Original Research Article

Intensive monitoring of adverse drug reactions to antipsychotic medications in the inpatient psychiatry department of a secondary care hospital of UAE

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Abstract

Background: Antipsychotics are a class of medications used primarily for the treatment of psychotic disorders. However, these medications are associated with potential adverse drug reactions (ADRs).

Aim: To monitor the incidence and nature of ADRs in the psychiatric inpatient department of a secondary care hospital of Ras Al Khaimah, UAE.

Materials and Methods: This was an observational, prospective, noninterventional study, conducted in the psychiatric inpatient setting of a secondary care hospital. Psychiatric inpatients of all age groups and both the gender, diagnosed with any psychotic disorder, and hospitalized in the psychiatry ward and managed with at least one antipsychotic medication were included in the study. The causality, severity, and preventability of ADRs were assessed using different assessment scales.

Results: Out of 170 patients, 38 patients reported at least one ADR with an incidence rate of 22.3%. The most common ADRs were weight gain 15 (29.4%) due to olanzapine, followed by pseudo-parkinsonism 11 (21.6%) due to parenteral haloperidol. Schizophrenia (18, 35.3%), followed by bipolar I disorder (10, 19.6%) was the most common condition associated with ADRs. Female gender and duration of hospital stay were found to be significant ($P < 0.05$) predictors of occurrence of ADRs.

Conclusion: A high incidence of ADRs was observed in the inpatients of psychiatry department, especially of mild nature and probably preventable types. The study highlights the importance of intensive monitoring by pharmacists to identify high ADR risk psychiatric inpatients. To reduce the ADR risk, specific and frequent monitoring for antipsychotics is recommended such as weight and extrapyramidal symptoms.

Keywords: Adverse drug reaction, adverse drug reaction monitoring, antipsychotic medications, pharmacovigilance, psychiatric inpatient department

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INTRODUCTION

Antipsychotics are a class of medications used primarily for the treatment of psychotic disorders, including schizophrenia, psychoses, and mood disorders such as bipolar disorder.[1] According to the chemical characteristics, effects on psychotic symptoms, and adverse effect

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profile, antipsychotics are classified into first-generation antipsychotics (FGAs) or typical antipsychotics and second-generation antipsychotics (SGAs) or atypical antipsychotics.[2,3]

Psychotropic medications, including antipsychotics, have many potential adverse drug reactions (ADRs), some of which can be quite severe. Both FGAs and SGAs are known to cause serious adverse effects. Higher incidence of serious adverse effects such as extrapyramidal reactions or extrapyramidal symptoms (EPSs) such as pseudo-parkinsonism, akathisia, acute dystonia, and tardive dyskinesia (TD) have been reported with FGAs,[4,5] while higher incidence of metabolic and endocrine adverse effects including weight gain, insulin resistance, and hyperlipidemia have been reported with use of SGAs.[1,4-6] Antipsychotics also have several specific monitoring recommendations for side effects to help guide therapy.[4-6]

ADRs are commonly reported in patients receiving both typical and atypical antipsychotic medications. Many studies have documented the occurrence and nature of ADRs associated with antipsychotic medication usage.[2,7] The incidence rate of ADRs in hospitalized psychiatric patients varies from 43.5% to 94.6% as documented in pharmacovigilance studies from different parts of the world.[8-10]

The knowledge of antipsychotics-related ADRs and their management among healthcare providers can help in their safe and rational use and helps in early detection. In addition, hospitals also need a mechanism to help identify more severe adverse drug events and ADRs comprising minor side effects. Facilities should develop policies and procedures on how to identify, report, and prevent future events if determined to be potentially preventable with appropriate monitoring and prescribing. Hence, this study focused to improve and reinforce the pharmacovigilance activity in the UAE regarding the use of antipsychotics and promote the role of pharmacist in ADR monitoring and reporting.

This study aimed to observe and record the incidence, pattern, nature, and management of ADRs in the psychiatric inpatient department of a secondary care hospital in Ras Al Khaimah, UAE.

