

Antipsychotic and Anticholinergic Drug Prescribing Pattern in Psychiatry: Extent of Evidence-Based Practice in Bahrain*

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ABSTRACT

The aim of this study is to determine the antipsychotic prescribing pattern and the prevalence of concurrent anticholinergic prescribing in a psychiatric referral hospital. A retrospective audit of prescriptions issued for outpatients was carried out at the Psychiatric Hospital, the only facility that provides psychiatric services for both inpatients and outpatients in the Kingdom of Bahrain. Antipsychotic monotherapy was prescribed for 89.2% patients, whereas polytherapy with two- and three-drugs in 10.4% and 0.4%, respectively. Atypical antipsychotics were prescribed more often (67.7%) than typical antipsychotics. Risperidone and haloperidol were the most frequently prescribed antipsychotics. Long-acting risperidone injection was the only depot preparation prescribed. The mean antipsychotic dose expressed as chlorpromazine equivalent (CPZeq; mg/day) was 242 (220 for monotherapy and 414 for polytherapy). The prevalence of high dose antipsychotic (mean CPZeq > 1000 mg/day) was 1.8%, prescribed at a mean CPZeq dose of 1531 (1925 for monotherapy and 1137 for polytherapy), mainly attributed to haloperidol. Anticholinergics were co-prescribed for almost two third of patients receiving antipsychotics, particularly for those on polytherapy (monotherapy 57.3%; polytherapy 87.5%). Antipsychotic polytherapy, high dose and co-prescription of an oral with a depot antipsychotic preparation were strongly associated with concurrent prescription of anticholinergics. Procyclidine and orphenadrine were the most often prescribed anticholinergics. In Bahrain, antipsychotic monotherapy is a common practice for outpatients with psychotic disorders. Some of the antipsychotic polytherapies, dosage strategies, and high prevalence of anticholinergic use are therapeutic issues that need to be addressed to foster evidence-based prescribing practice.

Keywords: Anticholinergics; Antipsychotics; Best Evidence; Prescribing; Psychiatry

1. Introduction

Numerous studies have reported that there are wide inter-country [1-4] and intra-country [4-6] variations in antipsychotic prescribing pattern for patients with psychotic disorders. These variations include the prevalence of antipsychotic polytherapy compared to monotherapy, typical versus atypical antipsychotics, preference for high-dose antipsychotics or depot antipsychotics, and anticholinergic co-prescription. Such variations have been attributed to difficulty in adhering to treatment guidelines and therapeutic algorithms in clinical practice, differences in healthcare settings, availability and cost of antipsychotics, introduction of atypical antipsychotics with improved adverse effects profile and efficacy, and socio-

cultural determinants [3,4,7-9].

Extra-pyramidal symptoms (EPS) such as acute dystonia, akathisia and Parkinsonism are among the most common adverse effects of antipsychotics. In clinical practice, anticholinergics are widely used to treat and prevent antipsychotic-induced EPS. Anticholinergics should be prudently prescribed because these drugs in addition to their well-known peripheral side-effects, may worsen positive symptoms, appear to partially ameliorate negative symptoms and are associated with impaired cognitive functioning of schizophrenic [10] and cognitive impairment in elderly patients [11]. A recent report [12] has confirmed that there is a wide variation in anticholinergic medication prescribing across various countries; a combination of clinical, social, economic and cultural factors are the determinants of the use of these drugs suggesting that there are considerable differences between treatment guidelines and clinical practice.

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The initial enthusiasm about the second generation of atypical antipsychotic drugs has changed into criticism and debate culminating in the controversial CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness), CUtLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study) and EUFEST (European First-Episode Schizophrenia Trial) trials. The debate seems to be driven more by values than by data; some place an emphasis on cost, others focus on extra-pyramidal side effects, weight gain or efficacy [13,14].

Based on PubMed database searching (up to January 2011) using MeSH terms- antipsychotic/prescribing pattern/Middle East, we were unable to identify any publication in the last 30 years that has explored the antipsychotic prescription pattern in patients with psychotic disorders in Middle Eastern countries. The present study, therefore, focused on determining the antipsychotic prescribing pattern and the prevalence of concurrent anticholinergic prescribing to outpatients in a psychiatric referral hospital.

