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Prescription patterns of quetiapine for multiple drug abuse, depression, and psychosis: A retrospective study

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ABSTRACT

Background: Quetiapine is an atypical antipsychotic prescribed for schizophrenia, bipolar disorder, multiple drug abuse (MDA), generalized anxiety disorder, severe depression, dementia, and mood disorders. Prescription of quetiapine varies according to use, with side effects increasingly reported with higher doses. Many previous case reports highlighted the misuse of the drug. Here we studied the prescribing patterns of quetiapine in multiple drug abuse (MDA), depression, and psychosis patients in the Madinah region in Saudi Arabia.

Methods: This is a retrospective single-center study carried out in the main referral hospital for mental health in Madinah, Saudi Arabia for the period December 2020 till December 2021.

Results: A total of 158 patients were included in this study. The mean age of the patients was 30.5 ± 10.1 years. Male presented for 89.9 % of the patients. In terms of quetiapine indications, 46.2 % of patients used it for MDA, 29.7 % for psychosis, and 24.1 for depression. For all patients, quetiapine was used with a mean daily dose of 285.2 ± 222 mg and for a mean duration of 13.9 ± 15.4 weeks. Quetiapine was prescribed with a mean of 2.1 ± 2.2 prescriptions. Comparison between different indications shows that quetiapine was more frequently prescribed for MDA ($p < 0.001$). The MDA patients were significantly younger than in other groups ($p = 0.001$). All patients who received quetiapine for MDA were males. However, MDA patients received a smaller dose of quetiapine than other indications ($p < 0.001$). There were no significant differences between groups in terms of the number of prescriptions, duration, and whether the patient was on other medications or not. These results have been confirmed by regression analysis, where male and younger ages represented a significant contributing factor to MDA compared to psychosis, 95 % CI: 8×10^7 ($8 \times 10^7 - 8 \times 10^7$) and 0.943 (0.900—0.987), respectively.

Conclusion: Quetiapine was prescribed more frequently in MDA patients and younger individuals. Low dose was predominant in those patients, indicating a probability of drug abuse.

1. Introduction

Quetiapine belongs to a group of medications called second-generation antipsychotics (SGAs) with demonstrated efficacy in treating various mental illnesses such as schizophrenia, bipolar disorder, generalized anxiety disorder, severe depression, dementia, and mood disorders (Vento et al., 2020). Chemically, quetiapine is a dibenzothiazepine derivative (Farah 2005). At low doses (50 mg per day) it has a

hypnotic and sedative effect due to the blockade of H1 receptors. while with midrange doses (300 mg per day) it has mood effects and is used as an anti-psychotic agent due to both D2 and 5HT2A receptors blockade. With higher doses (800 mg per day) the clinical effects of quetiapine, also as an anti-psychotic agent, are mediated through serotonergic, muscarinic, alpha-adrenergic, and histaminergic receptor blockade (Curry and Richards 2022).

Quetiapine, like many other SGAs agents, has different side effects e,

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g.; weight gain and metabolic effects (increased blood glucose and low-density lipoprotein cholesterol levels) which can lead to a higher risk of cardiovascular disease and stroke. Unfortunately, these side effects are seen in low doses of quetiapine as well. Other reported side effects are extrapyramidal effects, QTC prolongation, sedation, prolactin elevation and associated amenorrhea, galactorrhea, sexual dysfunction, and osteoporosis (Modesto-Lowe et al., 2021).

The off-label use of quetiapine has increased in recent years and has become common in clinical practice, which has the potential to increase its risk of abuse (Bastaki et al., 2021). Also, quetiapine has been recognized as the most commonly prescribed drug for non-FDA-approved use due to its anxiolytic and sedative effects (Carney 2013). Different routes of administration were reported regarding quetiapine abuse, such as oral, intravenous (IV), rectal, and nasal (Hanley and Kenna 2008). Most quetiapine abusers are psychiatric patients taking other drugs or patients with a history of substance use disorders (SUDs). Quetiapine abuse usually starts with a low dose and gradually increases (Gugger and Cassagnol 2008, Reeves 2012).

