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RESEARCH ARTICLE

Prescribing patterns of psychotropic medications in psychiatric disorders: a descriptive study from Palestine

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Abstract

Background The practice patterns of psychiatrists have changed over the last two decades. *Objectives* This study describes the pattern of prescribing psychotropic drugs in treating common psychiatric disorders, and investigates the rate of polypharmacy and potential drug-drug interactions. *Setting* Psychiatry governmental outpatient clinic in the north of West Bank, Palestine. *Methods* Cross-sectional study that included all prescriptions which were issued over the period October 2018 to January 2019, for patients diagnosed with schizophrenia, depression, anxiety, bipolar disorder and schizoaffective disorders, and checked for the presence and the grade of potential drug-drug interactions using "Medscape drug interactions checker". *Main outcome measure* Prescribing patterns of psychotropic drugs. *Results* A total of 1045 prescriptions were examined. The mean age of the patients was 47.3 years (SD = 13.6), two-thirds of the patients (64.5%) were males. Fifty-two percent of the patients were diagnosed with schizophrenia while 15.2% were diagnosed with depression. The later third was diagnosed with bipolar disorder, schizoaffective and anxiety disorders (15.8%, 11.1% and 5.1% respectively). The most commonly prescribed drugs were typical antipsychotics for schizophrenia, bipolar and schizoaffective disorders, selective serotonin reuptake inhibitors for depression and tricyclic anti-depressants for anxiety. Polypharmacy was found in 877 prescriptions (84%), and drug-drug interactions (DDIs) were identified in 823 (94%) prescriptions. The DDIs were classified as minor (4, 0.5%), significant (418, 50.8%) and serious (401, 48.7%). *Conclusions* Our results suggest that the pharmacotherapy of psychiatric disorders in Palestine may not be in accordance to international guidelines and the incidence of polypharmacy and DDIs is high.

Keywords Drug-drug interaction · Polypharmacy · Psychiatric disorders · Psychopharmacology

Impact of findings on practice statements

- The pharmacotherapy of psychiatric disorders in Palestine may not be in accordance to international guidelines. Another study may be needed to explore the factors that led to this result.
- The incidence of polypharmacy and drug-drug interactions high. It is necessary to differentiate justified from irrational polypharmacy, in order to decrease the harmful effects of drug-drug interactions.
- Our results highlight the need for clinical pharmacists and pharmacovigillance units in this part of the mental health services in Palestine, in order to provide effective and safe treatment.

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Introduction

Over the last two decades, the pharmaceutical industry has introduced newer classes as well as newer psychotropic drugs. These agents have expanded the effective treatment options available to clinicians for treating major mental disorders. It is believed that these drugs have better efficacy, safety and tolerability compared to the older

psychotropic drugs and are considered as first-line therapy for psychiatric disorders [1]. For example, several studies compared the efficacy and safety of selective serotonin reuptake inhibitors (SSRIs) in comparison with tricyclic antidepressants (TCAs), and found that SSRIs are better tolerated and have fewer side effects while the efficacy was comparable [2]. Likewise, different studies show that the use of atypical anti-psychotics (AP) is favorable for treating patients with schizophrenia due to their higher safety, tolerability and efficacy especially for treating negative symptoms of schizophrenia in comparison with typical agents [3].

Polypharmacy defined as "the prescription of two or more psychiatric medications concurrently" has become a common clinical practice for many psychiatric conditions, and the prevalence of polypharmacy among psychiatric patients is increasing with a significant decline in patients being treated with monotherapy [4–6]. Among all types, multi-class polypharmacy which is defined as "the use of full therapeutic doses of more than one medication from different classes for the same symptom cluster" is the most prevalent [7].

Polypharmacy seems to be multi-factorial and is associated with different clinical, economic, and cultural factors [8]. Some studies found that polypharmacy is higher in adult women than in men as well as in patients with schizophrenia, schizotypal and delusional disorders [4, 9].

As the prevalence of polypharmacy increases, the debate about its merits and demerits continues. In some cases the use of psychotropic drug combinations is justified especially when monotherapy is ineffective for treating the patient's symptoms, or when treating two co-morbid illnesses. In addition, some drugs are added to treat side effects produced by a primary drug [10–12]. On the other hand, several studies suggest that many used combinations are of unproven efficacy [6], and put patients at increased risk of adverse effects and drug-drug interactions (DDIs) because most of these drugs are metabolized by liver enzymes [13]. These medications may interact with medications prescribed for nonpsychiatric ones as well as with other psychiatric medications [14].