2. Material and Methods

2.1. Setting

The Kingdom of Bahrain, with a population of 1.1 million is a group of small islands located in the Arabian Gulf. A Directorate of Health Centres, has a network of 21 primary-care health centres spread across the islands and provides free health care services to both citizens and expatriates, including dispensing of essential drugs. Patients requiring psychiatric consultation are referred to the Psychiatric Hospital under the Ministry of Health. There are several well-established private hospitals.

This prescription-based study was carried out at the Psychiatric Hospital, the only public hospital for psychiatric services in Bahrain. This hospital with 201 beds provides both inpatient and outpatient services, and is the only facility for substance abuse rehabilitation in the country.

Data source and collection: All prescriptions dispensed *gratis* at Psychiatric Hospital pharmacy for outpatients during September 2007 were collected. Prescriptions were initially screened and those with antipsychotics were analyzed. The following inclusion criteria were used: 1) prescriptions comprising one or more antipsychotic(s) alone or with an anticholinergic agent; 2) prescriptions with a refill period of minimum six weeks (in order to ensure that dose-titration has been achieved and to avoid prescription duplication). Prescriptions wherein antipsychotics were co-prescribed with antidepressant(s) were excluded to avoid the potential influence of intrinsic anticholinergic activity due to antidepressant(s) on prescribing rate of anticholinergic medications. The following data were collected: age and gender for each pa-

tient; type, route of administration and dose of antipsychotics; dose and type of co-prescribed anticholinergics.

2.2. Drugs

Antipsychotics included on the psychiatric hospital essential drug list at the time of data collection were typical antipsychotics with high potency (haloperidol, trifluoperazine), moderate potency (zuclopenthixol), and low potency (chlorpromazine and thioridazine). Atypical antipsychotics included clozapine, olanzapine, risperidone and sulpiride. Parenteral preparations included decanoate formulations of haloperidol, flupenthixol, fluphenazine and zuclopenthixol, and risperidone long-acting injection (LAI).

2.3. Operational Definitions

According to evidence-based criteria [15] antipsychotic-induced EPS were categorized as follows: absent or negligible (0) for clozapine; low (1+) for olanzapine, sulpiride and thioridazine; moderate (2+) for chlorpromazine and risperidone; moderately severe (3+) for trifluoperazine and zuclopenthixol; and severe (4+) for haloperidol. Conversion of oral antipsychotic dose to chlorpromazine equivalent (CPZeq) dose was derived from evidence-based published data [1,15-17]. Antipsychotic polytherapy (combination antipsychotic therapy) is defined as concomitant use of ≥ 2 antipsychotics (either typical/atypical/composition of both). High-dose antipsychotics are defined as mean CPZeq doses > 1000 mg/day [18]. As per Diagnostic and Statistical Manual (DSM)-IV criteria, psychotic disorders include schizophrenias, schizoaffective and schiziform disorders. In this report, antipsychotics, particularly atypical, may also be used as off-label medications for dementia, major depression disorders, autism spectrum disorders, obsessive compulsive disorders, combat-related post traumatic stress disorders and generalized anxiety disorders.

2.4. Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS/PC+, version 15). Chi-square (χ^2) and Fisher's exact tests, as appropriate, were used to test differences between proportions, and two-tailed t-test was used for continuous variables. A p-value of < 0.05 was considered statistically significant.

3. Results

Out of 1591 prescriptions, 454 (28.5%) met the inclusion criteria. However, 1137 outpatient prescriptions (71.4%) were excluded because: 912 (57.3%) were on antidepressant(s) and 225 (14.1%) were on antipsychotic co-prescribed with antidepressant(s). The mean age (\pm SD)

of patients who were on antipsychotic monotherapy was 38.4 ± 15.1 (median = 39; range 5 - 80 years), whereas 38.7 ± 11.7 (median = 41; range 17 - 63 years) was for patients who were on antipsychotic polytherapy. No significant differences with respect to mean age of patients prescribed antipsychotic monotherapy and polytherapy was evident. The proportion of male patients was 59.8 and 55.1 for mono and polytherapy, respectively ($p = 0.541$). Antipsychotic and anticholinergic medication characteristics are shown (Table 1). Overall 61% of pa-

tients (57.3% in monotherapy; and 87.5% polytherapy) on antipsychotic therapy were prescribed a single anticholinergic drug: procyclidine (41%, $n = 186/454$), orphenadrine (10.8%, $n = 49/454$), benztropine (7.9%, $n = 36/454$), and trihexyphenidyl (0.9%, $n = 4/454$).

