonergic/dopaminergic	− 2.156	0.730
Oral muscarinic	Oral dopaminergic	− 1.544	0.931
Oral muscarinic	LAI muscarinic	− 4.247	0.043
Oral muscarinic	LAI adrenergic	− 2.696	0.476
Oral muscarinic	LAI serotonergic/dopaminergic	− 2.675	0.486
Oral adrenergic	Oral serotonergic/dopaminergic	0.693	0.999
Oral adrenergic	Oral dopaminergic	− 1.052	0.990
Oral adrenergic	LAI muscarinic	− 2.488	0.576
Oral adrenergic	LAI adrenergic	− 1.640	0.909
Oral adrenergic	LAI serotonergic/dopaminergic	− 0.208	1.000
Oral serotonergic/dopaminergic	Oral dopaminergic	− 1.347	0.964
Oral serotonergic/dopaminergic	LAI muscarinic	− 2.969	0.353
Oral serotonergic/dopaminergic	LAI adrenergic	− 1.925	0.823
Oral serotonergic/dopaminergic	LAI serotonergic/dopaminergic	− 0.783	0.998
Oral dopaminergic	LAI muscarinic	0.000	1.000
Oral dopaminergic	LAI adrenergic	− 0.720	0.999
Oral dopaminergic	LAI serotonergic/dopaminergic	0.859	0.997
LAI muscarinic	LAI adrenergic	− 0.449	1.000
LAI muscarinic	LAI serotonergic/dopaminergic	2.064	0.769
LAI adrenergic	LAI serotonergic/dopaminergic	1.393	0.957

LAI long-acting injectable

Table 9 Kruskal–Wallis test comparing antipsychotic dosage

Kruskal–Wallis				
	χ^2	*df*	*p*-value	ε^2
UKU total	8.62	2	0.013	0.06898
Psychological AEs	5.90	2	0.052	0.04723
Neurological AEs	1.56	2	0.459	0.01247
Autonomic AEs	6.79	2	0.034	0.05433
Other AEs	8.56	2	0.014	0.06848
Sexual AEs	4.93	2	0.085	0.03944
WHODAS total	2.73	2	0.256	0.02181
Cognition	2.40	2	0.301	0.01920
Mobility	1.76	2	0.414	0.01412
Self-care	2.04	2	0.361	0.01629
Getting along	1.19	2	0.553	0.00949
Life activities	3.91	2	0.141	0.03131
Participation	3.31	2	0.191	0.02651

UKU Udvalg for Kliniske Undersogelser, *WHODAS* World Health Organization Disability Assessment Schedule 2.0, *AEs* adverse effects

Table 10 Dwass–Steel–Critchlow–Fligner pairwise comparisons

		W	*p*-value
UKU total			
Target (LAI)	Target (oral)	2.68	0.140
Target (LAI)	Low (oral)	3.93	0.015
Target (oral)	Low (oral)	2.21	0.262
Other adverse effects			
Target (LAI)	Target (oral)	2.07	0.308
Target (LAI)	Low (oral)	3.88	0.017
Target (oral)	Low (oral)	2.99	0.087

LAI long-acting injectable, *UKU* Udvalg for Kliniske Undersogelser

hippocampus and prefrontal cortex, are critical for learning and memory [31]. Postmortem studies reveal a significant reduction of M1 receptors in the brains of schizophrenic subjects [32], and a decrease of M4 receptors is also involved in cognitive dysfunctions [33]. This reduction, likely due to neuronal loss, is specific to schizophrenia and is not seen in depression, bipolar disorder, Alzheimer's disease, or Parkinson's disease [34]. Animal studies indicate that M1 and M4 receptor dysfunction in the striatum leads to motor hyperactivation, mirroring psychotic symptoms. Recent findings suggest altered muscarinic receptors affect intracortical communication, impairing external perception and enhancing internal perception, contributing to psychosis [35]. Therefore, it is important to carefully use drugs with anticholinergic properties, selecting those with the lowest anticholinergic burden, assuming equal efficacy. Indeed, adverse effects have often limited the use of drugs that act on