Aims of the study

In the present study, we aim, for the first time in Palestine, to explore the prescription pattern of psychotropic drugs used for treating common psychiatric disorders. In addition, we intended to study the rate of psychotropic polypharmacy and drug interactions in outpatient prescriptions made at a central psychiatric clinic in Palestine, compared to the international guidelines.

Ethics approval

This study was conducted in accordance with the regulations and ethics followed at An-Najah National University and in compliance with Declaration of Helsinki. The study received ethical approval from the Institutional Review Board of An-Najah National University (April 10th, 2018). Moreover, the project was approved by the continuing education unit at the Ministry of Health. No patient interviewing was conducted as part of this investigation.

Methods

Study design and setting

This study was conducted in a cross-sectional design. The targeted documented patient prescriptions were used to collect information on sex, age and diagnosis of patients. In addition, the prescribed psychotropic drugs were classified into eight classes; typical antipsychotics, atypical antipsychotics, SSRIs, TCAs, benzodiazepines, anticonvulsants, lithium, and anticholinergic. Typical AP included fluphenazine, promethazine, haloperidol and chlorpromazine. Atypical AP included olanzapine, clozapine, quetiapine and risperidone. SSRI included fluoxetine, citalopram and escitalopram. TCA included amitriptyline and clomipramine. Benzodiazepines included alprazolam, clonazepam and diazepam. Antiepileptics included carbamazepine, valproic acid, lamotrigine, phenytoin, topiramate and phenobarbital. The only used anti-cholinergic was trihexyphenidyl.

The public psychiatric health services in the West Bank, Palestine are provided by the Department of Mental Health Services in the Ministry of Health. In the West Bank, there is one central referral psychiatry hospital located in Bethlehem. It provides secondary psychiatric services for the population in the West Bank. The primary psychiatric health services as well as some of the neurologic disorders services are provided for both adolescents and adults by outpatient health clinics located in the main cities. This study was conducted in one of the main outpatient public psychiatric clinics in the north of the West Bank of Palestine.

The study targeted outpatient prescriptions stored in an electronic system called Avicenna used by the medical centers that belong to the Palestinian Ministry of Health. All prescriptions made between October 2018 until January 2019 were collected. Out of those prescriptions, we included only those that were issued for patients diagnosed with schizophrenia, depression, anxiety disorders, bipolar

affective disorder, and schizoaffective disorders (diagnosis was made using Diagnostic and Statistical Manual of Mental Disorders, 5th Edition). For each of the patients, the last prescription that contains all prescribed medications was considered. As the study setting is exclusive for mental health services where the use of non-psychotropic drugs was not documented, we couldn't study the interactions between psychotropic and non-psychotropic medications. Prescriptions made for neurological disorders such as epilepsy and intellectual disability were excluded.

Current guidelines issued by the Royal Australian and New Zealand College of Psychiatrists which recommend the use of newer psychotropic drugs in lieu of old agents for treating major mental disorders, were considered to compare our results with the international guidelines.

Drug interaction checking

The prescribed psychotropic drugs for each patient were entered into the "Medscape Drug Interactions Checker" to check for potential DDIs as well as to check the degree of interaction. This software classifies DDIs into minor, significant and serious. Significant DDI means that the combined drugs have to be monitored closely or used with caution, while serious DDI means that the combination should be avoided or an alternative to be used.

Statistical analysis

All collected data were analyzed using Statistical Package for the Social Sciences (SPSS), Version21 (IBM Corp, USA). Rates and frequencies were made for gender, age, and diagnosis. In addition, prescribed psychotropic classes for each diagnosis were identified.

Results

Sample size and general characteristics of the patients and prescriptions

Overall, 1535 prescriptions were issued during the study period. Of these, only 1045 (68%) were retained for further analyses after exclusion of prescriptions made for neurological disorders such as epilepsy, intellectual disability or other diagnoses other than those mentioned in the methods. Characteristics of patients for whom the prescriptions were issued are shown in Table 1. Two-thirds of the patients (64.5%) were males with an average age of 47.3 ± 13.6 years (mean ± standard deviation [SD]), the majority were adults (> 18 years) and half of them were between 36 and 55 years of age. The documented diagnosis for half of the patients was schizophrenia, while the rest were diagnosed with bipolar affective disorder, depression, schizoaffective and anxiety respectively. The number of drugs prescribed per patient was

Table 1 Characteristics of patients and frequency of prescribed psychotropic medicationsin an outpatient psychiatric clinic in Palestine