3.1. Antipsychotic Monotherapy

Prescribing patterns of antipsychotic monotherapy are shown (Table 2). A total of 89.2% ($n = 405/454$) outpa-

Table 1. Medication characteristics.

| | Antipsychotic monotherapy | Antipsychotic polytherapy | <i>p</i> -value |
|--|---------------------------|---------------------------|-----------------|
| Rate of antipsychotic therapy <i>n</i> (%) | 405 (89.2) | 49 ^a (10.8) | |
| Mean CPZeq dose (mg/day) | 220 ± 251 | 414 ± 278 | <0.0001 |
| Median (mg) | 150 | 350 | |
| Range (mg) | 12.5 - 3000 | 25 - 1250 | |
| Dose > 1000 mg CPZeq <i>n</i> (%) | 4 (1) | 4 (8.2) | 0.0006 |
| Mean CPZeq doses of antipsychotics ^b (median) | 1925 ± 788 (1750) | 1137 ± 75 (1100) | |
| Depot antipsychotic, <i>n</i> (%) | 19 (4.7) | 9 ^c (18.4) | 0.001 |
| Prescription rate of anticholinergic, <i>n</i> (%) | 232 (57.3) | 43 (87.5) | <0.000 |
| Anticholinergics mean dose ± SD (<i>n</i>) | | | |
| Procyclidine | 8.5 ± 4.2 (156) | 11.2 ± 4.1 (30) | 0.004 |
| Orphenadrine | 81.8 ± 37.5 (43) | 116.7 ± 40.8 (6) | 0.039 |
| Benztropine | 3.8 ± 1.4 (30) | 3.3 ± 1 (6) | 0.525 |
| Trihexyphenidyl | 4.0 ± 1.7 (3) | 10 ± 0 (1) | - |

CPZeq = chlorpromazine equivalents; ^aonly 2 patients (0.4%) were on three-antipsychotic combination; ^bmean CPZeq doses of antipsychotics > 1000 mg; ^c2 out of 9 patients who received risperidone long-acting injection were on antipsychotic three-drug combination.

Table 2. Prescribing patterns of antipsychotic monotherapy in psychiatric hospital outpatients.

| Antipsychotics | Number of patients (%) | Anticholinergic prescribed concurrently (%) | Anticholinergic co-prescribing rate per antipsychotic | Antipsychotic mean ± SD doses (median) | CPZeq mean ± SD doses (median) |
|-----------------------------|------------------------|---|---|--|--------------------------------|
| Typical: | | | | | |
| Chlorpromazine (2+) | 29 (7.2) | 16 (4) | 55.5 | 153 ± 96 (100) | 153 ± 96 (100) |
| Haloperidol (4+) | 42 (10.4) | 30 (7.4) | 71.2 | 10.8 ± 11.1 (10) | 540 ± 556 (500) |
| Thioridazine (1+) | 1 (0.2) | - | - | 50 ± 0 (50) | 50 ± 0 |
| Trifluoperazine (3+) | 33 (8.1) | 20 (4.9) | 60.5 | 9.0 ± 8.9 (5) | 191 ± 181 (100) |
| Zuclopenthixol (3+) | 17 (4.2) | 15 (3.7) | 88.1 | 23.5 ± 10.6 (20) | 94 ± 42 (80) |
| Subtotal | 122 (30.1) | 81 (20) | 66.4 | | 288 ± 388 (155) |
| Atypical: | | | | | |
| Clozapine (0) | 14 (3.5) | 5 (1.2) | 34.3 | 278 ± 137 (278) | 557 ± 275 (575) |
| Olanzapine (1+) | 38 (9.4) | 14 (3.5) | 37.2 | 9.2 ± 5.6 (7.5) | 184 ± 112 (150) |
| Risperidone (2+) | 194 (47.9) | 125 (30.9) | 64.5 | 3.5 ± 2 (3) | 174 ± 97 (150) |
| Risperidone LAI (2+) | 14 (3.5) | 2 (0.5) | 5.7 | 31.3 ^a ± 8.8 (31) | ** |
| Risperidone oral + LAI (2+) | 5 (1.20) | 4 (1) | 83.3 | ** | ** |
| Sulpiride ^b (1+) | 18 (4.4) | 1 (0.2) | 4.5 | 169 ± 75 (200) | 85 ± 37 (100) |
| Subtotal | 283 (69.9) | 151 (37.3) | 53.3 | | 193 ± 146 (150) |
| Total | 405 (100) | 232 (57.3) | | | 220 ± 251 (150) |