muscarinic receptors for the treatment of schizophrenia [36]. However, evidence that LAIs in the same category might limit such adverse effects represents a useful contribution to future pharmacodynamic perspectives. These results are supported by the finding that LAIs produced fewer adverse effects compared with low-dose oral antipsychotics. The LAI muscarinic subgroup included patients treated with the olanzapine LAI, showing significantly fewer autonomic adverse effects, such as weight gain, and a lower risk of anticholinergic adverse effects compared with its oral form, in line with other recent studies [37]. These findings might encourage the use of LAIs for patients with poor adherence or cognitive dysfunction, aligning with existing literature [38]. Evidence shows that LAIs effectively preserve cognitive functions, improving verbal learning, memory, executive function, sustained attention, and visuomotor speed when transitioning from oral medication to LAIs [39, 40].

4.2 Future Research Suggestions

Future research should explore targeted interventions to mitigate medication adverse effects, to ensure they do not contribute to functional impairment. Incorporating real-time monitoring through digital health devices and algorithmic analysis might help distinguish adverse effects from underlying psychiatric conditions, and may help to discern associations with medication administration and dosage adjustments [41]. In light of these results, future clinical studies should expand data regarding possible significant differences in terms of drug formulation, examining in a larger sample the extent to which LAIs might lead to reduced adverse effects, both in the short- and long-term. When choosing the best treatment option, the pharmacological history of patients should be taken into account, including past responses and tolerability, as well as individual patient preferences [42]. It is advisable to use psychotropic drugs judiciously, with the lowest dosage, to maintain a reasonable quality of life without compromising therapeutic efficacy, aligning with recent literature recommendations [43, 44].

4.3 Limitations and Strengths

The present study has several limitations. One limitation is that the clinician-administered scales used to evaluate disability and adverse effects may have introduced reporting bias, despite aiding in item comprehension. Another limitation is the naturalistic study design, which made it challenging to differentiate whether specific adverse effects were caused by antipsychotics or other medications, even though patient history and drug initiation were considered [45]. Additionally, the retrospective nature of the study limited the ability to infer temporal relationships; future research should incorporate longitudinal assessments. On the other hand, this study also has strengths. Data collection utilized gold-standard instruments, meticulously administered following manual instructions. All subjects completed the scales entirely, ensuring data integrity. The recruitment of patients from real-world psychiatric clinic settings enhanced ecological validity. Furthermore, the use of a data-driven taxonomy, which provides a scientifically sound classification of antipsychotic drugs, offers a valuable alternative to the chronological classification of antipsychotics used in many other reports.

5 Conclusions

This observational, retrospective study found significant correlations between disability and all adverse effect subcategories, with psychological effects being the most impactful. Patients taking LAIs had lower UKU total scores and fewer psychological, autonomic, other, and sexual adverse effects compared with those taking oral antipsychotics. Preliminary data suggest LAIs are superior in reducing inner unrest, sleep duration issues, constipation, and itching. Further analysis showed fewer autonomic adverse effects in the LAI muscarinic subgroup than in the oral counterpart. These findings suggest that both formulation and pharmacodynamic profiles with receptor binding affinity should be considered in antipsychotic selection to minimise adverse effects and improve daily functioning in patients with a diagnosis of schizophrenia-spectrum or bipolar disorder.

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Declarations

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Conflicts of interest Alessandro Rodolico, Sofia Francesca Aprile, Pierfelice Cutrufelli, Gabriele Privitera, Sabrina Castellano, Carmen Concerto, Rosaria Furnari, Claudia Savia Guerrera, Ludovico Mineo, Giuseppe Alessio Platania, Antonino Petralia, Filippo Caraci, and Maria Salvina Signorelli have no competing interests to declare that may be relevant to the contents of this article.

Availability of Data and Material The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval This study was approved by the Institutional Review Board of the University of Catania (protocol IERB-EdUnict-20240603/01).