	Characteristics ($n = 1045$)	Frequency (n)	Percentage (%)
Gender	Male	674	64.5
	Female	371	35.5
Age class (years)	2–9	1	0.1
	10–17	7	0.7
	18–35	227	21.7
	36–55	539	51.6
	> = 56	271	25.9
Diagnosis	Schizophrenia	552	52.8
	Depression	159	15.2
	Anxiety disorder	53	5.1
	Bipolar disorder	165	15.8
	Schizoaffective disorder	116	11.1
Psychotropic drug classes	Typical anti-psychotics	606	58
	Anti-cholinergic drugs	542	52
	Atypical anti-psychotics	396	37.9
	Anti-convulsant drugs	250	23.9
	Benzodiazepines (BZ)	243	23.3
	Selective serotonin reuptake inhibitors (SSRIs)	211	20.2
	Tricyclic anti-depressants (TCA)	201	19.2
	Lithium	48	4.6

2.72 ± 1.24 (mean ± SD). Irrespective of diagnosis, the most commonly prescribed psychotropic drug classes were typical anti-psychotics (58%) followed by atypical anti-psychotics and anticonvulsant drugs (37.9%, 23.9% respectively) while the least used drug was lithium (4.6%).

Pharmacotherapy of common psychiatric disorders according to diagnosis

The pharmacotherapy of psychiatric disorders according to diagnosis is shown in Table 2. The most frequently prescribed psychotropic drugs for patients who were diagnosed to have schizophrenia, were typical anti-psychotics (72.2%), followed by atypical antipsychotics (62.8%). Combination therapy was common among those patients and the most frequent combination was the use of typical anti-psychotic combined with an anticholinergic drug (55.8%). Atypical antipsychotics were combined with anticholinergic drug in 28.6% of patients while typical/atypical antipsychotics combination was used by 25.7% of the patients.

For patients diagnosed to have depression, the most commonly prescribed classes were SSRIs (45.3%), TCAs (38.3%), and benzodiazepines (34.5%). It was observed that a combination of anti-depressant (SSRI + TCA) agents was used in (8.1%) of cases while anti-depressants were more frequently combined with benzodiazepines (25.7%). Regarding the pharmacotherapy of patients who suffered from anxiety disorders, about half of the cases were managed by using TCAs (54.7%), followed by benzodiazepines (35.9%) and SSRIs (28.3%).

For bipolar affective disorder patients, most of them were managed using typical antipsychotics (55.7%), followed by anti-cholinergics (44.8%), anti-convulsants (37.5%) and atypical antipsychotics (35.7%), while lithium was used only for 10.9% of patients. Combination therapy composed of typical anti-psychotic and an anticholinergic drug was employed in 36.3% of the patients. Finally, the pharmacotherapy of patients diagnosed to have schizoaffective disorder resembled that of schizophrenia. That is the most frequently prescribed drugs were typical anti-psychotics (71.6%), followed by anti-cholinergics (65.5%) and atypical antipsychotics (44.8%). Combination therapy composed of typical antipsychotic and anticholinergic drug was used in (60.3%).

Polypharmacy and drug-drug interactions

Polypharmacy was observed in 877 prescriptions (84%). Among those, about one-third of the patients (31.3%) received two drugs, 28% were prescribed three drugs, while 16.1% were prescribed four drugs. Few patients received more than four drugs (Table 3). Among patients with polypharmacy, DDIs were noticed in 94% of the prescriptions; half of those DDIs were significant while the other half were serious. The most common serious interaction was found when two typical anti-psychotics were combined (chlorpromazine/fluphenazine, fluphenazine/haloperidol, and chlorpromazine/haloperidol respectively). These combinations increase QTc interval, increase antidopaminergic effects, including extrapyramidal symptoms and neuroleptic malignant syndrome in addition to their ability to induce sedation. Second most common serious interaction was found when tricyclic antidepressants were combined to SSRIs (amitriptyline/citalopram and amitriptyline/fluoxetine), both of the combinations increase serotonin levels which could increase risk of serotonin syndrome or neuroleptic malignant syndrome. Amitriptyline/citalopram combination has the potential risk for QT prolongation which necessitates ECG monitoring. The most common significant interaction was found when typical anti-psychotics were combined with trihexyphenidyl (chlorpromazine/trihexyphenidyl, fluphenazine/trihexyphenidyl). Although trihexyphenidyl is added to decrease the extrapyramidal side effects of chlorpromazine and fluphenazine, it decreases the levels of chlorpromazine and fluphenazine by pharmacodynamic antagonism. In addition, potential for additive anticholinergic effects necessitates caution when the combination is used.