(0), (1+), (2+), (3+) and (4+) represent antipsychotics with negligible, low, moderate, moderately severe, and severe extrapyramidal symptoms, respectively; CPZeq = chlorpromazine equivalents; LAI = long-acting injection; ^amean dose of intramuscular LAI risperidone mg/fortnight; ^ban atypical antipsychotic structurally similar to amisulpride; ^cmean & median dose not calculated.

tients were prescribed antipsychotic monotherapy; of these, 69.9% (n = 283/405) were on atypical antipsychotics such as oral risperidone (47.9%, n = 194), olanzapine (9.4%, n = 38), sulpiride (4.4%, n = 18), clozapine (3.5%, n = 14), risperidone long-acting injection (3.5%, n = 14) and oral plus LAI risperidone (1.2%, n = 5). Risperidone, both oral and LAI, was the most frequently prescribed antipsychotics, accounted for 75.3% (n = 213/283) of all atypical antipsychotic monotherapies. Nevertheless, 30.1% (n = 122/405) of patients received monotherapy with typical antipsychotics: haloperidol (10.4%, n = 42), trifluoperazine (8.1%, n = 33), chlorpromazine (7.2%, n = 29), zuclopenthixol (4.2%, n = 17) and thioridazine (0.2%, n = 1). Haloperidol accounted for 34.4% (n = 42/122) of all typical antipsychotic monotherapies. The

three antipsychotics most frequently prescribed as monotherapy were risperidone (52.6%), followed by haloperidol (10.4%) and olanzapine (9.4%).

Anticholinergics were prescribed for 57.3% of patients on antipsychotic monotherapy. The rate of individual antipsychotics along with anticholinergics co-prescribed were: zuclopenthixol (88.1%), risperidone oral + LAI (83.3%), haloperidol (71.2%), oral risperidone (64.5%), trifluoperazine (60.5%), chlorpromazine (55.5%), olanzapine (37.2%), clozapine (34.3%), risperidone LAI (5.7%), and sulpiride (4.5%).

3.2. Antipsychotic Polytherapy

The prescribing patterns of antipsychotic polytherapy are shown (Table 3). Antipsychotic polytherapy was used

Table 3. Prescribing patterns of antipsychotic polytherapy in psychiatric hospital outpatients.

