Adverse Drug Reactions Among Hospitalized Psychiatric Patients, Prevalence, Severity, Preventability, and Opportunities For Intervention

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Abstract

Objectives: The objective of this study was to boost pharmacovigilance activity in our psychiatry referral hospital and highlight the role of the pharmacist preventing, detecting, and managing adverse drug reactions (ADRs). Our goal was to promote patient safety and compliance with psychotropic medication by identifying ADR patterns among hospitalized patients in our psychiatry hospital. We aimed to assess and evaluate the causality, severity, and management of documented ADRs, along with establishing a hospital-based ADR reporting platform.

Methods: We enrolled adult patients (18–60 years) admitted to our psychiatric facility between 1 September 2020 and 30 September 2021 who received at least one psychotropic agent for at least two months. Patients with a history of substance abuse, pregnant females, and patients on clozapine were excluded. Medical records were examined for demographics, clinical details, and psychotropic-related ADRs. ADRs were analyzed for causality using Naranjo's algorithm, for severity using modified Hartwig and Siegel, and for preventability using modified Schumock and Thornton scales.

Results: Among 506 admitted patients, 327 suspected psychotropic-related ADRs corresponding to 217 (42.9%) patients, were recorded. Hormonal ADRs were five-times higher in men, while the odds of neurological ADRs were significantly higher for women. Otherwise, other ADRs were not statistically affected by gender. Combined therapy was associated with high odds of ADRs, whereas cardiovascular and neurological ADRs were statistically related to monotherapy. Neurological ADRs predominated (47.4%), followed by cardiovascular (18.7%), and hormonal (15.0%). ADRs were more prevalent among antipsychotics, followed by antidepressants, then mood stabilizers. According to the Naranjo algorithm, (22.9%) of ADRs were definite, while the majority (74.3%) were probable. As per the Hartwig severity scale, the majority of ADRs (74.0%) were moderate, and (26.0%) were mild. The Modified Schumock and Thornton assessment questionnaire revealed that 75.2% of ADRs were unpreventable, 19.3% were probably preventable, and 5.5% were preventable. In 46.8% of the cases, a new medication was required to manage the emerging ADRs; one-third of ADRs necessitate the replacement of the suspected medication. Close monitoring without any pharmacological intervention was sufficient in 23.2% of cases, while dose reduction was the solution in 7.6% of cases. **Conclusion:** ADR monitoring in the psychiatry setting by a multidisciplinary team helps recognize the initial signs of ADRs, contributing to better compliance. Hospital-based reporting programs or data-capturing tools will aid in the spontaneous and active assessment of ADRs by healthcare practitioners.

Keywords: Antipsychotic Agents; Pharmacovigilance; Drug-Related Side Effects and Adverse Reactions; Prevalence.

Introduction

The World Health Organization (WHO) defines an adverse drug reaction (ADR) as "any response to a drug that is noxious and unintended and that occurs at a dose normally used in man for prophylaxis, diagnosis, or treatment of diseases for the modification of physiological function."[1,2] Pharmacovigilance is the monitoring of drug safety, encompassing all activities related to the collection, detection, assessment, monitoring, and prevention of ADRs and other drug-related problems.[3] The worldwide incidence of ADRs has been recognized as a substantial cause of lengthy hospitalizations, potentially life-threatening healthcare-related problems and increased healthcare expenditures. This includes additional medical consultations, hospitalizations, laboratory tests, and medications required to manage the ADRs or indirectly to lost productivity due to time off work, transportation expenses to healthcare appointments, and high mortality rates.[4,5]

Over the last two decades, systematic reviews reported ADR prevalences of 6–24%.[6–9] The Institute of Medicine in 2000 reported that in the USA, 44 000 to 98 000 individuals die each year due to medication errors, of which approximately 7000 die due to preventable ADRs.[10] Other studies have placed higher estimates of serious ADRs; they reported the occurrence of serious ADRs in almost 7% of hospitalized patients with a fatality rate of 0.32%, while over 350 000 ADRs occur in US nursing homes each year, ranking ADRs as the fourth leading cause of death — ahead of respiratory disease, diabetes, HIV, and traffic accidents.[11–14]

Psychotropic (psychiatric) medications, influencing behavior, mood, thoughts, mental status, or perception, even at therapeutic and maintenance doses, have been linked to several ADRs, most likely due to their prolonged use, impaired clearance, the common practice of using combined therapy, and their proclivity to interact with a wide range of other medications.[15–17] These side effects are significant determinants of negative impacts on the patient's physical and mental health, which eventually may lead to non-adherence to treatment, unmet clinical outcomes, and a substantial rise in the overall cost of healthcare that may reach 6% of the healthcare budget.[18]

Studies have identified a high burden of psychotropics-related ADRs ranging from 0.7–10%, particularly among patients using second-generation antipsychotics and SSRIs.[19–23] These side effects may vary in severity from mild to severe dermatologic, cardiovascular, hepatic, sexual, neurological, and hematological side effects. Thomas and colleagues reported that psychiatric medications accounted for 48% of the ADRs in hospitalized patients[21], while Sridhar and fellows reported a 10% incidence of ADRs in outpatients.[15]

The National Institute for Health and Care Excellence (NICE) guidelines recommend monitoring ADRs associated with psychotropics. They have set several parameters to be checked at baseline before initiation of psychotropic medications, after a few months of medication initiation, and then periodically.[24] ADR monitoring in hospitalized patients is an important process for identifying patients who are at high risk of developing ADRs so that tailored interventional strategies can be developed to manage, prevent, and minimize the risk of developing ADRs and maximize clinical outcomes.[25]

Many factors, including lack of awareness among healthcare professionals and patients, the preoccupation of practitioners on busy wards with other areas of practice, and the work-environment punishment culture, may contribute to the underreporting of ADRs in the hospital setting. Establishing an effective pharmacovigilance program in psychiatry units can be remarkably beneficial in preventing underreporting and promoting the patient safety concept through preventing avoidable harm.[26] Therefore, the ultimate objective of this study was to boost pharmacovigilance activity in our psychiatry referral hospital and highlight the role of the pharmacist in ADRs prevention, detection, and management. We aim to promote patient safety and compliance toward psychotropic medication by detecting the pattern of ADRs among hospitalized patients in our psychiatry hospital, assessing and evaluating the causality, severity, and management of the documented ADRs, and establishing a hospital-based ADR reporting platform.