Quetiapine misuse is well documented, and an increase in misuse and abuse cases is evident in the literature. From January 1991 to July 2008, Tcheremissine et al. (2008) reported a case series of quetiapine misuse and abuse (Tcheremissine 2008), while Cubala et al. (2014) reported more than 25 cases from 1996 to 2012 identifying quetiapine abuse/dependence in psychiatric patients (Cubala and Springer 2013). A study in Victoria, Australia, between 2001 and 2009 identified 224 deaths associated with quetiapine use, with an average age of death was 43 years and toxicity as the leading cause of death (Lee et al., 2018). Quetiapine was also reported to be the most common antipsychotic addicted by American patients for non-medical purposes or as illegal medication compared to other antipsychotics, with a percentage of 96 % vs. Olanzapine 28 %, risperidone 20 %, and aripiprazole 20 % (Montebello and Brett 2017). In addition, the side effects of drugs were soothed by quetiapine, which may explain its popularity in a special population (Jahnsen et al., 2021). However, quetiapine addiction is still not clear whether it can cause a euphoric effect by acting on dopamine receptors or not (Montebello and Brett 2017). This study aims to assess and analyze the prescribing patterns of quetiapine between different indications (Multiple drug abuse, depression, and psychosis).

2. Material and methods

2.1. Study design and procedures

The electronic health records system (Medica®) of the main referral hospital for mental health in Madinah (Al-Amal & psychiatric Hospital), Saudi Arabia was retrospectively screened for patients diagnosed with one of the following conditions: depression, psychosis, or MDA using DSM-5 criteria and received quetiapine as part of their treatment protocol for the period December 2020 till December 2021. Depression is defined as the presence of one of the following conditions: a. disruptive mood dysregulation disorder, b. major depressive disorder, c. persistent depressive disorder (dysthymia), while patients with depressive disorder due to other medical conditions have been excluded. Psychosis is defined as I. The presence of one (or more) of the following symptoms. At least one of these must be (1), (2), or (3): 1. Delusions. 2. Hallucinations. 3. Disorganized speech. 4. Grossly disorganized or catatonic behavior. II. With duration of an episode of the disturbance is at least 1 day but less than 1 month, with an eventual full return to a premorbid level of functioning. C. The disturbance is not better explained by major depressive or bipolar disorder with psychotic features or another psychotic disorder such as schizophrenia or catatonia, and is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition. Inclusion criteria were a. Adult patient ≥ 18 years, b. diagnosed with depression, psychosis, or MDA using DSM-5 criteria, and c. received quetiapine as part of his/her treatment protocol. The study was approved by the Ministry Of Health

(MOH) institutional review board and registered under IRB# H-03-M-084 with a waiver of consent and followed the principles specified in the declaration of Helsinki.

2.2. Data collection

Data collected includes demographical data, diagnosis, dose of quetiapine (mg/day), number of prescriptions, duration of therapy (weeks), and previous & current anti-psychotic medications. All extracted data were stored in electronic format using a Microsoft Excel sheet and retrospectively analyzed.

2.3. Statistical analysis

The categorical variables are presented as absolute numbers and percentages. Continuous variables are presented as mean \pm Standard Deviation (SD). Differences in the studied categorical variables (gender and previous medications) between different treatment groups were assessed by the Chi-square test of independence. The differences in studied continuous variables (patient age, quetiapine dose, duration of therapy, and number of prescriptions) between different treatment groups were assessed by one-way ANOVA. The results with a significant difference were further analyzed for pairwise comparison using Bonferroni correction for both post hoc ANOVA and chi-square test as appropriate. Multinomial logistic regression was used to compare variables between different indication groups (depression and MDA) versus psychosis groups, and the results are presented as Odds ratio and 95 % confidence interval (CI). All conducted tests were two-tailed and considered significant when p-value < 0.05 . No imputations were made for missing data points. All data used in the study were analyzed using SPSS 25.0 (IBM SPSS Statistics for Windows, Version 25.0 IBM Corp., Armonk, NY, USA).