| Antipsychotics | Number of patients (%) | Anticholinergic prescribed concurrently (%) | Anticholinergic co-prescribing rate per antipsychotic | Antipsychotic mean \pm SD doses (median) | CPZeq mean \pm SD doses (median) |
|-----------------------------|------------------------|---|---|--|------------------------------------|
| Typical + typical: | | | | | |
| Chlorpromazine (2+) plus | | | | | |
| Haloperidol (4+) | 2 (4.3) | 2 (4.3) | 100 | 12.5 \pm 10.6 (12.5) | 700 \pm 565 (700) |
| Zuclopenthixol (3+) | 1 (2.1) | 1 (2.1) | 100 | 60 \pm 0 (60) | 290 \pm 0 (290) |
| Subtotal | 3 (6.4) | 3 (6.4) | 100 | | 563 \pm 464 (300) |
| Atypical + atypical: | | | | | |
| Risperidone (2+) plus | | | | | |
| Olanzapine (1+) | 4 (8.5) ^a | 3 (6.4) | 75.3 | 7.5 \pm 3.5 (7.5) | 275 \pm 125 (300) |
| Sulpiride (1+) | 4 (8.5) ^b | 3 (6.4) | 75.3 | 117 \pm 76 (100) | 225 \pm 90 (250) |
| Subtotal | 8 (17) | 6 (12.8) | 75.3 | | 275 \pm 100 (300) |
| Atypical + typical: | | | | | |
| Clozapine (0) plus | | | | | |
| Zuclopenthixol (3+) | 1 (2.1) | 1 (2.1) | 100 | 10 \pm 0 (10) | 540 \pm 0 (540) |
| Olanzapine (1+) plus | | | | | |
| Haloperidol (4+) | 2 (4.3) | 2 (4.3) | 100 | 7.5 \pm 3.5 (7.5) | 575 \pm 176 (575) |
| Trifluoperazine (3+) | 2 (4.3) | 2 (4.3) | 100 | 7.5 \pm 3.5 (7.5) | 220 \pm 113 (220) |
| Zuclopenthixol (3+) | 2 (4.3) | 2 (4.3) | 100 | 30 \pm 28.3 (30) | 270 \pm 183 (270) |
| Risperidone (2+) plus | | | | | |
| Chlorpromazine (2+) | 7 (14.9) | 6 (12.8) | 85.9 | 93 \pm 53 (100) | 293 \pm 93 (300) |
| Haloperidol (4+) | 7 (14.9) ^c | 6 (12.8) | 85.9 | 13.3 \pm 7.5 (15) | 791 \pm 406 (850) |
| Trifluoperazine (3+) | 8 (17) ^d | 7 (14.9) | 87.6 | 7.4 \pm 5.1 (5) | 408 \pm 198 (400) |
| Zuclopenthixol (3+) | 6 (12.8) | 6 (12.8) | 100 | 23.3 \pm 15 (20) | 308 \pm 110 (310) |
| Sulpiride (1+) plus | | | | | |
| Trifluoperazine (3+) | 1 (2.1) | - | - | 5 \pm 0 (5) | 125 \pm 0 (125) |
| Subtotal | 36 (76.7) | 32 (68.3) | 89 | | 444 \pm 285 (400) |
| Total | 47 (100) | 41 (87.5) | | | 414 \pm 278 (350) |

(0), (1+), (2+), (3+) and (4+) represent antipsychotics with negligible, low, moderate, moderately severe, and severe extrapyramidal symptoms, respectively; CPZeq = chlorpromazine equivalents; ^a2 out of 4 patients received risperidone long-acting injection (LAI); ^b1 out of 4 patients received risperidone LAI; ^c1 out of 7 patients received risperidone LAI; ^d3 out of 8 patients received risperidone LAI.

for 10.8% (n = 49/454) outpatients; of these 10.4% (n = 47/454) were on two antipsychotics, whereas 0.4% (n = 2/454) were on three antipsychotics. Pattern of antipsychotic two-drug therapy in descending order was as follows: an atypical with a typical antipsychotic (76.6%, n = 36/47), two atypical antipsychotics (17%, n = 8/47), and two typical antipsychotics (6.4%, n = 3/47; **Table 3**). The antipsychotic two-drug combinations prescribed most often were risperidone/trifluoperazine (17%), followed by risperidone with either chlorpromazine (14.9%) or haloperidol (14.9%) or zuclopenthixol (12.8%). The three antipsychotics most commonly prescribed as polytherapy were risperidone (73.5%), followed by haloperidol (22.4%) and trifluoperazine (22.4%).

Anticholinergics were prescribed for 87.5% of patients on antipsychotic polytherapy (two antipsychotic combination); a typical antipsychotic co-prescribed with another typical or with an atypical antipsychotic had a greater likelihood of being prescribed with anticholinergic medications (**Table 3**).

Antipsychotic three-drug combination comprising chlorpromazine plus zuclopenthixol plus risperidone LAI was prescribed for 0.4% (n = 2/454) outpatients (Data not shown).

4. Discussion

Antipsychotics: This study provides insights, based on audit of prescriptions, into the prescribing patterns of antipsychotic and anticholinergic medications for outpatients with psychotic disorders receiving treatment at a public referral hospital in Bahrain. The data suggest that atypical antipsychotic monotherapy is the most preferred treatment. Antipsychotic monotherapy was prescribed for most of the patients (89.2%), a rate which is comparable to 86.5% reported in New Zealand [5], 87% in Australia [19], 87% - 91% in USA [20,21] and 82.6% in UK [22], consistent with clinical guidelines [8,16]. With the exception of haloperidol and clozapine (**Table 2**), the individual antipsychotic daily dose for other monotherapies was generally lower than the recommended therapeutic range [8,18], deemed to be inadequate for many with psychosis [8,18,23].