Consent to Participate Informed consent was obtained from all individual participants included in this study.

Consent for Publication Not applicable.

Code Availability Not applicable.

Authors' Contributions Conceptualization: FC, AR, MSS. Methodology: PC, SFA, AR. Validation: AR, SC. Formal analysis: SFA, AR. Investigation: PC, CSG, GAP, GP. Resources: CC, RF, LM, MSS, AP. Data curation: SFA, GP, PC. Writing—original draft: SFA, AR, PC. Writing—review and editing: FC, MSS, AR. Visualization: AR, SFA. Supervision: FC, MSS. Project administration: PC, SFA, AR.

References

1. Cieza A, Sabariego C, Bickenbach J, Chatterji S. Rethinking disability. BMC Med. 2018;16(1):14. https://doi.org/10.1186/s12916-017-1002-6.
2. Jiménez Buñuales MT, González Diego P, Martín Moreno JM. International classification of functioning, disability and health (ICF). Rev Esp Salud Publica. 2002;76:271–9. https://doi.org/10.1590/s1135-57272002000400002.
3. Rudnick A. What is a psychiatric disability? Health Care Anal. 2014;22:105–13. https://doi.org/10.1007/s10728-012-0235-y.
4. Juvva S, Newhill CE. Rehabilitation contexts: a holistic approach. J Hum Behav Soc Environ. 2011;21:179–95. https://doi.org/10.1080/10911359.2010.525081.
5. Leung JYT, Barr AM, Procyshyn RM, Honer WG, Pang CCY. Cardiovascular side-effects of antipsychotic drugs: The role of the autonomic nervous system. Pharmacol Ther. 2012;135:113–22. https://doi.org/10.1016/j.pharmthera.2012.04.003.
6. Emsley R. Antipsychotic maintenance treatment in schizophrenia and the importance of preventing relapse. World Psychiatry. 2018;17:168–9. https://doi.org/10.1002/wps.20521.
7. Wu H, Siafis S, Hamza T, Schneider-Thoma J, Davis JM, Salanti G, Leucht S. Antipsychotic-induced weight gain: dose-response meta-analysis of randomized controlled trials. Schizophr Bull. 2022;48:643–54. https://doi.org/10.1093/schbul/sbac001.
8. Lingjærde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale: a new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand. 1987;76:100–100. https://doi.org/10.1111/j.1600-0447.1987.tb10566.x.
9. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018;392:1789–858. https://doi.org/10.1016/S0140-6736(18)32279-7.
10. Reddy R, Sureshkumar K, Balasubramania S, Sridhar O, Kailash S. Certifiable disability in schizophrenia and its correlates: a cross-sectional study. Indian J Soc Psychiatry. 2019;35:201. https://doi.org/10.4103/ijsp.ijsp_10_19.
11. Chow RTS, Whiting D, Favril L, Ostinelli E, Cipriani A, Fazel S. An umbrella review of adverse effects associated with antipsychotic medications: the need for complementary study designs. Neurosci Biobehav Rev. 2023;155: 105454. https://doi.org/10.1016/j.neubiorev.2023.105454.