3. Results

3.1. Cohort characteristics

A total of 158 patients were included in this study. The mean age of the patients was 30.5 ± 10.1 years. In the whole sample, 89.9 % of the patients were males, and 10.1 % were females. In terms of indications, 46.2 % of patients used quetiapine for MDA, 29.7 % for psychosis, and 24.1 % for depression. For all indications, quetiapine was used with an average daily dose of 285.2 ± 222 mg and for a duration of 13.9 ± 15.4 weeks. Quetiapine was prescribed as 2.1 ± 2.2 prescriptions per patient (Table 1).

3.2. Prescription pattern of quetiapine according to age, daily dose, duration of therapy, and number of prescriptions

One-way ANOVA was used to compare the characteristics of different quetiapine indication groups. There was a statistically

Table 1
Characteristics of the study population (n = 158).

	Frequency	Percent
Age, mean	30.5 \pm 10.1 years	
Gender	Male	142 89.9 %
	Female	16 10.1 %
Indication	MDA	73 46.2 %
	Depression	38 24.1 %
	Psychosis	47 29.7 %
Previous medications	No	63 39.9 %
	Yes	95 60.1 %
Dose (mg/day), mean	285.2 \pm 222	
Duration of therapy (weeks)	13.9 \pm 15.4	
Number of prescriptions	2.1 \pm 2.2	

significant difference between groups in terms of patients' age ($p < 0.001$) and mean daily dose ($p < 0.00001$). In terms of pairwise comparison, the post-hoc ANOVA test revealed that the significant difference was between (MDA & depression group) and (MDA & psychosis groups) concerning patient age and quetiapine daily dose, while the difference was not significant between depression and psychosis groups for both patient age and daily dose.

The mean patients' age was significantly lower in the MDA group (mean = 32 ± 8.1 years) compared with the depression (mean = 36.8 ± 11.7 years) and the psychosis (mean = 38.8 ± 10.1 years) groups (Table 2). Furthermore, the largest variability in age was seen in the depression group (Fig. 1).

Regarding daily dose, the mean daily dose was significantly lower in the MDA group (mean = 191.8 ± 165.4 mg) compared with the psychosis and the depression groups (mean = 354.4 ± 247.8 mg and 378.95 ± 217.4 mg, respectively), indicating that quetiapine was prescribed to treat MDA at a significantly lower dose than the two other groups. Furthermore, half of the patients used a daily dose ranging from 200 mg up to 600 mg in both the psychosis and the depression groups, while half of the patients in the MDA group used a daily dose ranging from 100 mg to 200 mg (Fig. 2).

However, there were no statistically significant differences in the number of prescriptions ($p = 0.132$) and duration of therapy ($p = 0.06$) between the three groups, indicating that the prescription frequency did not vary between groups.

3.3. Prescription pattern of quetiapine according to gender and previous drug use

Subgroup analysis was conducted to determine if the patient's gender was a factor in the prescribing of quetiapine. The results revealed that there was a significant difference between the three groups in terms of patient gender ($p < 0.001$), where all patients in the MDA group were males (100 %). In contrast, 86.8 % and 76.6 % were males in the depression and psychosis groups, respectively (Table 3). Post-hoc chi-square test using Bonferroni correction revealed that the significant difference based on the patient's gender was between MDA-depression and MDA-psychosis groups ($p < 0.01$ and $p < 0.00001$, respectively) with no significant difference between depression and psychosis groups ($p = 0.23$).

In terms of the previous use of medications, there were no statistically significant differences between groups ($p = 0.223$), indicating that the history of using other drugs was not a factor in the prescribing pattern of quetiapine (Table 3).

Table 2
Prescription dose, frequency, and duration.

		N	Mean	SD	P-value
Age	MDA ^a	73	31.97	8.11	<0.001***
	Depression	38	36.84	11.69	
	Psychosis	47	38.81	10.11	
Dose (mg/day)	MDA ^b	73	191.78	165.41	<0.001***
	Depression	38	378.95	217.36	
	Psychosis	47	354.36	247.80	
Number of prescriptions	MDA	73	1.97	1.71	0.132
	Depression	38	1.76	1.28	
	Psychosis	47	2.64	3.12	
Duration of therapy (weeks)	MDA	71	10.87	12.64	0.06
	Depression	38	14.63	16.21	
	Psychosis	47	17.79	17.77	

*** $p < 0.001$ is statistically extremely signify.

^a The mean age (years) of the MDA patients was significantly smaller than the other two groups.