Despite the superior clinical effectiveness, EPS safety profile [24], and as being the preferred drug for patients with schizophrenia who are unresponsive to adequate multiple antipsychotic monotherapy trials [8,18], clozapine is significantly under-prescribed and accounted for only 3.3% of overall antipsychotics (**Tables 2 and 3**). In contrast, other studies reported clozapine to be the most commonly prescribed antipsychotic medication in up to 25% - 60% of schizophrenic inpatients in China [25] and in 34.5% of outpatients in New Zealand [26]. In general, limited clinical utility of clozapine appears to be due to propensity to cause agranulocytosis and the need for

mandatory hematological monitoring of patients [27]. Psychiatrists, therefore, may find it appealing to prescribe antipsychotic polytherapy rather than to prescribe clozapine [21]. Moreover, clozapine was included in the drug list only few months prior to data collection and prescribing was restricted to consultants in psychiatric hospital in Bahrain at that time.

The combination antipsychotic therapy in our study was rarely used (10.8%), and conforms with expert guidelines [8]. A low trend towards polytherapy may be related to the nature of study population in our study, *i.e.*, outpatients. Of note, symptoms of psychotic disorders in outpatients perhaps are less severe and persistent than those of inpatients. Thus outpatients may less often be prescribed with antipsychotic polytherapy than inpatients [21]. In our study, concomitant antipsychotic therapy (a typical with an atypical) comprised 76.6% of overall antipsychotic polytherapy (**Table 3**) which is in line with rates reported elsewhere [5,21]. Moreover, polytherapy in our survey may have resulted from adding a typical to an atypical (top up strategy) to improve persistent positive symptoms [21,28], or adding an atypical to a typical to switch to the atypical regimen [21] or cross-tapering designed to change antipsychotic regimen (cross-titration trap) [2,21,28]. A prospective study combining quantitative and qualitative approaches can address the primary reason for the use of antipsychotic polytherapy.

The overall prevalence of high-dose antipsychotics was 1.8%, prescribed at a mean daily CPZeq dose of 1531 ± 668 mg (median = 1225, data not shown). High-dose antipsychotic practice was found to be more likely related to antipsychotic polytherapy (8.2% [polytherapy] vs. 1% [monotherapy]; $p = 0.0006$, **Table 1**); it is mainly attributed to the high dose of haloperidol prescribed as both monotherapy and combination antipsychotic therapy. The rate of high-dose antipsychotic was equivalent to that reported recently for psychiatric outpatients in Hong Kong (1.8%) [29]. Moreover, we found that the rate of high-dose antipsychotic monotherapy (1%) was less than the 2.5% reported for outpatients in USA [22].

Anticholinergics: Notwithstanding considerable differences between anticholinergics, these medications are the mainstay for treatment of EPS-induced by antipsychotics. EPS occur mostly with typical antipsychotics, particularly those with high potency, and occasionally with atypical antipsychotics. We found that anticholinergic drugs were co-prescribed extensively along with both typical and atypical antipsychotics. The prevalence of anticholinergic use was 57.3% and 87.5% for outpatients on antipsychotic monotherapy and polytherapy, respectively. These rates were significantly greater than those reported for outpatients elsewhere [2,5,9,30] (regardless of type and therapy of antipsychotics studied) which suggests the possibility that cultural and institutional pra-

ctices would have contributed to these findings. In our study anticholinergics may have been routinely prescribed even in the absence of EPS, although experts disagree about the prophylactic use of these agents [16,18]. This therapeutic dilemma has been addressed by Gjerden *et al.* [31] who viewed that anticholinergic use appears to be superfluous for at least one-third of patients, and their use exceeded the incidence of EPS [32].

Our study has identified that antipsychotic polytherapy is a key predictor for the use of anticholinergics since both proportion and mean dose of co-prescribed anticholinergic (specifically for most often prescribed procyclidine and orphenadrine) increase proportionally with the increase in number of prescribed antipsychotic medications (**Table 1**). Anticholinergics should be prudently prescribed because these drugs, in addition to their peripheral side effects, can impair cognition, especially in the elderly patients [11]. Anticholinergics may worsen positive symptoms, appear to partially ameliorate negative symptoms, and are associated with impaired cognitive functioning of schizophrenic patients [10]. Prescribers should be aware of the potential anticholinergic—related peripheral side effects, particularly, when anticholinergic medications are prescribed with antipsychotics that have greater intrinsic anticholinergic activity, such as the phenothiazines.