Methods

This retrospective hospital-based study investigates the psychotropic-related ADRs in a tertiary care psychiatry hospital (Almasarra Hospital, Oman), with a 245 bed capacity comprising general adult psychiatry, child and adolescent psychiatry, geriatrics psychiatry, and forensic psychiatry. The hospital also treats patients who suffer from substance abuse.

Adult patients (18–60 years) admitted between 1 September 2020, and 30 September 2021, who had received at least one psychotropic agent for at least two months were enrolled. Excluded were patients with a history of substance abuse, pregnant

females, and those on clozapine therapy due to unique monitoring requirements. A convenient sampling technique was used for sample size calculation.

Electronic patient medical records were examined demographics (age, gender, race), clinical details (diagnosis, admission details, psychotropic treatment, monitoring parameters, any ADRs, and ADR corrective actions). After obtaining ethical approval, psychiatry-trained clinical pharmacists screened the patient's records for ADRs. The screening of ADRs included all potential side effects that may be developed from medication administrations and their impact on various body systems. All ADRs were assessed for causality, severity, and preventability.

Before 2020, clinical pharmacists at the hospital manually reported ADRs monthly, resulting in a limited number of reports and pharmacist interventions. From 2018 to 2019, only 14 ADRs were officially documented. However, a noteworthy improvement in the reporting of ADRs associated with psychiatric medications was observed in 2020 and 2021 following the implementation of a pharmacist led ADRs reporting and intervention program. This initiative primarily focused on enhancing pharmacists' awareness of proactive ADRs reporting and management through comprehensive training sessions. Gathering data posed a formidable challenge, primarily due to the absence of a dedicated ADR reporting channel within the Alshifa© system. To surmount this obstacle, data acquisition was meticulously conducted through a comprehensive review encompassing clinical summaries, physician notes, and laboratory investigations in conjunction with pharmacist-led clinical rounds, which occurred during the admission of all study participants.

Antipsychotics (first and second generation), mood stabilizers (lithium and anticonvulsants), and antidepressants (SSRIs and TCA) were studied.

ADRs were analyzed for causality using Naranjo's algorithm scale[27] and for severity using modified Hartwig and Siegel scales.[28] Additional assessments for ADR preventability were performed using modified Schumock and Thornton scales.[29]

Naranjo's causality assessment identifies the relationship between ADR and the administration of medications. The total score of the causality questions in the table below indicates whether there is a definite, probable, or possible link between ADR and medications (see Supplementary 1). Total scores range from -4 to +13. The reaction is considered definite if the score is 9 or higher, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or less.

A modified Hartwig and Siegel scale is used to assess the severity, it describes the extent to which the ADRs influence the patient's everyday life. Supplementary 2 shows questions that determine the level of severity of ADR. Seigel and Schneider categorized ADRs into seven severity levels. Levels one and two are less severe, levels three and four are moderate, and levels five, six and seven are severe.[30]

Supplementary 3 provides an assessment of preventability in which any question with a yes answer determines whether the ADR is preventable, probable, or not preventable.

Descriptive statistics were applied to present the study results; normally distributed continuous variables were expressed using the mean ± standard deviation (SD), whereas when normality is violated, data are expressed as the median and interquartile range (IQR). Categorical data were expressed using frequencies and percentages. The chi-square test was employed to compare the differences in proportions for the categorical variables, whereas the student's t-test was used to compare the means for normally distributed data, and the Mann-Whitney U-test was used when the data were not normally distributed. A p-value less than 0.05 was considered statistically significant. Data were entered and analyzed using (R) Software "Already Tomorrow" version (4.3.0).

This study was approved by the Ministry of Health Center of Studies and Research Committee, (MH/DGHS/DPT/72/2022) dated: 31/06/2022.

Results

During the study period, among 506 admitted adult patients (18–60 years), 327 suspected psychotropic-related ADRs were identified affecting 217 (42.9%) patients. Among them, 60% (n =130) were men and 40.1% (n =87) were women. Hormonal ADRs were five-fold greater in men compared to women [$p < 0.001$], whereas neurological ADRs had a higher odds ratio among women [$p = 0.011$]. The remainder of the ADR categories were not statistically affected by gender variation [Table 1].