MATERIALS AND METHODS

This prospective, observational study was conducted from November to May 2016 at the psychiatric inpatient department of a secondary care hospital in Ras Al-Khaimah, UAE. Institutional Research and Ethics Committee and the Regional Research and Ethics Committee approved this study (RAK MHSU-REC: 8-2015-PG-P). The convenience sampling method was used to include the subjects. This study included a total of 170 (of all age groups) patients of either gender diagnosed with any psychotic disorder and hospitalized in the psychiatry ward and managed with at least one antipsychotic medication. The study included monitoring of psychiatric inpatients those starting antipsychotic treatment for the first time and as well as those switching to a new antipsychotic on admission and who are taking antipsychotics with no other specifiers.

Psychiatric inpatients who were not managed/prescribed with any antipsychotic medications, readmitted patients for recurrences or relapses, and patients who were managed with antipsychotics but admitted in the other ward/specialties of the hospital were excluded from the study.

The study investigator (clinical pharmacist) attended the psychiatry ward – rounds with treating psychiatrists on a regular basis and intensively monitored patients satisfying the criteria of the study prospectively, from the day of admission to day of discharge on a daily basis for the presence or occurrence of any adverse effects or reactions. All the included patients were screened for ADRs. All the suspected ADRs observed by the pharmacist and as well as reported by treating doctors were included in the study. The required data were collected directly from the patients, their electronic medical records, and caretakers, if required. The data were entered into a predesigned ADR reporting and documentation form, including the details of demographic information, clinical features of the disease, ADR history and medication, and other related information.

The World Health Organization-The Uppsala Monitoring Centre (WHO-UMC) probability scale[11] and the Naranjo scale[12] were used for the causality assessment of the documented ADRs. The severity and preventability of ADRs were assessed using Hartwig *et al*. scale[13] and modified Schumock and Thornton scale,[14] respectively.

Statistical analysis

Microsoft Excel Sheet was used to summate the collected data, and Statistical Package for the Social Sciences 24 (IBM, Armonk, New York, USA) was used to analyze the data. The categorical data were expressed as a percentage, while the continuous data were expressed as mean ± standard deviation. The association between ADRs and sociodemographic, disease, and treatment-related variables was analyzed by Chi-square test and the significant

difference in the weight of the patients who reported weight gain due to antipsychotic medications was analyzed by paired Student's *t*-test. Bivariate logistic regression was done to assess the predictors of ADRs. Odds ratio (ORs) with 95% confidence intervals (95% CI) was performed. A $P < 0.05$ was considered as statistically significant.

RESULTS

A total of 170 patients (98 [57.6%] males and 72 [42.4%] females) were included in the study. A total of 51 ADRs were reported among 38 patients with the incidence of 22.3%. Among patients who experienced ADR to antipsychotic medications, 13 (34.2%) were men and 25 (65.8%) were women. A total of 17 (44.7%) patients were UAE nationals, while the remaining 21 (55.3%) patients were expatriates. The total length of stay of these patients was 17.1 ± 17.2 days. Majority of the patients who experienced ADR were taking 2–3 drugs (i.e., both psychiatric and medical) (24 [63.2]) followed by 4–5 drugs (n = 12, 31.6%) and two patients (5.3%) were on single medication.

Among the suspected ADRs, weight gain (15, 29.4%) was the most common, followed by pseudo-parkinsonism (11, 21.6%) and constipation (9, 17.6%). Out of 51 suspected ADRs, few ADRs contributed to an incidence rate of 2% each. These ADRs were fatigue associated with olanzapine, risperidone-induced enuresis, acne associated with two suspected drugs (risperidone and quetiapine), and hypersalivation associated with parenteral chlorpromazine [Table 1].

The average weight of the patients (n = 15) before initiating antipsychotic drugs was 81.1 ± 18.1 kg. However, after receiving treatment with suspected antipsychotic drugs, it was 84.4 ± 18.7 kg (P = 0.0003). The total length of stay of these patients was 26.4 ± 26.1 days. The time period between the weight gain was minimum of 7 days to maximum of 88 days [Table 2].

