Pharmacology & Pharmacy, 2012, 3, 409-416
http://dx.doi.org/10.4236/pp.2012.34055 Published Online October 2012 (http://www.SciRP.org/journal/pp)

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

Khalid A. J. Al Khaja[1#], Mohammed K. Al-Haddad[2], Reginald P. Sequeira[1], Adel R. Al-Offi[3]

[1]Department of Pharmacology & Therapeutics, Arabian Gulf University, Manama, Bahrain; [2]Department of Psychiatry, Arabian Gulf University, Manama, Bahrain; [3]Psychiatric Hospital, Ministry of Health, Manama, Bahrain.
Email: #khlidj@agu.edu.bh

Received May 7th, 2012; revised June 13th, 2012; accepted July 12th, 2012

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 alogarithms 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, akathesia 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.

*The abstract of this paper was presented at the 19th European Congress of Psychiatry, 12-15 March 2011, Vienna, Austria.
#Corresponding author.

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 publiccation 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 patient; 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 $\geq$2 antipsychotics (either typical/atypical/combination 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 schizoform 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 (x^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 (±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 patients (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), benzatropine (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	*p*-value
Rate of antipsychotic therapy n (%)	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 n (%)	4 (1)	4 (8.2)	0.0006
Mean CPZeq doses of antipsychotics[b] (median)	1925 ± 788 (1750)	1137 ± 75 (1100)	
Depot antipsychotic, n (%)	19 (4.7)	9[c] (18.4)	0.001
Prescription rate of anticholinergic, n (%)	232 (57.3)	43 (87.5)	<0.000
Anticholinergics mean dose ± SD (n)			
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
Benzatropine	3.8 ± 1.4 (30)	3.3 ± 1 (6)	0.525
Trihexyphenidyl	4.0 ± 1.7 (3)	10 ± 0 (1)	-

CPZeq = chlorpromazine equivalents; [a]only 2 patients (0.4%) were on three-antipsychotic combination; [b]mean CPZeq doses of antipsychotics > 1000 mg; [c]2 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; [a]mean dose of intramuscular LAI risperidone mg/fortnight; [b]an atypical antipsychotic structurally similar to amisulpride; [**]mean & 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 ± SD doses (median)	CPZeq mean ± SD doses (median)
Typical + typical:					
Chlorpromazine (2+) *plus*					
Haloperidol (4+)	2 (4.3)	2 (4.3)	100	12.5 ± 10.6 (12.5)	700 ± 565 (700)
Zuclopenthixol (3+)	1 (2.1)	1 (2.1)	100	60 ± 0 (60)	290 ± 0 (290)
Subtotal	3 (6.4)	3 (6.4)	100		563 ± 464 (300)
Atypical + atypical:					
Risperidone (2+) *plus*					
Olanzapine (1+)	4 (8.5)[a]	3 (6.4)	75.3	7.5 ± 3.5 (7.5)	275 ± 125 (300)
Sulpiride (1+)	4 (8.5)[b]	3 (6.4)	75.3	117 ± 76 (100)	225 ± 90 (250)
Subtotal	8 (17)	6 (12.8)	75.3		275 ± 100 (300)
Atypical + typical:					
Clozapine (0) *plus*					
Zuclopenthixol (3+)	1 (2.1)	1 (2.1)	100	10 ± 0 (10)	540 ± 0 (540)
Olanzapine (1+) *plus*					
Haloperidol (4+)	2 (4.3)	2 (4.3)	100	7.5 ± 3.5 (7.5)	575 ± 176 (575)
Trifluoperazine (3+)	2 (4.3)	2 (4.3)	100	7.5 ± 3.5 (7.5)	220 ± 113 (220)
Zuclopenthixol (3+)	2 (4.3)	2 (4.3)	100	30 ± 28.3 (30)	270 ± 183 (270)
Risperidone (2+) *plus*					
Chlorpromazine (2+)	7 (14.9)	6 (12.8)	85.9	93 ± 53 (100)	293 ± 93 (300)
Haloperidol (4+)	7 (14.9)[c]	6 (12.8)	85.9	13.3 ± 7.5 (15)	791 ± 406 (850)
Trifluoperazine (3+)	8 (17)[d]	7 (14.9)	87.6	7.4 ± 5.1 (5)	408 ± 198 (400)
Zuclopenthixol (3+)	6 (12.8)	6 (12.8)	100	23.3 ± 15 (20)	308 ± 110 (310)
Sulpiride (1+) *plus*					
Trifluoperazine (3+)	1 (2.1)	-	-	5 ± 0 (5)	125 ± 0 (125)
Subtotal	36 (76.7)	32 (68.3)	89		444 ± 285 (400)
Total	47 (100)	41 (87.5)			414 ± 278 (350)

(0), (1+), (2+), (3+) and (4+) represent antipsychotics with negligible, low, moderate, moderately severe, and severe extrapyramidal symptoms, respectively; CPZeq = chlorpromazine equivalents; [a]2 out of 4 patients received risperidone long-acting injection (LAI); [b]1 out of 4 patients received risperdone LAI; [c]1 out of 7 patients received risperidone LAI; [d]3 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 anti-cholinergic 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 $\geq$6 mg/day (*i.e.*, $\geq$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 significant 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 sociocultural 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 effecttive 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.