^b The mean dose (mg/day) of the MDA patients was significantly lower than the other two groups.

3.4. Prescription pattern of quetiapine according to prescription frequency and duration of use

Analysis revealed that the average number of prescriptions was the same in the three groups (2 prescriptions), and 50 % of the patients had a maximum of two prescriptions in all groups. However, the maximum number of prescriptions was seen in the psychosis group (up to 19 prescriptions), followed by the MDA group (up to 11 prescriptions) and the depression group (up to 6 prescriptions) (Fig. 3). On the other hand, the highest median duration of therapy was in the psychosis group, followed by depression, then the MDA group (Fig. 4).

3.5. Multinomial logistic regression analysis

Multinomial regression analysis was used to further investigate the prescribing patterns of quetiapine. The results confirmed that male and younger ages were significantly contributing to MDA compared to psychosis, 95 % CI: 8×10^7 (8×10^7 - 8×10^7) 0.943 (0.900–0.987), respectively (see Table 4).

4. Discussion

The current study aims to assess and analyze the prescribing patterns of quetiapine between different indications (Multiple drug abuse, depression, and psychosis). Our study shows that the prescribing patterns of quetiapine vary among patients depending on the disease conditions (e.g., MDA, depression, and psychosis) and males were using quetiapine more than females, and the males were younger, and this may be referred to the conservative nature of the Saudi population where it considers kind of shame of having a female with a psychological disorder. So usually, families do not declare nor seek any medical support.

In the current study, quetiapine was mostly prescribed for patients with MDA history; this may indicate the potential abuse of quetiapine. Several studies have reported the misuse of quetiapine, and numerous emergency room visits were reported for patients who misused or abused quetiapine (Pierre et al., 2004, Hussain et al., 2005, Waters and Joshi 2007, Mattson et al., 2015, Klein et al., 2017). Compared to other SGAs, quetiapine was found to be used for recreational purposes (Klein et al., 2017), and intranasal and intravenous quetiapine abuse was noticed among imprisoned inmates, specifically for those with a substance abuse history (Pierre et al., 2004, Hussain et al., 2005). Q-ball is a mixture of cocaine and quetiapine, which was reported to be used intravenously, orally, and intranasally among inmates for its anxiolytic properties (Waters and Joshi 2007). All the previously discussed evidence questioned whether quetiapine is addictive. In a study aimed to find if quetiapine may increase the risk of fatal opioid poisoning by additive inhibitory effects on the central nervous system, quetiapine was detected in 20.4 % of fatal opioid poisonings with a significantly increased frequency over time, primarily in low or therapeutic concentrations, and was not associated with opioid concentrations (Andersen et al., 2022). On the other hand, Javdan et al. in a study aimed to assess the impacts of quetiapine administration on cognitive function and mental health scale in patients with methamphetamine abuse under methadone maintenance treatment found that quetiapine significantly decreased depression and sleep disorder, and had favorable effects on some of cognitive functions and mental health parameters (Javdan et al., 2019, Javdan et al., 2020).

The reward system plays a crucial role via the dopaminergic pathway (Solinas et al., 2019). One study found that the administration of a dopamine antagonist prevents the quetiapine-induced conditioned place preference in mice, indicating the dopamine system's possible role in quetiapine addiction (Chew et al., 2008, Althobaiti 2021). Although the exact mechanism behind quetiapine-induced addiction is still unknown, the abused drugs exert their drug-seeking behaviors by modulating the dopamine release in the nucleus accumbens in the basal ganglia (Baik