Oral olanzapine was the most commonly involved drug in ADR (25, 49%) followed by chlorpromazine, intramuscular haloperidol injection, and oral risperidone (6, 11.8% each) [Table 3].

Among psychiatric conditions in patients who developed ADRs, schizophrenia (18, 35.3%) was most common followed by bipolar I disorder (10, 19.6%) [Table 4].

The most commonly affected organ systems due to ADRs were the central and peripheral nervous system followed by the metabolic system [Table 5].

Table 1: Spectrum of different adverse drug reactions and drug (s) implicated (*n*=51)

Types of ADRs	*n* (%)	Drug (s) implicated
Weight gain	15 (29.4)	Olanzapine (*n*=12), risperidone (*n*=2), quetiapine (*n*=1)
Pseudo-parkinsonism	11 (21.6)	Injection chlorpromazine (*n*=1), injection haloperidol (*n*=4), olanzapine (*n*=3), injection risperidone (*n*=1), prochlorperazine (*n*=1), haloperidol (*n*=1)
Constipation	9 (17.6)	Olanzapine (*n*=4), aripiprazole (*n*=3), risperidone (*n*=2)
Drowsiness	7 (13.7)	Injection chlorpromazine (*n*=4), olanzapine (*n*=3)
Akathisia	4 (7.8)	Injection haloperidol (*n*=2), olanzapine (*n*=1), trifluoperazine (*n*=1)
Fatigue	1 (2)	Olanzapine (*n*=1)
Risperidone-induced enuresis	1 (2)	Risperidone (*n*=1)
Acne	1 (2)	Risperidone (*n*=1)
Hypersalivation	1 (2)	Injection chlorpromazine (*n*=1)
Dry eyes	1 (2)	Olanzapine (*n*=1)

ADRs: Adverse drug reactions

Table 2: Body weight profile of the patients who reported weight gain

Weight of the patients	*n*	Mean±SD (kg)	df	*P*
Pretreatment	15 (29.4)	81.1±18.1	11	0.0003*
Posttreatment	15 (29.4)	84.4±18.7		

*$P<0.001$ highly statistically significant. SD: Standard deviation

Table 3: Different antipsychotics associated with adverse drug reactions (*n*=51)

Name of the drug	*n* (%)
Injection chlorpromazine	6 (11.8)
Injection haloperidol	6 (11.8)
Tablet olanzapine	25 (49)
Tablet risperidone	6 (11.8)
Tablet aripiprazole	3 (5.9)
Tablet quetiapine	1 (2)
Injection risperidone	1 (2)
Tablet trifluoperazine	1 (2)
Tablet prochlorperazine	1 (2)
Tablet haloperidol	1 (2)

Table 4: Psychiatric disorders associated with suspected adverse drug reactions (*n*=38)

Diagnosis	Patients, *n* (%)
Schizophrenia	11 (28.9)
Schizoaffective disorder	7 (18.4)
Unspecified schizophrenia spectrum and other psychotic disorder	4 (10.5)
Delusional disorder	1 (2.6)
Bipolar I disorder	8 (21.1)
Major depressive disorder	1 (2.6)
Major depressive disorder with psychotic features	1 (2.6)
Borderline personality disorder	2 (5.3)
Adjustment disorder	2 (5.3)
Substance use disorder	1 (2.6)

According to the WHO-UMC probability assessment, the majority of the suspected ADRs were possible (27, 52.9%)

Table 5: Different organ systems affected by adverse drug reactions (*n*=51)