We also found that high anticholinergic drug prevalence is less likely to be associated with the mean CPZeq doses, particularly atypical antipsychotics (**Table 2**). These findings suggest that overt anticholinergic prescribing may arguably be superfluous for several reasons. First, clozapine and olanzapine have significant intrinsic anticholinergic activity, which may be partly responsible for fewer EPS and obviates the need for an anticholinergic agents [33]. Approximately 35% of patients who received these medications were prescribed anticholinergic medications (**Table 2**), perhaps to mitigate clozapine-induced hypersalivation [34]. Second, dose-dependent EPS have been reported to appear in 60% to 70% of patients taking risperidone at dosages of ≥ 6 mg/day (*i.e.*, ≥ 300 mg/day CPZeq) [35-37]. Nonetheless, approximately 65% of patients on risperidone monotherapy (who received a mean dose of 3.5 mg/day, *i.e.*, 175 mg/day CPZeq) were prescribed anticholinergic drugs (**Table 2**). Third, most guidelines converge on a recommendation that doses of antipsychotics should range between 300 and 1000 mg CPZeq in order to achieve effective control of positive symptoms [8,18] while avoiding EPS and the use of anticholinergic drugs [38]. In contrast to this, the mean CPZeq doses especially as monotherapy (**Table 2**), the most sought practice in our cohort, was significantly below this range [8,18,23]. Fourth, atypical antipsychotics as a class, generally produce fewer or no EPS relative to typical antipsychotics, which can produce clinically sig-

nificant EPS in 60% of patients [33]. Moreover, risperidone is considered the most likely atypical antipsychotic agent to produce EPS [15]. It is, therefore, the high prevalence of anticholinergic co-prescription in patients who received atypical antipsychotic monotherapy (53.3%; **Table 2**) can be attributed, in addition to the suggested superfluous prescribing trend, to the frequent use of this agent in this group.

Sulpiride was rarely prescribed with anticholinergic medications (4.5%, **Table 2**). This may be attributed to: 1) its classification as an atypical benzamide antipsychotic associated with low incidence of EPS; and 2) its prescription in low dose (85 mg CPZeq), a dose which is significantly lower than the recommended antipsychotic therapeutic range (400 - 1200 mg) required for controlling both negative and positive symptoms of schizophrenia [16].

In our study, different aspects related to prescription patterns of antipsychotics and the concurrent prescriptions of anticholinergics appear either to be at variance or in agreement with a large body of literature worldwide. These inter-country variations may be due to several determinants such as healthcare setting, availability and cost of antipsychotics, population sample (outpatients versus inpatients), treatment settings (psychiatric hospital versus psychiatric unit in a general hospital or emergency setting versus nonemergency setting), standard treatment guidelines, psychiatrists' training background and socio-cultural context of clinical presentations [1,39]. We suggest that the cultural or institutionally biased approach may play a determinant role in prescribing patterns of these drugs. Moreover, inter-racial differences in effective therapeutic dosage of antipsychotics in treating psychotic symptoms and variations in psychotic symptoms response to antipsychotic therapy should also be considered [39,40].

4.1. Limitations of the Study

Several limitations need to be considered while interpreting the findings of this study. Since the diagnosis of psychotic disorder is not stated in prescriptions, the therapeutic rationale for antipsychotics prescribed is uncertain. Moreover, factors that would influence the antipsychotic selection such as history of previous treatment response, drug safety in overdose, overall adverse effect profile, comorbid condition, non-psychotic medications used, and patient preference, if any, are uncertain. Therefore the observations of this study need to be interpreted with caution.

4.2. Conclusion

In Bahrain, antipsychotic monotherapy is the common practice for outpatients with psychotic disorders. Some

of the antipsychotic polytherapies, dosing strategies and high prevalence of anticholinergic use are therapeutic issues that need to be addressed to foster evidence-based prescribing practice.

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6. Conflict of Interest

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