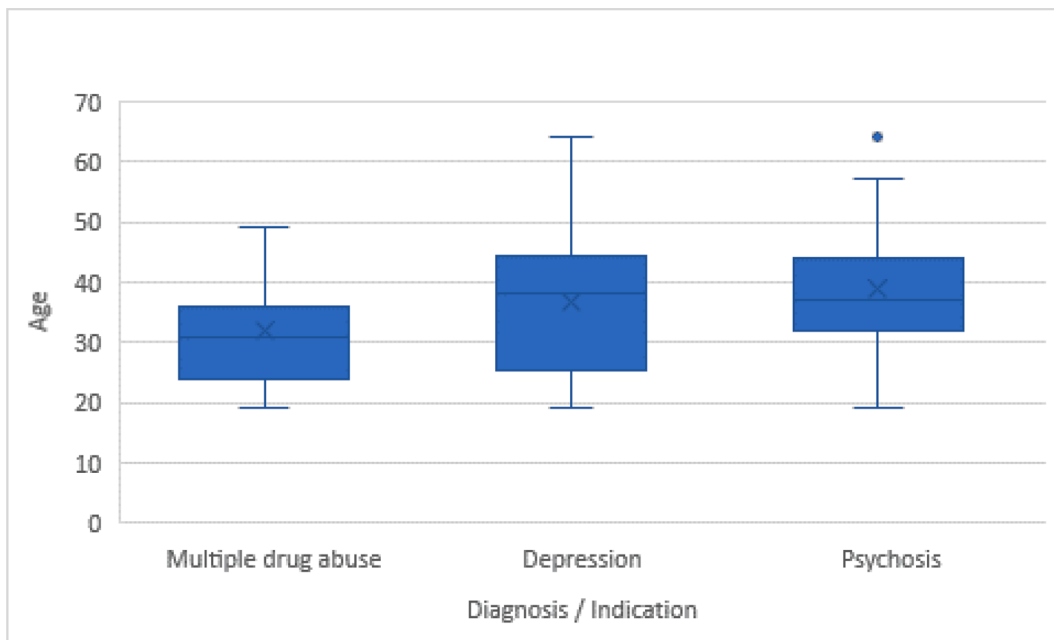


Fig. 1. Prescription pattern of quetiapine according to age.

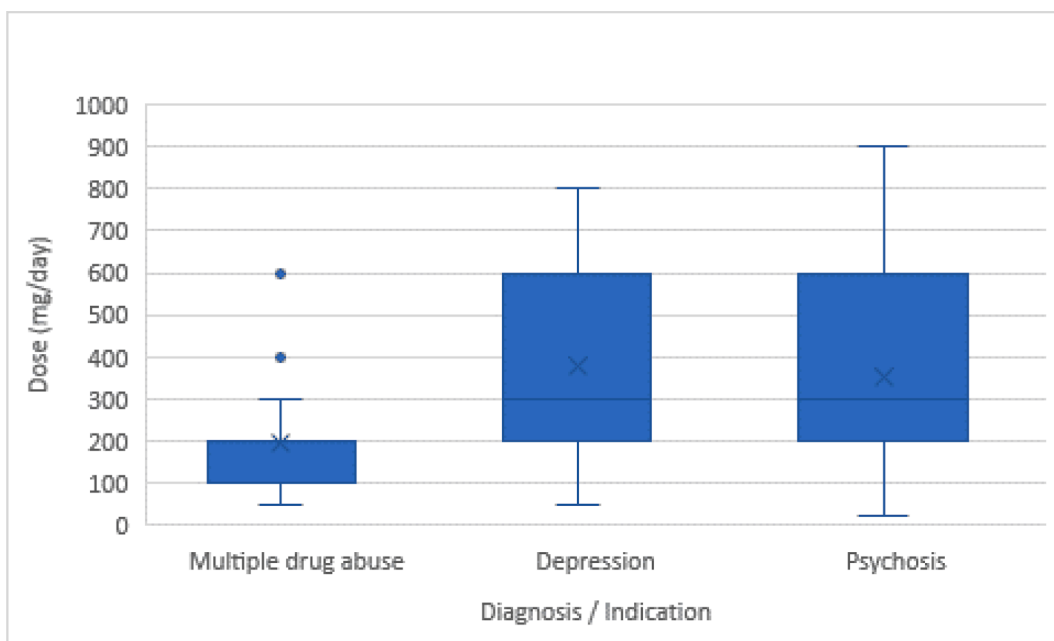


Fig. 2. Prescription pattern of quetiapine according to daily doses.