SOC (WHO ART SOC code)	Type of ADRs	*n* (%)
Central and peripheral nervous system disorders (0410)	Drowsiness	7 (13.7)
	Pseudo-parkinsonism	11 (21.6)
	Akathisia	4 (7.8)
Gastrointestinal system disorders (0600)	Constipation	9 (17.6)
	Hypersalivation	1 (2)
Metabolic and nutritional disorders (0800)	Weight gain	15 (29.4)
Skin and appendages disorder (0100)	Acne	1 (2)
Vision disorders (0431)	Dry eyes	1 (2)
Body as a whole-general disorder (1810)	Fatigue	1 (2)
Urinary system disorders (1300)	Risperidone-induced enuresis	1 (2)

SOC: System-organ classification, WHO: World Health Organization, ADR: Adverse drug reaction

in nature followed by probable type (24, 47.1%). However, according to Naranjo probability assessment, the majority of the suspected ADRs were probable in nature (31, 60.8%) followed by possible type (20, 39.2%). According to Hartwig severity assessment scale, the majority of the suspected ADRs were of mild severity type (28, 54.9%) followed by moderate type (23, 45.1%). Further, a total of 48 (94.1%) suspected ADRs were of the predictable type, and only 3 (5.9%) ADRs were not predictable. Modified Schumock and Thornton scale revealed that majority of the suspected ADRs (31, 60.8%) were of the probably preventable type followed by not preventable (11, 21.6%).

In 28 (54.9%) cases, no changes were made with regard to antipsychotic medication to manage ADRs. However, in 17 (33.3%) patients, the suspected drug was withheld, and six (11.8%) patients were managed by an alteration in the prescribed dose of antipsychotic medication. Approximately, half of the suspected ADRs were treated symptomatically (25, 49%) and the remaining ADRs were not treated (26, 51%). Majority of the suspected ADRs (24, 47.1%) were recovered; however, the outcomes of ADRs in 14 (27.5%) cases were unknown followed by a continuation of symptoms in 13 (25.5%) cases.

For the majority (36, 70.6%) of the cases, no dechallenge of suspected drug was done followed by definite improvement of ADRs upon dechallenge in 13 (25.5%) cases. Rechallenge of the suspected drug was not done for any of the subjected patients.

Gender ($\chi^2 = 11.01$; df = 1; $P = 0.001$) and duration of stay ($\chi^2 = 8.59$; df = 1; $P = 0.003$) were significantly associated with occurrence of ADRs. Further, we performed binary logistic regression to determine the predictors of ADRs keeping occurrence of ADRs as dependent variable and gender, duration of stay, and polypharmacy as independent variables. Female gender ($P < 0.01$; OR 0.214; 95% CI = 0.093–0.493) and duration of stay of >17 days ($P = 0.03$; OR 0.314; 95% CI = 0.152–0.799) were found to be the significant predictors of occurrence of ADRs.

DISCUSSION

The highlight of our study is this was the first UAE-based study where ADRs to different antipsychotic medications were intensively monitored in a psychiatric inpatient setting. Second, the study involved pharmacist in the monitoring, documentation, and assessment of ADRs. This study reported an incidence of 23.3%; however, a study conducted in the psychiatry outpatient department of the same hospital reported an incidence rate of 10.2%.[15] Earlier studies have reported higher incidence rate varying from 43.5% to 94.6% in hospitalized psychiatric patients.[8-10] The present study documented the suspected ADRs related only to antipsychotic drugs, while other studies included general psychotropic drugs, which could explain the difference in incidence rate of ADRs compared to other studies.

Further, oral olanzapine was the most frequent drug associated with ADRs and weight gain was the most common documented ADR. A significant increase was observed in the weight of the patients who received olanzapine. Similar observations have been reported in other studies.[9,16] In contrast to our findings, a study reported olanzapine as the most common drug responsible for ADRs (45.45%) in which tremor was the most common.[8] The postulated mechanisms of weight gain due to olanzapine are said to be complex; however, weight gain has been linked to increase in appetite, blood glucose level, body fat hormonal function, and alteration in metabolism rate.[17]