Table 1: Correlation between gender and ADR classes.

	n (%)		n (%)	OR	CI	*p*-value
Hematological ADR	8 (2.4)	F	0 (0.0)	*	*	0.963
		M	8 (100)	*	*	
Cardiovascular ADR	61 (18.7)	F	23 (37.7)	1.26	(0.71, 2.23)	0.431
		M	38 (62.3)	0.79	(0.45, 1.41)	
Endocrinological ADR	8 (2.4	F	4 (50.0)	0.72	(0.18, 2.95)	0.652
		M	4 (50.0)	1.38	(0.34, 5.62)	
Dermatological ADR	3 (0.9)	F	2 (66.7)	0.36	(0.03, 4.03)	0.408
		M	1 (33.3)	2.76	(0.25, 30.79)	
Gastrointestinal ADR	9 (2.8)	F	5 (55.6)	0.58	(0.15, 2.18)	0.416
		M	4 (44.4)	1.74	(0.46, 6.59)	
Hormonal disturbances	49 (15.0)	F	36 (73.5)	0.21	(0.11, 0.41)	< 0.001
		M	13 (26.5)	4.78	(2.42, 9.43)	
Neurological ADR	155 (47.4)	F	54 (34.8)	1.79	(1.14, 2.79)	0.011
		M	101 (652)	0.56	(0.36, 0.87)	
Organ dysfunction	11 (3.4)	F	3 (27.3)	1.99	(0.52, 7.64)	0.317
		M	8 (72.7)	0.50	(0.13, 1.93)	
Others	23 (7.0)	F	11 (47.8)	0.78	(0.33, 1.83)	0.572
		M	12 (52.2)	1.28	(0.55, 2.99)	

F: female; M: male; ADR: adverse drug reaction; Others: ex hyponatremia and weight gain.
*The value is too low to be detected by the analysis software.

The affected patient's median age (IQR) was 37 (30–46) years; 36 (29–46) for women and 38 (31–47) for men. Patients aged 39 years or younger had a higher likelihood of cardiovascular ADRs, while those older than 39 were more prone to miscellaneous ADRs [Table 2].

Table 2: Correlation between age and ADR classes.

ADR type	n (%)			n (%)	OR	CI	*p*-value
Hematological	8 (2.4)	> years	39	3 (37.5)	0.85	(0.20, 3.62)	0.826
		≤ years	39	5 (62.5)	1.18	(0.28, 5.01)	
Cardiovascular	61 (18.7)	> years	39	16 (26.2)	0.44	(0.24, 0.82)	0.009
		≤ years	39	45 (73.8)	2.28	(1.23, 4.23)	
Endocrinological	8 (2.4)	> years	39	2 (25.0)	0.47	(0.09, 2.35)	0.355
		≤ years	39	6 (75.0)	2.15	(0.43, 10.79)	
Dermatological	3 (0.9)	> years	39	1 (33.3)	0.71	(0.06, 7.89)	0.780
		≤ years	39	2 (66.7)	1.41	(0.13, 15.71)	

	n (%)	Age	n (%)	OR	CI	p-value
Gastrointestinal	9 (2.8)	> 39 years	4 (44.4)	1.14	(0.30, 4.33)	0.845
		≤ 39 years	5 (55.6)	0.88	(0.23, 3.32)	
Hormonal disturbances	49 (15.0)	> 39 years	23 (46.9)	1.31	(0.71, 2.41)	0.382
		≤ 39 years	26 (53.1)	0.76	(0.41, 1.40)	
Neurological	155 (47.4)	> 39 years	69 (44.5)	1.29	(0.83, 2.00)	0.260
		≤ 39 years	86 (55.5)	0.78	(0.49, 1.21)	
Organ dysfunction	11 (3.4)	> 39 years	2 (18.2)	0.31	(0.07, 1.44)	0.134
		≤ 39 years	9 (81.8)	3.27	(0.69, 15.38)	
Others	23 (7.0)	> 39 years	15 (65.2)	2.88	(1.18, 6.98)	0.020
		≤ 39 years	8 (34.8)	0.35	(0.14, 0.85)	

*F: female; M: male; ADR: adverse drug reaction; Others: Ex hyponatremia and weight gain.*The value is too low to be detected by the analysis software.*

Combined therapy was associated with high odds of ADRs, only cardiovascular and neurological ADRs were statistically related to monotherapy [Table 3].

Table 3: Correlation between the number of concurrent medications and ADR classes.

|		n (%)	OR	CI	p-value
Hematological ADR n = 8	Mono.	5 (62.5)	0.81	(0.19, 3.44)	0.771
	Comb.	3 (37.5)	1.24	(0.29, 5.29)	
Cardiovascular ADR n = 61	Mono.	48 (78.7)	2.02	(1.04, 3.91)	0.038
	Comb.	13 (21.3)	0.50	(0.26, 0.96)	
Endocrinological ADR n = 8	Mono.	4 (50.0)	0.48	(0.12, 1.94)	0.302
	Comb.	4 (50.0)	2.10	(0.51, 8.55)	
Dermatological ADR n = 3	Mono.	1 (33.3)	0.24	(0.02, 2.67)	0.246
	Comb.	2 (66.7)	4.17	(0.37, 46.52)	
Gastrointestinal ADR n = 9	Mono.	7 (77.8)	1.73	(0.35, 8.45)	0.501
	Comb.	2 (22.2)	0.58	(0.12, 2.84)	
Hormonal disturbances n = 49	Mono.	33 (67.3)	1.00	(0.53, 1.92)	0.991
	Comb.	16 (32.7)	1.00	(0.52, 1.90)	
Neurological ADR n = 155	Mono.	113 (72.9)	1.63	(1.02, 2.61)	0.040
	Comb.	42 (27.1)	0.61	(0.38, 0.98)	
Organ dysfunction n = 11	Mono.	5 (45.5)	0.39	(0.12, 1.31)	0.129
	Comb.	6 (54.5)	2.55	(0.76, 8.57)	
Others n = 23	Mono.	4 (17.4)	0.09	(0.03, 0.26)	< 0.001
	Comb.	19 (83.6)	11.66	(3.86, 35.25)	

Others: ex hyponatremia and weight gain.