5. Acknowledgements

We acknowledge the help and assistance given to us by Mrs. Radha Raghavan in preparing and typing of this manuscript.

6. Conflict of Interest

There is no conflict of interest to declare. This work is not supported or funded by any drug company.

REFERENCES

[1] K. Sim, H. C. Su, S. Y. Fujii, M. Y. Chong, G. Ungvari, T. Si, Y. L. He, E. K. Chung, Y. H. Chan, N. Shinfuku, E. H. Kua, C. H. Tan and N. Sartorius, "High-Dose Antipsychotic Use in Schizophrenia: A Comparison between the 2001 and 2004. Research on East Asia Psychotropic Prescription (REAP) Studies," *British Journal of Clinical Pharmacology*, Vol. 67, No. 1, 2009, pp. 110-117. doi:10.1111/j.1365-2125.2008.03304.x

[2] W. J. Broekema, I. W. de Groot and P. N. van Harten, "Simultaneous Prescribing of Atypical Antipsychotics, Conventional Antipsychotics and Anticholinergics—A European Study," *Pharmacy World Sciences*, Vol. 29, No. 3, 2007, pp. 126-130. doi:10.1007/s11096-006-9063-1

[3] M. Y. Chang, C. H. Tan, S. Fujii, S. Y. Yang, G. S. Ungvari, T. Si, E. K. Chung, K. Sim, H. Y. Tsang and N. Shinfuku, "Antipsychotic Drug Prescription for Schizophrenia in East Asia: Rationale for Change," *Psychiatry and Clinical Neurosciences*, Vol. 58, No. 1, 2004, pp. 61-67. doi:10.1111/j.1440-1819.2004.01194.x

[4] I. Bitter, J. C. Chou, G. S. Ungvari, W. K. Tang, Z. Xiang, A. Iwanami and P. Gaszner, "Prescribing for Inpatients with Schizophrenia: An International Multi-Center Comparative Study," *Pharmacopsychiatry*, Vol. 36, No. 4, 2003, pp. 143-149. doi:10.1055/s-2003-41199

[5] A. Wheeler, "Atypical Antipsychotic Use for Adult Outpatients in New Zealand's Auckland and Northland Regions," *New Zealand Medical Journal*, Vol. 119, No. 1237, 2006, p. U2055.

[6] L. Koen, P. Magni, D. J. H. Niehaus and A. le Roux, "Antipsychotic Prescription Patterns in Xhosa Patients with Schizophrenia or Schizoaffective Disorders," *African Journal of Psychiatry*, Vol. 11, No. 4, 2008, pp. 287-290.

[7] S. Leucht, "Psychiatric Treatment Guidelines: Doctors' Non-Compliance or Insufficient Evidence?" *Acta Psychiatrica Scandinavica*, Vol. 115, No. 6, 2007, pp. 417-419. doi:10.1111/j.1600-0447.2007.01030.x

[8] W. Gaebel, S. Weinman, N. Sartorius, W. Kutz and J. S. McIntyre, "Schizophrenia Practice Guidelines: International Survey and Comparison," *British Journal of Psychiatry*, Vol. 189, 2005, pp. 248-255. doi:10.1192/bjp.187.3.248

[9] S. Mace and D. Taylor, "A Prescription Survey of Antipsychotic Use in England and Wales Following the Introduction of NICE Guidance," *International Journal of Psychiatry in Clinical Practice*, Vol. 9, No. 2, 2005, pp. 124-129. doi:10.1080/13651500510028995

[10] I. Cancelli, G. L. Gigli, A. Piani, B. Zanchettin, F. Janes, A. Rinaldi and M. Valante, "Drugs with Anticholinergic Properties as a Risk Factor for Cognitive Impairment in Elderly People: A Population-Based Study," *Journal of Clinical Psychopharmacology*, Vol. 28, No. 6, 2008, pp. 654-659. doi:10.1097/JCP.0b013e31818ce849

[11] I. Carriere, A. Fourrier-Reglat, J. F. Dartigues, O. Rouaud, F. Pasquier, K. Ritchie and M. L. Ancelin, "Drugs with Anticholinergic Properties, Cognitive Decline, and Dementia in an Elderly General Population: The 3-City Study," *Archives of Internal Medicine*, Vol. 169, No. 14, 2009, pp. 1317-1324. doi:10.1001/archinternmed.2009.229