Table 3
Prescription pattern according to gender and previous medication use.

			Indication			P-value
			MDA	Depression	Psychosis	
Gender	Male	N	73	33	36	<0.001**
		%	100.0 %	86.8 %	76.6 %	
	Female	N	0	5	11	0.223
		%	0.0 %	13.2 %	23.4 %	
Previous medications	No	N	33	16	14	0.223
		%	45.2 %	42.1 %	29.8 %	
	Yes	N	40	22	33	0.223
		%	54.8 %	57.9 %	70.2 %	

***p < 0.001 is statistically extremely signify.

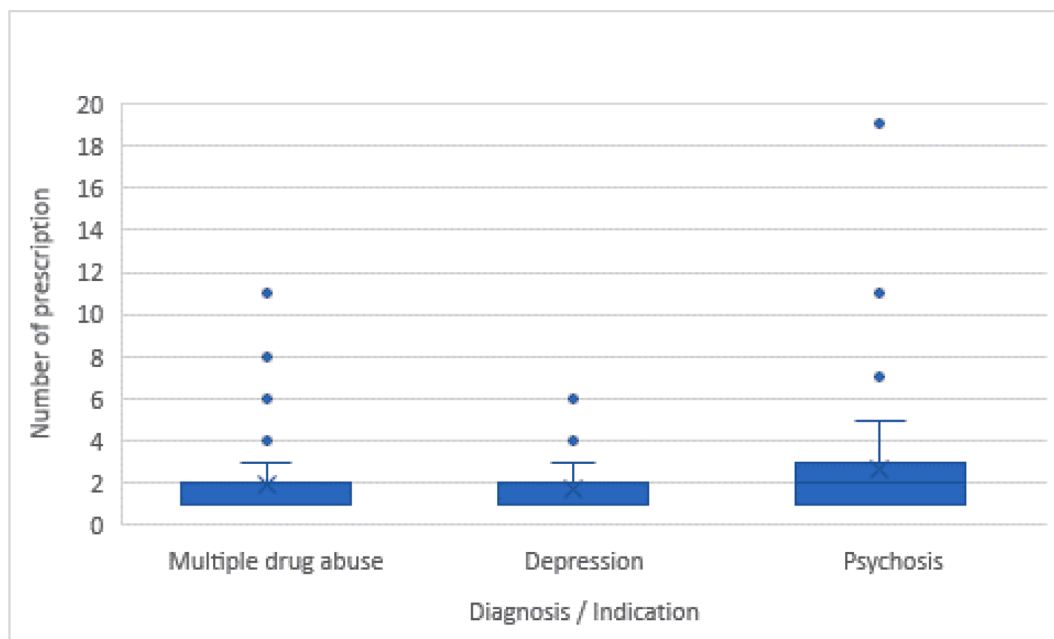


Fig. 3. Range and the median number of Quetiapine prescriptions.