The most commonly prescribed psychotropic medications were included in the study, mainly categorized into antipsychotics, antidepressants, and mood stabilizers. Figures 1 and 2a detail the prescribed medications, and related-ADRs prevalence. Antipsychotics were most commonly prescribed (65.3%) followed by mood stabilizers and antidepressants. ADRs were more prevalent with antipsychotic, followed by antidepressants, and mood stabilizer use.
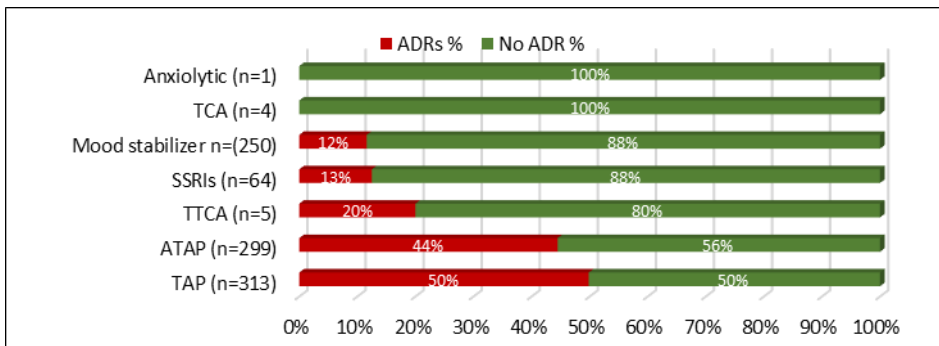
TAP: first-generation antipsychotics; ATAP: second-generation antipsychotics; SSRIs: serum serotonin reuptake inhibitors; TTCA: tetracyclic antidepressants; TCA: tricyclic antidepressants.

Figure 1: Categories of prescribed psychotropic medications and the percentage of related ADRs.
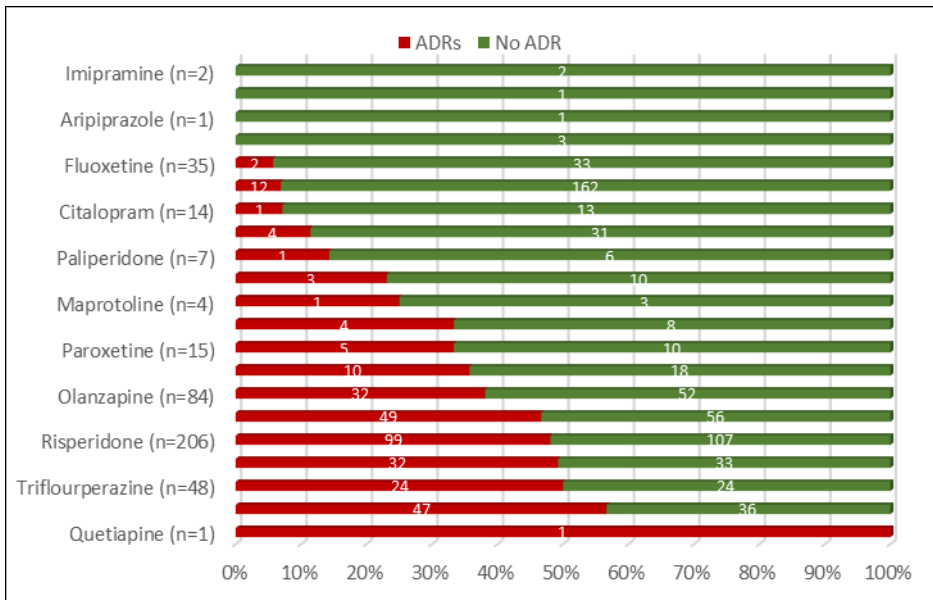
The identified 327 ADRs represent 34 unique clinical manifestations [Figure 2b] categorized into nine groups [Table 2]. We used Medscape© as an approved reference for adverse reactions associated with the drugs identified[31] and we found that the majority of the ADRs (267, 81.7%) had previously been reported, while (60, 18.3%) were not registered in the reference database. Figure 3 details the distribution of ADR prevalence as reported by Medscape.

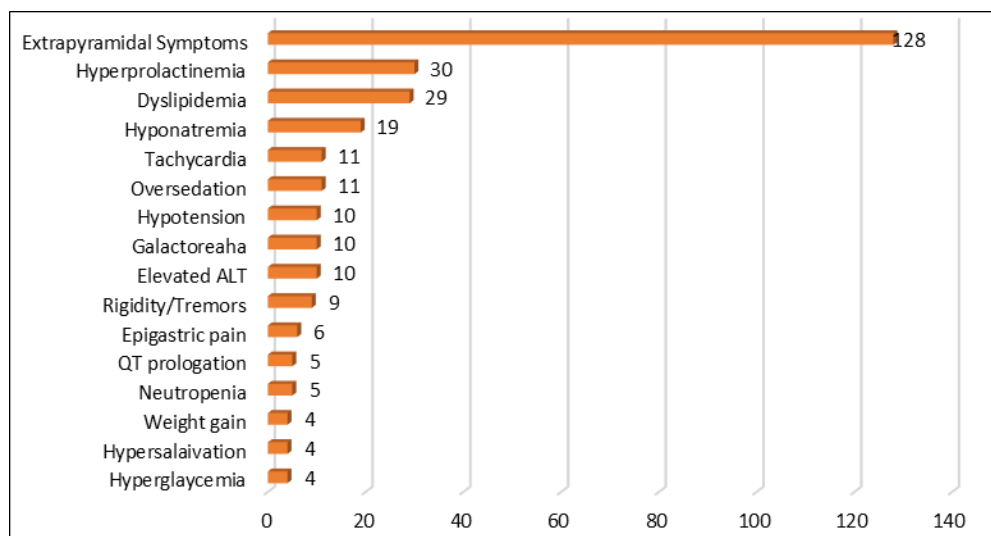**Figure 2a:** Psychotropic medications (prescribed vs. reported ADRs).
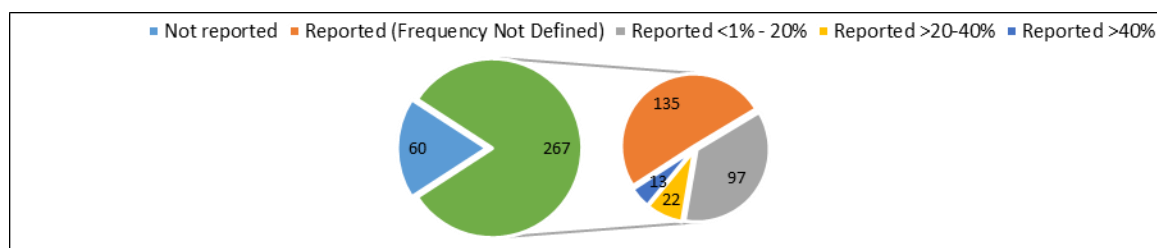
Figure 2b: Prevalence of ADRs.