Discussion

This study was conducted to explore the pharmacotherapy of common psychiatric disorders in area of conflict; Palestine. Moreover, we examined the prevalence of polypharmacy and potential DDIs in prescriptions issued for patients diagnosed to have schizophrenia, depression, anxiety, bipolar affective disorder and schizoaffective disorders. Generally, the results of this study show that the pharmacotherapy of psychiatric disorders in Palestine may not be in accordance to international guidelines. In addition, polypharmacy and varying degrees of DDIs ranging from significant to serious were present in the majority of these prescriptions.

Mental disorders are highly prevalent globally, affecting people across all regions of the world. In Palestine mental disorders remain underreported, under-resourced, undertreated, and mental health services are underfunded. These services are unable to meet the burden of need. There is a severe lack of human and infrastructure resources [15]. A meta-analysis regarding the global prevalence of mental disorders was conducted and showed that the pooled lifetime prevalence of common mental disorders across 85 surveys in 39 countries was 29.2% [16]. This analysis also found that anxiety disorders had the highest prevalence rates, followed by mood and substance use disorders, while the prevalence of schizophrenia was the least [17]. Results of our study were different and showed that about half of

Table 2 Pharmacotherapy of common psychiatric disorders according to diagnosis in an outpatient psychiatric clinic in Palestine

	Psychotropic drug class	Frequency (*n*)	Percentage (%)
Schizophrenia (*n* = 552)	Typical anti-psychotics	399	72.2
	Anti-cholinergic drugs	368	66.7
	Atypical anti-psychotics	347	62.8
	Benzodiazepines (BZ)	106	19.2
	Anti-convulsant drugs	105	19
	Tricyclic anti-depressants (TCA)	66	11.9
	Selective serotonin reuptake inhibitors (SSRIs)	59	10.6
	Lithium	19	3.4
	Typical anti-psychotics + Anti-cholinergic	308	55.8
	Atypical anti-psychotics + Anti-cholinergic	158	28.6
	Typical anti-psychotics + Atypical anti-psychotics	142	25.7
Depression (*n* = 159)	Selective serotonin reuptake inhibitors (SSRIs)	72	45.3
	Tricyclic anti-depressants (TCA)	61	38.3
	Benzodiazepines (BZ)	55	34.5
	Anti-convulsant drugs	35	22.1
	Atypical anti-psychotics	30	18.8
	Typical anti-psychotics	22	13.8
	Anti-cholinergic drugs	21	13.2
	Lithium	4	2.5
	SSRI + TCA	13	8.1
	SSRI + BZD	26	16.3
	TCA + BZD	15	9.4
Anxiety (*n* = 53)	Tricyclic anti-depressants (TCA)	29	54.7
	Benzodiazepines (BZ)	19	35.9
	Selective serotonin reuptake inhibitors (SSRIs)	15	28.3
	Anti-convulsant drugs	12	22.3
	Typical anti-psychotics	10	18.9
	Atypical anti-psychotics	8	15.1
Bipolar (*n* = 165)	Typical anti-psychotics	92	55.7
	Anti-cholinergic drugs	74	44.8
	Anti-convulsant drugs	62	37.5
	Atypical anti-psychotics	59	35.7
	Selective serotonin reuptake inhibitors (SSRIs)	43	26.0
	Benzodiazepines (BZ)	42	25.5
	Tricyclic anti-depressants (TCA)	30	18.2
	Lithium	18	10.9
	Typical anti-psychotics + Anti-cholinergic	60	36.3
	Atypical anti-psychotics + Anti-cholinergic	29	17.6
	Typical anti-psychotics + Atypical anti-psychotics	27	16.3
Schizoaffective (*n* = 116)	Typical anti-psychotics	83	71.6
	Anti-cholinergic drugs	76	65.5
	Typical anti-psychotics + Anti-cholinergic	70	60.3
	Atypical anti-psychotics	52	44.8
	Anti-convulsant drugs	36	31.0
	Typical anti-psychotics + Atypical anti-psychotics	32	28.4
	Atypical anti-psychotics + Anti-cholinergic	31	26.7
	Selective serotonin reuptake inhibitors (SSRIs)	22	19.0
	Benzodiazepines (BZ)	21	18.1
	Tricyclic anti-depressants (TCA)	15	12.9

Table 3 Polypharmacy (> 2 drugs) and drug-drug interactions among psychotropic drugs in prescriptions issued by an outpatient psychiatric clinic in Palestine

	Characteristics	Frequency (*n*)	Percentage (%)
Number of prescribed drugs	I	168	16.1
	II	327	31.3
	III	293	28
	IV	177	16.9
	V	55	5.3
	VI	16	1.5
	VII	7	0.7
	VIII	2	0.2
Poly-pharmacy	Yes	877	84.0
	No	168	16.0
Drug-drug interaction	Yes	823	94.0
	No	54	6.0
Grade of DDI	Minor	4	0.5
	Significant	418	50.8
	Serious	401	48.7

the prescriptions were issued for patients diagnosed to have schizophrenia, followed by depression and bipolar affective disorder with approximately equal proportions, while the least proportion was for anxiety disorders. This difference could be explained by the fact that our prevalence is among patients visiting public outpatient psychiatric clinic, while the meta-analysis was made on the general population. A recently published study from Bahrain showed similar results to ours [18].