[12] Y. T. Xiang, C. Y. Wang, T. M. Si, E. H. Lee, Y. L. He, G. S. Ungvari, H. F. Chiu, S. Y. Yang, M. Y. Chong, C. H. Tan, E. H. Kua, S. Fujii, K. Sim, K. H. Yong, J. K. Trivedi, E. K. Chung, P. Udomratn, K. Y. Chee, N. Sartorius and N. Shinfuku, "Use of Anticholinergic Drugs in Patients with Schizophrenia in Asia from 2001 to 2009," *Pharmacopsychiatry*, Vol. 44, No. 3, 2011, pp. 114-118. doi:10.1055/s-0031-1275658

[13] S. Leucht, W. Kissling and J. M. Davis, "Second-Generation Antipsychotics for Schizophrenia: Can We Resolve the Conflicts," *Psychological Medicine*, Vol. 39, No. 10, 2009, pp. 1591-1602. doi:10.1017/S0033291709005455

[14] G. Foussias and G. Remington, "Antipsychotics and Schizophrenia: From Efficacy and Effectiveness to Clinical Decision Making," *Canadian Journal of Psychiatry*, Vol. 55, No. 3, 2010, pp. 117-125.

[15] R. J. Baldessarini, "Drug Therapy of Depression and Anxiety Disorders," In: L. L. Brunton, J. S. Lazo and K. L. Parker, Eds., *The Pharmacological Basis of Therapeutics*, McGraw-Hill, New York, 2006, pp. 429-459.

[16] "British National Formulary (BNF) March 2010," BMJ Group and RPS Publishing, London, 2010.

[17] R. A. Endow-Eyer, M. M. Michell and J. P. Lacro, "Schizophrenia," In: M. A. Koda-Kimble, L. Y. Young, B. K. Aldredge, R. L. Corelli, B. J. Guglielmo, W. A. Kradjan and B. R. Williams, Eds., *Applied Therapeutics—The Clinical Use of Drugs*, Lippincott Williams and Wilkins, Philadelphia, 2009, pp. 78.1-78.34.

[18] A. F. Lehman and D. M. Steinwachs, "Translating Research into Practice: The Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations," *Schizophrenia Bulletin*, Vol. 24, No. 1, 1998, pp. 1-10. doi:10.1093/oxfordjournals.schbul.a033302

[19] N. A. Keks, K. Altson, J. Hope, N. Krapivensky, C. Culhane, A. Tanaghow, P. Doherty and A. Bootle, "Use of Antipsychotic and Adjunctive Medications by an Inner Urban Community Psychiatric Service," *The Australian and New Zealand Journal of Psychiatry*, Vol. 33, No. 6, 1999, pp. 896-901. doi:10.1046/j.1440-1614.1999.00639.x

[20] R. R. Aparasu, E. Jano and V. Bhatara, "Concomitant

Antipsychotic Prescription in US Outpatient Settings," *Research in Social and Administrative Pharmacy*, Vol. 5, No. 3, 2009, pp. 234-241. doi:10.1016/j.sapharm.2008.08.005

[21] A. Tapp, A. E. Wood, L. Secrest, J. Erdmann, L. Cubberley and N. Kilzieh, "Combination Antipsychotic Therapy in Clinical Practice," *Psychiatric Services*, Vol. 54, No. 4, 2003, pp. 55-59. doi:10.1176/appi.ps.54.4.574-a

[22] N. Ranceva, W. Ashraf and D. Odelola, "Antipsychotic Polypharmacy in Outpatients at Birch Hill Hospital: Incidence and Adherence to Guidelines," *Journal of Clinical Pharmacology*, Vol. 50, No. 6, 2010, pp. 699-704. doi:10.1177/0091270009350625

[23] R. J. Baldessarini, B. M. Cohen and M. H. Teicher, "Significance of Neuroleptic Dose and Plasma Level in Pharmacological Treatment of Psychoses," *Archives of General Psychiatry*, Vol. 45, No. 1, 1988, pp. 79-90. doi:10.1001/archpsyc.1988.01800250095013

[24] A. Essali, N. Al-Haj Hassan, C. Li and J. Rathbone, "Clozapine versus Typical Neuroleptic Medication for Schizophrenia," *Cochrane Database System Review*, Vol. 21, No. 1, 2009, CD 000059.