Chart data (Prevalence of ADRs):
- Extrapyramidal Symptoms: 128
- Hyperprolactinemia: 30
- Dyslipidemia: 29
- Hyponatremia: 19
- Tachycardia: 11
- Oversedation: 11
- Hypotension: 10
- Galactoreaha: 10
- Elevated ALT: 10
- Rigidity/Tremors: 9
- Epigastric pain: 6
- QT prologation: 5
- Neutropenia: 5
- Weight gain: 4
- Hypersalaivation: 4
- Hyperglaycemia: 4

Figure 3: Distribution of ADR prevalence as reported by Medscape.

Legend: Not reported ■ Reported (Frequency Not Defined) ■ Reported <1% - 20% ■ Reported >20-40% ■ Reported >40%
Values: 60, 267; breakout: 135, 97, 22, 13

Neurological ADRs predominated (155, 47.4%), and most commonly presented as EPS (128, 82.6%) and were closely linked to the use of first generation (103, 66.5%) and second generation antipsychotics (45, 29.0%). Fluphenazine (35, 22.5%), risperidone (35, 22.6%), and haloperidol (33, 21.3%) were statistically significant causatives of neurological ADRs, ($p = 0.001$), ($p = 0.005$), and ($p = 0.001$), respectively, the same statistical impact was copied with the EPS. Table 4

Table 4: The statistical relationship between medications and ADRs.

	Olanzapine n = 32		Risperidone n = 99		Haloperidol n = 47		Trifluoperazine n = 24		Fluphenazine n = 49		Flupentixol n = 32		Sodium Valproate n = 12	
	n (%)	p	n (%)	p	n (%)	p	n (%)	p	n (%)	p	n (%)	p	n (%)	p
Hematological ADR	2 (6.3)	0.179	2 (2.0)	1.000									1 (8.3)	0.261
Thrombocytopenia													1 (8.3)	0.037
Neutropenia	2 (6.3)	0.077	2 (2.0)	0.641										
Cardiovascular ADR	10 (31.3)	0.090	27 (27.3)	0.013	6 (12.8)	0.316	2 (8.3)	0.275	6 (12.2)	0.239	8 (25.0)	0.341		
QT prolongation	1 (3.1)	0.404	2 (2.0)	0.641	1 (2.1)	0.542					1 (3.1)	0.404		
Bradycardia			1 (1.0)	1.000					1 (4.2)	0.205	1 (3.1)	0.267		
Tachycardia	2 (6.3)	0.293	4 (4.0)	0.740			1 (4.2)	0.573	2 (4.1)	0.673	1 (3.1)	1.000		
Hypotension			6 (6.1)	0.072	1 (2.1)	1.000			2 (4.1)	0.650	1 (3.1)	1.000		
Hypertension			1 (1.0)	0.303										
Dyslipidemia	7 (21.9)	0.015	13 (13.1)	0.090	4 (8.5)	1.000			2 (4.1)	0.279	3 (9.4)	1.000		
Endocrinological ADR	4 (12.5)	0.004	2 (2.0)	1.000					1 (2.0)	1.000				
Hyperthyroidism	1 (3.1)	0.186	1 (1.0)	0.514										