12. Lally J, MacCabe JH. Antipsychotic medication in schizophrenia: a review. Br Med Bull. 2015;114:169–79. https://doi.org/10.1093/bmb/ldv017.
13. Pillinger T, Howes OD, Correll CU, Leucht S, Huhn M, Schneider-Thoma J, et al. Antidepressant and antipsychotic side-effects and personalised prescribing: a systematic review and digital tool development. Lancet Psychiatry. 2023;10:860–76. https://doi.org/10.1016/S2215-0366(23)00262-6.
14. Iversen TSJ, Steen NE, Dieset I, Hope S, Mørch R, Gardsjord ES, et al. Side effect burden of antipsychotic drugs in real life—impact of gender and polypharmacy. Prog Neuropsychopharmacol Biol Psychiatry. 2018;82:263–71. https://doi.org/10.1016/j.pnpbp.2017.11.004.
15. McCutcheon RA, Harrison PJ, Howes OD, McGuire PK, Taylor DM, Pillinger T. Data-driven taxonomy for antipsychotic medication: a new classification system. Biol Psychiatry. 2023;94:561–8. https://doi.org/10.1016/j.biopsych.2023.04.004.
16. van Strien AM, Keijsers CJ, Derijks HJ, van Marum RJ. Rating scales to measure side effects of antipsychotic medication: a systematic review. J Psychopharmacol (Oxf). 2015;29:857–66. https://doi.org/10.1177/0269881115593893.
17. Federici S, Meloni F, Mancini A, Lauriola M, Olivetti BM. World Health Organisation Disability Assessment Schedule II: contribution to the Italian validation. Disabil Rehabil. 2009;31:553–64. https://doi.org/10.1080/09638280802240498.
18. Üstün TB, Chatterji S, Kostanjsek N, Rehm J, Kennedy C, Epping-Jordan J, et al. Developing the World Health Organization Disability Assessment Schedule 2.0. Bull World Health Organ. 2010;88:815–23. https://doi.org/10.2471/BLT.09.067231.
19. McKnight PE, Najab J. Mann-Whitney U Test. In: The Corsini Encyclopedia of Psychology. John Wiley & Sons Ltd; 2010, pp. 1–1.
20. Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiol Camb Mass. 1990;1:43–6.
21. Jamovi Project. Jamovi (Version 2.3) [Computer Software]. 2023. Available at: http://www.jamovi.org. Accessed 23 Aug 2024.
22. McAdam MK, Baldessarini RJ, Murphy AL, Gardner DM. Second international consensus study of antipsychotic dosing (ICSAD-2). J Psychopharmacol Oxf Engl. 2023;37:982–91. https://doi.org/10.1177/02698811231205688.
23. Evans JD. Straightforward statistics for the behavioral sciences. Brooks: Cole Publishing Company; 1996.
24. Haddad C, Salameh P, Sacre H, Clément J-P, Calvet B. Effects of antipsychotic and anticholinergic medications on cognition in