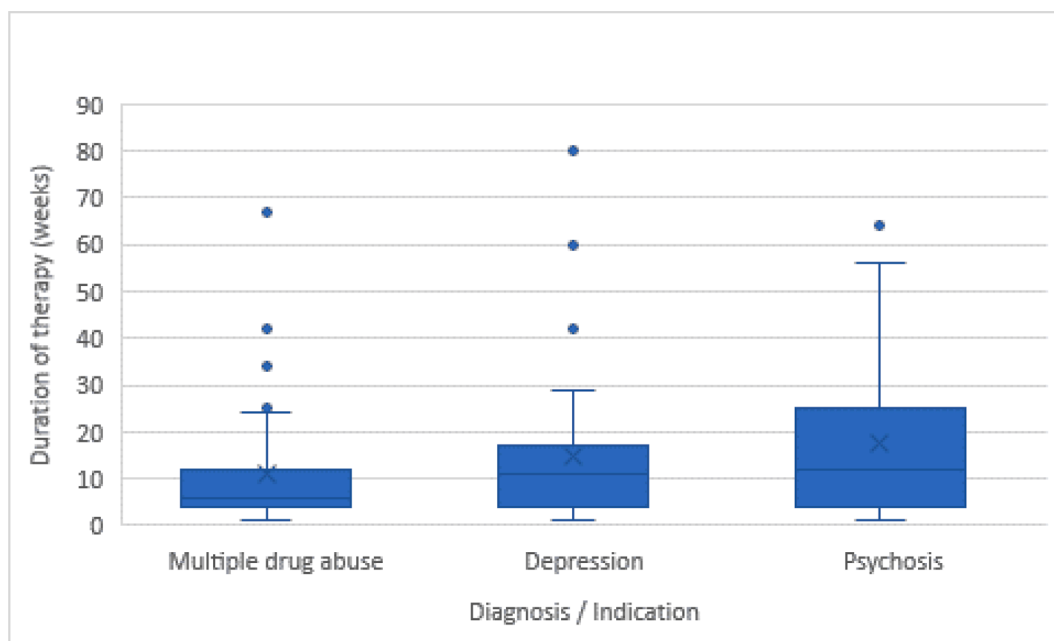


Fig. 4. Range and the median of the duration of Quetiapine therapy.

2013). Unlike other second-generation antipsychotic drugs, it is thought that quetiapine-induced seeking behaviors are due to its hypnotic and sedating properties, particularly in patients with a history of MDA (Kim et al., 2017, Evoy et al., 2019). This could be explained by the lower dopamine and higher histamine receptor affinity of quetiapine (Chew et al., 2008).

Quetiapine was mostly prescribed for the MDA group. Interestingly, all patients prescribed quetiapine for MDA were males and this was not unexpected as most of the adductors are male and consistent with other studies assessed quetiapine addiction (Piróg-Balcerzak et al., 2015). On the other hand, the females used quetiapine for depression and psychosis only. Moreover, we noticed a variation in the dose range among the different groups.

Consistent with our results, one retrospective study that used the poison centers data system in the United States from 2005 to 2011 reported that quetiapine abuse was most common among younger people with the average age of the patients was 23 years, while in our study 30 years, and the ratio of males to females was 1.7. Interestingly, in our study, the patients who used quetiapine were nine times more in the male group than females (Klein-Schwartz et al., 2014).

Quetiapine is dispensed in a wide dose range (150 to 800 mg per day) for different conditions (Klein-Schwartz et al., 2014). However, the common dose range for insomnia is smaller and ranges from 25 to 200 mg per day (Coe and Hong 2012). In our study, the dose range prescribed for MDA patients was smaller than for depressive and psychosis groups. This may indicate that those patients are using quetiapine for its

Table 4
Multinomial logistic regression of Comparison between Depression and MDA vs. psychosis.

Parameters	Depression		MDA	
	Odds ratio (95 % CI)	p-value	Odds ratio (95 % CI)	p-value
Gender (Male)	1.996 (0.564–7.061)	0.284	8 x10 ⁷ (8 x10 ⁷ -8 x10 ⁷)	0.01**
Age	0.985 (0.940–1.032)	0.519	0.943 (0.900–0.987)	0.011**
Dose (mg/day)	1.001 (0.999–1.003)	0.555	0.699 (0.499–0.899)	0.001***
Number of prescriptions	0.708 (0.460–1.090)	0.117	0.908 (0.734–1.124)	0.376
Duration of therapy (weeks)	1.010 (0.971–1.051)	0.614	0.994 (0.960–1.029)	0.745
Previous medications (yes)	0.662 (0.246–1.778)	0.413	0.738 (0.299–1.824)	0.511

**p < 0.01 is statistically very significant.

***p < 0.001 is statistically extremely signify.

sedative effects.

The strength of this study is that the first study in Saudi Arabia describes the clinicians' practices and behaviors in prescribing quetiapine with a reasonable sample size. However, its limitations can be summarized as the collected data represents a single-center study and the majority of the patients were male which limits its generalizability to the whole population. However, this center is the main referral hospital for mental health in Madinah, Saudi Arabia. Further and expanding work is needed to cover different centers and sites in the same region.

5. Conclusion

As quetiapine is not among controlled drugs and is often prescribed for its off-label uses, the clinician should prescribe it with caution, especially for populations at risk of quetiapine abuse or misuse.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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