ADR	n (%)	p	n (%)	p	n (%)	p	n (%)	p	n (%)	p	n (%)	p	n (%)	p
Hypothyroidism	1 (3.1)	0.186												
Hyperglycemia	2 (6.3)	0.049	1 (1.0)	1.000					1 (2.0)	0.479				
Dermatological ADR	1 (3.1)	0.267												
Itching	1 (3.1)	0.098												
Gastrointestinal ADR	3 (9.4)	0.048	2 (2.0)	0.728										
Vomiting			1 (1.0)	0.303										
Conistipation	2 (6.3)	0.009												
Epigastric pain	1 (3.1)	0.464	1 (1.0)	0.672										
Hormonal disturbance	1 (3.1)	0.064	26 (26.3)	0.001	5 (10.6)	0.508	7 (29.2)	0.067	3 (6.1)	0.080	3 (9.4)	0.443	4 (33.3)	0.088
Hyperprolactinemia	1 (3.1)	0.335	17 (17.2)	0.002	4 (8.5)	1.000	3 (12.5)	0.472	3 (6.1)	0.593	2 (6.3)	0.752		
Amenorrhea			1 (1.0)	1.000			2 (8.3)	0.015						
Galactorrhea			5 (5.1)	0.177	1 (2.1)	1.000	2 (8.3)	0.162			1 (3.1)	1.000	1 (8.3)	0.316
Hirsutism			1 (1.0)	1.000									2 (16.7)	0.004
Sexual dysfunction			2 (2.0)	0.219									1 (8.3)	0.106
Neurological ADR			35 (35.4)	0.005	33 (70.2)	0.001	15 (62.5)	0.141	35 (71.4)	0.001	17 (53.1)	0.577	1 (8.3)	0.006
Tremors/rigidity	2 (6.3)	0.217	2 (2.0)	0.728	1 (2.1)	1.000	1 (4.2)	0.501	1 (2.0)					
Oversedation	2 (6.3)	0.293	4 (4.0)	0.740							1 (3.1)	1.000	1 (8.3)	0.342
Hypersalivation	2 (6.3)	0.049	1 (1.0)	1.000										
Anticholinergic effects	2 (6.3)	0.026							1 (2.0)	0.387				
Extrapyramidal Syndrome	1 (3.1)	0.001	28 (28.3)	0.009	32 (68.1)	0.001	14 (58.3)	0.052	33 (67.3)	0.001	16 (50.0)	0.189		
Organ dysfunction			3 (3.0)	1.000					2 (4.1)	0.673	1 (3.1)	1.000	2 (16.7)	0.057
Elevated ALT			3 (3.0)	1.000					2 (4.1)	0.650	1 (3.1)	0.481	2 (16.7)	0.047
Others	2 (6.3)	1.000			3 (6.4)	1.000			2 (4.1)	0.549			4 (33.3)	0.006
Weight gain	2 (6.3)	0.049	1 (1.0)	0.018									1 (8.3)	0.140
Hyponatremia			1 (1.0)	0.018	3 (6.4)	0.743			2 (4.1)	0.750	3 (9.4)	0.414	3 (25.0)	0.026

Cardiovascular ADRs ranked second (61, 18.7%) and were more common among second generation antipsychotics (37, 60.7%), with dyslipidemia accounting for most events (29, 47.5%). Although risperidone (27, 44.2%), and olanzapine (10, 16.4%) were noticeable contributors to this category of ADRs, only risperidone was statistically correlated ($p = 0.013$) [Table 4].

Hormonal disturbances (49, 15.0%) ranked third, manifesting primarily as hyperprolactinemia (30, 61.2%) and galactorrhea (10, 20.4%). The highest proportions of hormonal ADRs were caused by risperidone (26, 53.1%) which demonstrated a high statistically significant relationship with neurological ADRs ($p = 0.001$), especially hyperprolactinemia ($p = 0.002$). Other miscellaneous ADRs account for the remaining 18.9% [Table 4].

According to the Naranjo algorithm, (22.9%) of ADRs were definite relative to the suspected medication, while the majority (74.3%) were probable [Figure 4].
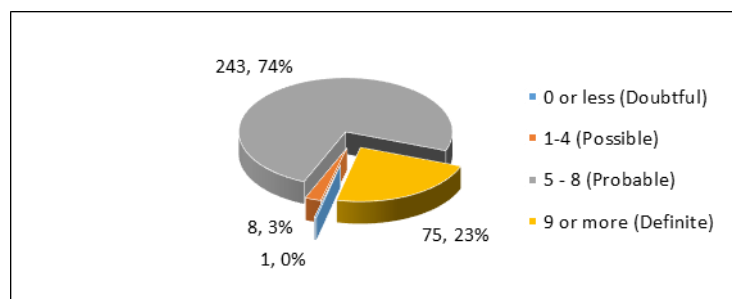

243, 74%
8, 3%
1, 0%
75, 23%

- 0 or less (Doubtful)
- 1-4 (Possible)
- 5 - 8 (Probable)
- 9 or more (Definite)

Figure 4: Assessment of causality using the Naranjo algorithm scale.

According to the Hartwig severity assessment scale, (74.0% were reported as moderate ADRs and 26.0% as mild. No severe reaction was reported [Figure 5].
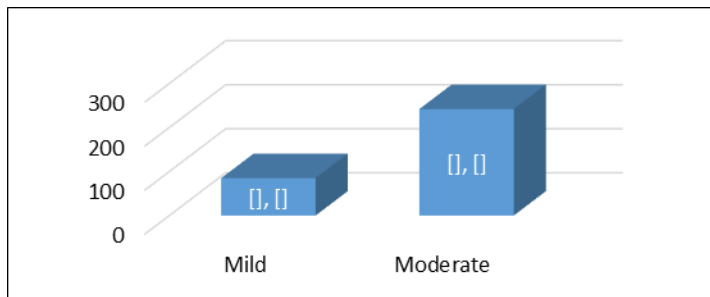

Figure 5: Assessment of severity by using the Hartwig and Seigel scale.

The modified Schumock and Thornton assessment questionnaire revealed that 75.2% of ADRs were unpreventable (), 19.3% were probably preventable (), and 5.5% were preventable (5.5%) [Figure 6].
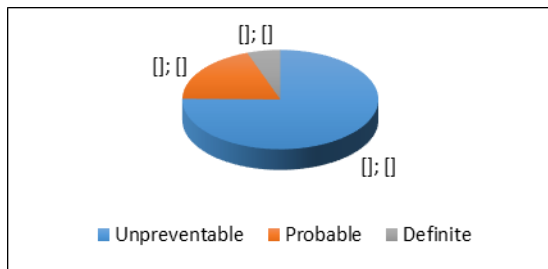

Figure 6: Preventability assessment using the Schumock and Seigel scale.

This study aimed to report the role of the clinical pharmacist in tracking and managing ADRs, as well as the prevalence of ADRs, which would not have been possible unless we made efforts to promote the culture of tracking and reporting ADRs among pharmacists, as well as other healthcare professionals.