The international guidelines regarding the treatment of psychosis suggest that atypical anti-psychotics should be considered as a first-line therapy for schizophrenia due to their higher safety, tolerability and efficacy especially in treating negative symptoms of schizophrenia in comparison with typical agents [3]. Our findings might not be in line with these international recommendations, as typical anti-psychotics were more commonly prescribed compared to atypical ones. In about one-fourth of the patients, typical and atypical antipsychotics were combined. Adjunctive use of antipsychotics and anti-cholinergic drugs was observed among most of the patients with schizophrenia in order to control extra-pyramidal symptoms associated with antipsychotics use [19]. As the pharmacotherapy of schizoaffective disorders is not established well yet [20], this could explain why most of the patients with schizoaffective disorders in this study were treated in a way similar to that of schizophrenia.

With regard to depression, several studies have been conducted to compare the newer anti-depressants, namely SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs) and atypical antidepressants to TCAs, and found that the newer agents have a superior efficacy and are better tolerated compared with TCA therapy, in addition to lower patient dropout rates [2, 21]. Based on these observations, the international guidelines suggest using the newer agents at the expense of TCAs [22]. In our study, although SSRIs were the most commonly prescribed anti-depressants, TCAs were prescribed for more than a third of the patients. Surprisingly, none of the patients was prescribed serotonin and norepinephrine reuptake inhibitors (SNRIs) or atypical antidepressant. This observation may be explained by the high cost of these drugs in comparison with TCAs, especially that the study was conducted in public governmental clinic rather than the private section.

As with depression, about one patient over six was diagnosed to have bipolar affective disorder. Despite its toxicity, lithium has the strongest evidence for long-term relapse prevention [23]. Antipsychotic drugs are effective in the acute treatment of mania, as well as anticonvulsants such as divalproex sodium and lamotrigine. The use of antidepressant drugs is controversial. In our study, we observed that the most commonly prescribed drugs were antipsychotics and anticonvulsants. Combination therapy was used in a great proportion of patients while lithium was used in a few patients. Lithium toxicity due to its narrow therapeutic index could explain its low rate of prescription [24].

Anxiety disorders are the most prevalent psychiatric disorders and are associated with a high burden of illness globally. Antidepressant drug treatment is the clinical standard of care for all types of anxiety disorders [25]. Due to their efficacy and safety, SSRIs and SNRIs are preferred over benzodiazepines which are no longer recommended for maintenance therapy [26]. In our study, TCAs and benzodiazepines were more commonly prescribed compared to SSRIs which were prescribed for less than one-third of the patients. Indeed, none of the patients was prescribed SNRIs.

Polypharmacy has been on the rise for many psychiatric conditions, and several studies suggest that many used

combinations are of unproven efficacy [6], and put patients at increased risk of adverse effects and drug-drug interactions (DDIs). These psychiatric medications may interact with medications prescribed for non-psychiatric reasons as well as with other psychiatric medications [14]. Polypharmacy was noted in a great proportion of patients in this study, and resulted in numerous DDIs. These DDIs were either significant DDI meaning that the combined drugs have to be monitored closely or used with caution, or serious DDI where that combination should be avoided or an alternative to be used. These findings are alarming.

The study setting is exclusive for mental health services and thus, the use of non-psychotropic drugs was not documented. If prescribed, potential DDIs might increase as interactions might occur between psychotropic and non-psychotropic drugs. In addition, the short duration of this cross-sectional study might affect the results as possible seasonal variations of the course of disease might impact the prescribing patterns over time. So that one prescription per patient will not capture these modifications on prescriptions. Furthermore, comorbid mental illnesses are not documented in patient's profile which is unusual in mental disorders.

Conclusions

Results from this study show that pharmacotherapy of psychiatric disorders in Palestine may not be in accordance to international guidelines. Polypharmacy was common and resulted in a high prevalence of DDIs among psychotropic drugs prescribed for these disorders. The results emphasize the need to review pharmacotherapy of psychiatric disorders at a governmental level, in order to improve the mental health in Palestine. In addition, these results emphasize the important role a clinical pharmacist can play in the psychiatry clinics in reviewing the prescriptions and suggesting changes in light of some of the serious drug interactions present.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

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