[25] Y. L. Tang, P. X. Mao, F. Jiang, Q. Chen, C. Y. Wang, Z. J. Cai and P. B. Michell, "Clozapine in China," *Pharmacopsychiatry*, Vol. 41, No. 1, 2008, pp. 1-9. doi:10.1055/s-2007-993224

[26] A. Wheeler, V. Humberstone, E. Robinson, J. Sheridan and P. Joyce, "Impact of Audit and Feed-Back on Antipsychotic Prescription in Schizophrenia," *Journal of Evaluation in Clinical Practice*, Vol. 15, No. 3, 2009, pp. 441-450. doi:10.1111/j.1365-2753.2008.01032.x

[27] S. Miyamoto, G. E. Duncan, C. E. Marx and J. A. Lieberman, "Treatments for Schizophrenia: A Critical Review of Pharmacology and Mechanisms of Action of Antipsychotic Drugs," *Molecular Psychiatry*, Vol. 10, No. 1, 2005, pp. 79-104. doi:10.1038/sj.mp.4001556

[28] S. M. Stahl, "Antipsychotic Polypharmacy. Part 1: Therapeutic Option or Dirty Little Secret?" *Journal of Clinical Psychiatry*, Vol. 60, No. 7, 1999, pp. 425-426. doi:10.4088/JCP.v60n0701

[29] G. B. Hung and H. K. Cheung, "Predictors of High-Dose Antipsychotic Prescription in Psychiatric Patients in Hong Kong," *Hong Kong Medical Journal*, Vol. 14, No. 1, 2008, pp. 35-39.

[30] Y. T. Xiang, Y. Z. Weng, C. M. Leung, W. K. Tang and U. G. Sandor, "Exploring the Clinical and Social Determinants of Prescribing Anticholinergic Medication for Chinese Patients with Schizophrenia," *Human Psychopharmacology*, Vol. 22, No. 3, 2007, pp. 173-180. doi:10.1002/hup.830

[31] P. Gjerden, L. Slordal and J. G. Bramness, "The Use of Antipsychotic and Anticholinergic Antiparkinson Drugs in Norway after the Withdrawal of Orphenadrine," *British Journal of Clinical Pharmacology*, Vol. 68, No. 2, 2009, pp. 238-242. doi:10.1111/j.1365-2125.2009.03446.x

[32] I. S. Hong and J. R. Bishop, "Anticholinergic Use in Children and Adolescence after Initiation of Antipsychotic Therapy," *Annals of Pharmacotherapy*, Vol. 44, No. 7, 2010, pp. 1171-1180. doi:10.1345/aph.1M643

[33] American Psychiatric Association, "American Psychiatric Association Practice Guidelines for the Treatment of Psychiatric Disorders, Compendium 2006," American Psychiatric Publishing Inc., Arlington, 2006.

[34] A. J. Wheeler, "Treatment Pathway and Patterns of Clozapine Prescribing for Schizophrenia in New Zealand," *Annals of Pharmacotherapy*, Vol. 42, No. 6, 2008, pp. 852-860. doi:10.1345/aph.1K662

[35] P. Seeman, "Atypical Antipsychotics: Mechanism of Action," *Canadian Journal of Psychiatry*, Vol. 47, No. 1, 2002, pp. 27-38.

[36] S. Leucht, G. Pitschell-Walz, D. Abraham and W. Kissling, "Efficacy and Extrapyramidal Side-Effects of the New Antipsychotic Olanzapine, Quetiapine, Risperidone, and Sertindole Compared to Conventional Antipsychotics and Placebo: A Meta-Analysis of Randomized Controlled Trials," *Schizophrenia Research*, Vol. 35, No. 1, 1999, pp. 51-68. doi:10.1016/S0920-9964(98)00105-4

[37] I. R. de Olivera, A. M. Mirand-Scippa, E. P. de Sena, E. L. Pereira, M. G. Ribeiro, E. de Castro-e-Silva and J. Bacaltchuk, "Risperidone versus Haloperidol in the Treatment of Schizophrenia: A Meta-Analysis Comparing Their Efficacy and Safety," *Journal of Clinical Pharmacology & Therapeutics*, Vol. 21, No. 5, 1996, pp. 349-358. doi:10.1111/j.1365-2710.1996.tb00030.x

[38] R. Tandon, R. H. Belmaker, W. F. Gattaz, J. J. Lopez-Iber Jr., A. Okasha, B. Singh, D. J. Stein, J. P. Olie, W. W. Fleischhacker and H. J. Moeller, "World Psychiatric Association Pharmacopsychiatry Section Statement on Comparative Effect of Antipsychotic in the Treatment of Schizophrenia," *Schizophrenia Research*, Vol. 100, No. 1-3, 2008, pp. 20-38. doi:10.1016/j.schres.2007.11.033

[39] M. O. Bakare, "Effective Therapeutic Dosage of Antipsychotic Medications in Patients with Psychotic Symptoms: Is There a Racial Difference?" *BMC Research Notes*, Vol. 1, No. 1, 2008, pp. 1-25.

[40] M. L. Chen, "Ethnic or Racial Differences Revisited: Impact of Dosage Regimen and Dosage form on Pharmacokinetics and Pharmacodynamics," *Clinical Pharmacokinetics*, Vol. 45, No. 10, 2006, pp. 957-964. doi:10.2165/00003088-200645100-00001