In nearly half of the cases, a new medication was required to manage the emerging ADR; procyclidine and bromocriptine were the most commonly prescribed adjuvants to manage EPS manifestations and hyperprolactinemia, respectively. Other transient conditions were managed using anti-dyslipidemics, hypoglycemics, and antacids. One-third of ADRs required discontinuation of the suspected medication and replacement with an alternative option. Close monitoring without any pharmacological intervention was sufficient in 23.2% of the cases, while dose reduction or dosage form modification was the solution in 7.6% of cases. Examining the patient's electronic records revealed a high level of healthcare professionals' commitment (95–100%) to request and follow-up on the laboratory investigation required for therapeutic and ADR monitoring [Figure 7].
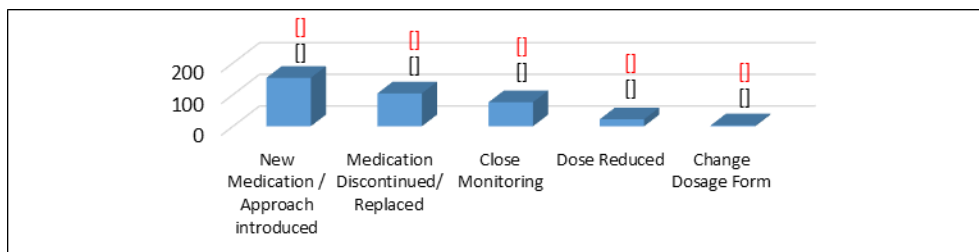

Figure 7: Pharmacist's interventions.

Discussion

This is the first large national study to investigate the incidence of psychotropics-related ADRs. A review of 937 medication orders corresponding to 506 admitted patients by psychiatry-trained clinical pharmacists revealed a prevalence of 34.9% ADRs corresponding to 42.9% of patients. The incidence of psychiatric medication-related adverse reactions varied greatly across the available literature. While comparable percentages were reported by some studies[32,33], others reported a range of 5–25% of psychotropic-related ADRs.[19,34–37] Extreme percentages were reported by a few.[38,39] This dramatic disparity in reported proportions can be explained by variations in patient demographics, case severity, healthcare standards, the drugs monitored in each study, and the differences in reporting, monitoring, and follow-up systems. Therefore, relying on standardized work strategies and procedures that enable monitoring, evaluating, and proposing solutions to such events remains the most effective intervention.

Advanced age, polypharmacy, liver and renal impairment, and gender are among the established risk factors for developing ADRs. Several studies have shown that ADRs are more common in women, particularly those brought on by the use of cardiac and psychotropic drugs.[40,41] Although there is no definite explanation for this, the differences between genders in physiological functions such as pharmacokinetic, immunological, and hormonal factors, lower lean body mass, and reduced hepatic clearance are possible explanations for such variance.[42,43] This was highlighted by the younger age of the affected women in the study sample compared to the men. In our study, hormonal ADRs were five-fold in men compared to women ($p < 0.001$), men were more likely to experience non-statistically significantly higher odds of endocrinological, dermatological, and gastrointestinal ADRs. Meanwhile, neurological ADRs were considerably more common in women ($p = 0.011$).

In our study, the majority (67.3%) of the patients were on psychotropic monotherapy. Combined therapy was associated with non-statistically significant high odds of ADRs; only cardiovascular and neurological ADRs were statistically related to monotherapy probably due to the low number of patients in the combined therapy category.[44] Jianfei and his colleagues replicated our findings, reporting an increased risk of psychotropic-related ADRs when using combinations of risperidone, olanzapine, and haloperidol.[45] In the same context, Stingl linked using combinations of psychotropics to potential harm in the elderly, which may lead to hospital emergency visits.[46] Contrarily, McCue's point of view was that patients being treated with more than one antipsychotic were less susceptible to ADRs and more likely to have improved indicators of patient outcome.[47]

Antipsychotics were the most commonly prescribed psychotropic drugs (65.3%), with both first and second-generation antipsychotics being equally distributed. ADRs appeared in almost 47% of the patients using antipsychotics, and this group was solely responsible for 81.7% of the reported ADRs. Many studies reported a wide range (5–70%) of antipsychotic-related ADRs[48–51], mainly EPS, and hormonal ADRs. Bahta[51] linked the high prevalence of ADRs among antipsychotics to medication non-adherence in more than one-third of schizophrenic patients. Therapeutic drug monitoring and non-pharmacological treatments remain preferable options to slow the presumed high prevalence of ADRs related to antipsychotics.[52–54]

EPS produced by first-generation antipsychotics was the most prominent neurological ADR, frequently a major cause of non-adherence to therapy, resulting in disease relapse and hospitalization. Advanced age, female gender, and high doses of antipsychotics have been identified as the main risk factors for EPS.[55,56] Janno and others linked the high prevalence of EPS in schizophrenic patients to the use of first-generation antipsychotics.[57–59] Fluphenazine, haloperidol, and risperidone were statistically significant contributors to the development of EPS in our investigation. Similar findings were replicated with the use of fluphenazine at a dose of 0.2 mg/kg per day, which was linked with higher clinical improvement but also with a significant incidence of EPS.[60] Second-generation antipsychotics having the lowest propensity to cause EPS made them an optimal treatment alternative based on the patient's condition. Effective management of EPS relies mainly on discontinuation or dose reduction of the causative drug or the addition of a central anticholinergic drug, such as procyclidine.