In the current study, EPSs such as pseudo-parkinsonism (21.6%) and akathisia (7.8%) were the most common and significant suspected ADRs associated mostly with FGA haloperidol. The findings of the current study were in accordance with the findings of other similar studies, which reported extrapyramidal motor symptoms to be mostly associated with FGA haloperidol followed by SGA amisulpride.[16] Other studies have also reported dose-dependent extrapyramidal side effects as one of the most significant ADRs associated with antipsychotics.[10] Another study conducted by Iuppa *et al.* reported movement disorders (acute dystonia, akathisia, and pseudo-parkinsonism) as the most common ADRs.[3]

Constipation (17.6%) was the third most common ADR documented in the present study. This adverse effect could reflect the anticholinergic effects exerted by antipsychotics. A similar study reported a case of severe constipation and bowel obstruction due to clozapine.[18]

Another study reported similar findings regarding anticholinergic side effects in general where dry mouth was one of the most common suspected ADRs.[10] Drowsiness was the fourth most common ADR documented in this study, which was in accordance with the finding of a study conducted by Jain *et al.*, which reported somnolence as one of the commonly observed ADRs.[10] Interestingly, the same study reported insomnia as the most common ADR, followed by somnolence, which could be due to overlap in the determination of the actual cause of sleep disturbances between antipsychotic medications and the psychiatric disorder itself.[10,19]

Majority of the suspected ADRs were seen with oral olanzapine followed by parenteral chlorpromazine, parenteral haloperidol, oral risperidone, and oral quetiapine (each of same incidence rates). These findings were similar to the findings of two studies, which reported the highest number of ADRs with olanzapine.[8,9] Another study reported that SGAs followed by FGAs were the most common medication classes associated with ADRs.[3] Schizophrenia was the most common psychiatric condition associated with ADRs in the present study. Similar findings were reported by Farhat *et al.*, who reported higher number of ADRs in patients with bipolar disorder followed by schizophrenia.[9] The higher number of suspected ADRs related to olanzapine could also be due to higher utilization pattern of this drug in our study setting.

Majority of the suspected ADRs were probable and mild in nature. This finding was in accordance with two other studies in which most of the ADRs were mild to moderate in severity and had a probable causal relationship with antipsychotics.[8,9] In contrast, a study conducted by Grohmann *et al.* reported a rate of 1.6% of severe ADRs.[16]

Majority of the suspected ADRs were of a predictable and probably preventable type. In contrast to our findings, the study conducted by Kurmi *et al.* reported the majority of ADRs as not preventable type followed by probably preventable.[8] Iuppa *et al.* reported that antipsychotics were the second most common drug class related to preventable ADRs.[3] The same study highlighted the role of pharmacist in preventing ADRs where 87 pharmacist interventions were considered as preventable ADRs.[3]

Age, gender, race, and number of drugs received/polypharmacy and other demographic variables are known to be the potential predictors of ADRs. Hence, the association between these demographic factors and number of ADRs were analyzed in this study. Gender and duration of stay were found to be the significant negative predictors of the number of ADRs in the current study. Similarly, a study conducted by Worner *et al.* identified race, female sex, and antidepressant-naive patients as the indicators of TD in elderly patients. This study was limited only to TD.[20] In contrast, another study reported no statistically significant relationship of ADRs with either sex or age.[9]

The main limitations of the study were small sample size, short duration, single-center-based, and of noninterventional type. Hence, the findings of this study may not be representative for all the samples. Henceforth, the study highlights the need for multicenter, interventional-centered studies to highlight the precise spectrum of antipsychotic ADRs and its predictability and preventability.

CONCLUSION

A high incidence of ADRs was observed in the inpatients of psychiatry department, especially of mild nature and probably preventable types. The study highlights the importance of intensive monitoring by pharmacists to identify high ADR risk psychiatric inpatients. To reduce the ADR risk, specific and frequent monitoring for antipsychotics is recommended such as weight and EPSs. The study findings represent the profile of ADRs in the in the psychiatric inpatient department in UAE and foster the clinical pharmacists' role in the monitoring and reporting of ADRs.

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Conflicts of interest

There are no conflicts of interest.

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