chronic patients with schizophrenia. BMC Psychiatry. 2023;23:61. https://doi.org/10.1186/s12888-023-04552-y.
25. Montejo AL, Montejo L, Baldwin DS. The impact of severe mental disorders and psychotropic medications on sexual health and its implications for clinical management. World Psychiatry. 2018;17:3–11. https://doi.org/10.1002/wps.20509.
26. Sullivan G, Lukoff D. Sexual side effects of antipsychotic medication: evaluation and interventions. Hosp Community Psychiatry. 1990;41:1238–41. https://doi.org/10.1176/ps.41.11.1238.
27. Datta A, Chetia D. Resilience and its relationship with disability in persons with bipolar disorder and schizophrenia: a comparative study. Indian J Psychiatry. 2023;65:361–7. https://doi.org/10.4103/indianjpsychiatry.indianjpsychiatry_238_22.
28. Misawa F, Kishimoto T, Hagi K, Kane JM, Correll CU. Safety and tolerability of long-acting injectable versus oral antipsychotics: a meta-analysis of randomized controlled studies comparing the same antipsychotics. Schizophr Res. 2016;176:220–30. https://doi.org/10.1016/j.schres.2016.07.018.
29. Tiihonen J, Walhbeck K, Lönnqvist J, Klaukka T, Ioannidis JPA, Volavka J, et al. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. BMJ. 2006;333:224. https://doi.org/10.1136/bmj.38881.382755.2F.
30. Zhornitsky S, Stip E. Oral versus long-acting injectable antipsychotics in the treatment of schizophrenia and special populations at risk for treatment nonadherence: a systematic review. Schizophr Res Treat. 2012. https://doi.org/10.1155/2012/407171.
31. Moran SP, Maksymetz J, Conn PJ. Targeting muscarinic acetylcholine receptors for the treatment of psychiatric and neurological disorders. Trends Pharmacol Sci. 2019;40:1006–20. https://doi.org/10.1016/j.tips.2019.10.007.
32. Mancama D, Arranz Mj, Landau S, Kerwin R. Reduced expression of the muscarinic 1 receptor cortical subtype in schizophrenia. Am J Med Genet B Neuropsychiatr Genet. 2003;119B:2–6. https://doi.org/10.1002/ajmg.b.20020.
33. Deng C, Huang X-F. Decreased density of muscarinic receptors in the superior temporal gyrusin schizophrenia. J Neurosci Res. 2005;81:883–90. https://doi.org/10.1002/jnr.20600.
34. Dean B, Bakker G, Ueda HR, Tobin AB, Brown A, Kanaan RAA. A growing understanding of the role of muscarinic receptors in the molecular pathology and treatment of schizophrenia. Front Cell Neurosci. 2023;17:1124333. https://doi.org/10.3389/fncel.2023.1124333.
35. McCutcheon RA, Weber LAE, Nour MM, Cragg SJ, McGuire PM. Psychosis as a disorder of muscarinic signalling: psychopathology and pharmacology. Lancet Psychiatry. 2024;11:554–65. https://doi.org/10.1016/S2215-0366(24)00100-7.
36. Yohn SE, Weiden PJ, Felder CC, Stahl SM. Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. Trends Pharmacol Sci. 2022;43:1098–112. https://doi.org/10.1016/j.tips.2022.09.006.
37. Wang D, Schneider-Thoma J, Siafis S, Qin M, Wu H, Zhu Y, et al. Efficacy, acceptability and side-effects of oral versus long-acting- injectables antipsychotics: systematic review and network meta-analysis. Eur Neuropsychopharmacol. 2024;83:11–8. https://doi.org/10.1016/j.euroneuro.2024.03.003.
38. Correll CU, Citrome L, Haddad PM, Lauriello J, Olfson M, Calloway SM, et al. The Use of Long-Acting Injectable Antipsychotics in Schizophrenia: Evaluating the Evidence. J Clin Psychiatry. 2016;77:21984. https://doi.org/10.4088/JCP.15032su1.
39. Kim S-W, Shin I-S, Kim J-M, Lee S-H, Lee Y-H, Yang S-J, et al. Effects of switching to long-acting injectable risperidone from oral atypical antipsychotics on cognitive function in patients with schizophrenia. Hum Psychopharmacol. 2009;24:565–73. https://doi.org/10.1002/hup.1057.
40. Petric PS, Teodorescu A, Miron AA, Manea MC, Ifteni P. Cognitive outcomes in nonacute patients with schizophrenia treated with long-acting injectable antipsychotics versus oral antipsychotics. Am J Ther. 2024;31:e219–28. https://doi.org/10.1097/MJT.0000000000001729.
41. Torous J, Jän Myrick K, Rauseo-Ricupero N, Firth J. Digital mental health and COVID-19: using technology today to accelerate the curve on access and quality tomorrow. JMIR Ment Health. 2020;7:e18848. https://doi.org/10.2196/18848.
42. Mauri MC, Paletta S, Maffini M, Colasanti A, Dragogna F, Di Pace C, et al. Clinical pharmacology of atypical antipsychotics: an update. EXCLI J. 2014;13:1163–91.
43. Bighelli I, Rodolico A, Siafis S, Samara MT, Hansen W-P, Salomone S, et al. Antipsychotic polypharmacy reduction versus polypharmacy continuation for people with schizophrenia. Cochrane Database Syst Rev. 2022;8:CD014383. https://doi.org/10.1002/14651858.CD014383.pub2.
44. Rodolico A, Siafis S, Bighelli I, Samara MT, Hansen W-P, Salomone S, et al. Antipsychotic dose reduction compared to dose continuation for people with schizophrenia. Cochrane Database Syst Rev. 2022;11:CD014384. https://doi.org/10.1002/14651858.CD014384.pub2.
45. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356:1255–9. https://doi.org/10.1016/S0140-6736(00)02799-9.