Cardiovascular ADRs were caused mainly by second-generation antipsychotics (risperidone and olanzapine), which coincides with earlier research.[61,62] Accurate cardiology assessment of patients receiving these medicines via scheduled electrocardiograms, cardiac enzymes, and lipid profile monitoring remains essential for the early detection and prevention of such problems.

Hyperprolactinemia, menstrual irregularities, and hirsutism were statistically significant reported hormonal ADRs, primarily caused by risperidone, trifluoperazine, and sodium valproate. Causative medication replacement was the main corrective action in the majority of the cases; however, adding bromocriptine remains a common practice to counteract risperidone-related hyperprolactinemia. The frequently reported hormonal disturbances in patients using risperidone[63,64] uncover the need for close monitoring and periodic assessment of hormonal levels during treatment.

Other ADRs were statistically linked to the use of certain medications, such as hyperglycemia and constipation with olanzapine, elevated liver enzymes with sodium valproate, and hyponatremia with risperidone, sodium valproate, and lithium. The observed physicians' high commitment to request and follow-up on patients' laboratory investigations remains an attitude to be fostered to early recognize and resolve such events. The clinical pharmacist's role in adopting preplanned therapeutic monitoring of these medications grants maximized outcomes with minor ADRs.[65,66]

The causality of the reported ADRs indicated that the majority were probable; comparable results were found in a secondary care psychiatric outpatient facility in the United Arab Emirates[15], and a similar pattern was copied in a hospital-based prospective observational study conducted in inpatients and outpatients on antipsychotics.[67] Identifying high-risk patient groups, increasing prescribers' awareness regarding the likelihood of the ADRs related to these drugs, and regular therapeutic monitoring are key tactics to minimize their occurrence.

The vast majority of ADRs in this study were moderate (74.0%), which were managed by the substitution of the used drug or adding another medication to manage the symptoms. The remaining mild cases were managed by reducing the dose and close monitoring of the ADR. Comparable findings were reported by a study in a psychiatry hospital in Kashmir, which reported 83% mild events and 17% moderate.[68] Meanwhile, Egberts and colleagues recently reported that 8.3% of serious ADRs related to either labeled or off-label use of psychotropics.[69]

Assessment of preventability showed that most ADRs were unpreventable (75.2%). In a retrospective investigation of long-term resident patients in nursing homes in the USA, 51% of the ADRs were judged to be preventable.[12] However, others reported that 57.3% were potentially avoidable.[70] This discrepancy is most likely due to variable patient demographics, prescribing patterns, and case severity. Psychotropic medications should be prescribed at the lowest effective dose and not combined unless a single medication is inadequate. In addition, regular and close monitoring of underlying health status, taking into account patient-specific regimen optimization, is essential.

The role of the clinical pharmacist encompasses the identification, monitoring, management, and causality assessment of ADRs in patients experiencing psychiatric illnesses with a great need to implement standardized tools to do so.[71] In this study, pharmacists made strenuous efforts to track side effects in the absence of an official documentation tool by directly following up with patients and reviewing their records during the admission period. Similar findings emerged in other countries with established reporting systems and well-trained clinical pharmacists.[72-74] The current study contributes valuable insights to the existing body of knowledge regarding the prevalence of ADRs. Furthermore, it underscores the indispensable role of clinical pharmacists in diligently monitoring and effectively addressing ADRs within resource-constrained work environments.

Conclusion

Psychotropics are associated with a wide variety of ADRs, which may contribute to unmet clinical outcomes due to nonadherence to treatment. ADR monitoring in the psychiatry setting by a multidisciplinary team helps to recognize the initial signs of ADRs and hence contributes to better compliance. Hospital-based ADR reporting programs or data capture tools will help in the spontaneous and active assessment and reporting of ADRs by healthcare practitioners.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study or connections, direct or indirect, or other situations that might raise the question of bias in the work reported or the conclusions, implications, or opinions stated—including pertinent commercial or other sources of funding for the individual author(s) or the associated department(s) or organization(s), personal relationships, or direct academic competition.

Supplementary

Supplementary 1: Naranjo's algorithm causality assessment scale.

Question	Yes	No	Do not know	Score
1. Are there previous conclusive reports on reaction?	+1	0	0	
2. Did the adverse drug appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	

4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

Total score:

Supplementary 2: Modified Hartwig and Siegel severity assessment scale.

Level	Description
1.	The ADR requires no change in treatment with the suspected drug
2.	The ADR requires the suspected drug to be withheld, discontinued, or otherwise changed. No antidote or other treatment is required. There is no increase in the length of hospital stay
3.	The ADR requires that the suspected drug be withheld, discontinued, or otherwise changed, and/or an antidote or other treatment is required. There is no increase in the length of hospital stay
4.	Level 4a – Any level 3 ADR that increases the length of hospital stay by at least one day Level 4b – The ADR is the reason for admission
5.	Any level 4 ADR that requires intensive medical care
6.	The ADR causes permanent harm to the patient
7.	The ADR either directly or indirectly leads to the death of the patient

Supplementary 3: Modified Schumock and Thornton preventability assessment scale.

Questions for assessment of preventability

Definitely preventable

Was there a history of allergy or previous reactions to the drug?

Was the drug involved inappropriate for the patient's clinical condition?

Was the dose, route, or frequency of administration inappropriate for the patient's age, weight, or disease state?

Was a toxic serum drug concentration (or laboratory monitoring test) documented?

Was there a known treatment for the Adverse Drug Reaction?

Probably preventable

Was required Therapeutic drug monitoring or other necessary laboratory tests not performed?

Was a drug interaction involved in the ADR?

Was poor compliance involved in the ADR?

Were preventative measures not prescribed or administered to the patient?

Not preventable

If all the above criteria are not fulfilled.

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