Open Access Library Journal
2020, Volume 7, e6530
ISSN Online: 2333-9721
ISSN Print: 2333-9705

Comparative Study on the Use of Long-Acting Injectable Antipsychotics in Three Different Psychiatric Treatment Facilities in Saskatchewan, Canada

Olajide O. Adelugba[1,2*], Inam U. Haq[1], Mansfield Mela[1,2], Deqiang Gu[1], Olubankole Obikoya[3], Laura Garratt[1]

[1]Regional Psychiatric Center, Saskatoon, Saskatchewan, Canada
[2]Department of Psychiatry, University of Saskatchewan, Saskatoon, Canada
[3]Saskatchewan Hospital North Battleford, Saskatchewan, Canada
Email: *adelugbaoo@csc-scc.gc.ca

How to cite this paper: Adelugba, O.O., Haq, I.U., Mela, M., Gu, D.Q., Obikoya, O. and Garratt, L. (2020) Comparative Study on the Use of Long-Acting Injectable Antipsychotics in Three Different Psychiatric Treatment Facilities in Saskatchewan, Canada. *Open Access Library Journal*, **7**: e6530.
https://doi.org/10.4236/oalib.1106530

Received: June 16, 2020
Accepted: August 4, 2020
Published: August 7, 2020

Abstract

This study examined the prevalence of Long Acting Injectable (LAI) antipsychotics prescription and explored the nature and scope of such prescriptions in the context of polypharmacy in three major psychiatric treatment facilities in Saskatchewan, Canada. A cross-sectional study approach was used to collect data on LAI antipsychotics prescription details and de-identified demographics on all patients on admission on a specified date at the three study sites. Despite the availability of second generation LAI antipsychotics, first generation LAI antipsychotics accounted for 83.3% of the prescriptions (N = 96). Risperdal Consta was the only second generation LAI antipsychotic medication prescribed out of the six LAI antipsychotics in use. The most commonly prescribed LAI antipsychotic was zuclopenthixol decanoate (44.1%, N = 53). Most of the LAI antipsychotics were prescribed within the recommended dosages. Biweekly administration was the most common interval for the prescription of LAI antipsychotics (75%, N = 90). Polypharmacy was present amongst all patients including those on LAI antipsychotics. Co-prescription of antiparkinsonian medication was associated with the prescription of LAI antipsychotics. Patients with the diagnosis of Schizophrenia had more prescriptions for Zuclopenthixol decanoate (44.4%) and Risperidone Consta (24.4%) than those with the diagnoses of bipolar disorder (23.3% and 14.7%, respectively). A longitudinal approach to examining the LAI antipsychotic prescription practice would help to determine if concomitant prescription of LAI antipsychotics is associated with

decrease in oral antipsychotic load.

Subject Areas

Psychiatry, Mental Health

Keywords

Prescription, Long Acting Injectable, Polypharmacy, Dosage Intervals, Antipsychotics, Schizophrenia, Bipolar Disorder

1. Introduction

Growing awareness about mental illnesses among the general population had led to the development of strategies to reduce the suffering and impairment of functioning associated with mental illness. Psychopharmacology helps in the development of psychotropic medications which are used in the management of mental illnesses. Psychotropic medications are very useful in managing mental illnesses, usually administered orally and by intramuscular routes. Challenges related to poor adherence to medications coupled with the ingenuity of the medical profession and pharmaceutical industry led to the development of forms of psychotropic medications that only need to be administered at long intervals ranging from weeks to months. An offshoot of this is the utilization of long-acting injectable (LAI) antipsychotics to address some of the challenges of chronic psychotic disorders like schizophrenia and bipolar disorders. LAI antipsychotics are primarily used for the management of schizophrenia, a major mental disorder affecting approximately 1% of global population (Song *et al.*, 2017) [1]. Long acting antipsychotics have demonstrable efficacy in the management of patients with bipolar disorder (Bond, Pratoomsri, & Yatham, 2007 [2]; De Risio & P. Lang, 2014 [3]; Malempati, Bond, & Yatham, 2008 [4]).

Lifetime prevalence of these major psychotic disorders varies, a recent study indicated lifetime prevalence of 2.47% for all psychotic disorder, 1.25% for schizophrenia, 0.15% for delusional disorder, 0.38% for psychotic disorder not otherwise specified, 0.31% for bipolar disorder with psychosis and 0.33% for depressive disorder with psychosis (Chang *et al.*, 2017) [5]. Clinical psychiatry continues to establish that the use of antipsychotics is the mainstay of the management of psychotic disorders and their use continues to be popular among patients suffering from other psychiatric disorders (Nørgaard, Jensen-Dahm, Gasse, Hansen, & Waldemar, 2017 [6]; Weber, Wehr, & Duchemin, 2016 [7]). The use of antipsychotics in chronic psychotic disorders has been demonstrably associated with improved outcomes as they relate to risk of relapse, rehospitalisation and quality of life (Bossie, Alphs, & Correll, 2015 [8]; Suzuki, 2016 [9]).

There are numerous studies reflecting that the use of antipsychotics in various forms at different healthcare settings is widespread in Canada (Doey, Handel-

man, Seabrook, & Steele, 2007 [10]; Larose, Landry, & Collerette, 1999 [11]; Martin, Arora, Fischler, & Tremblay, 2017 [12]; Warnock, Ferguson, & Lam, 2014 [13]). Numerous studies highlighted different aspects and issues related to antipsychotic drug prescriptions namely, associated side effects compliance, polypharmacy, co-prescription, refusal, prevalence, appropriateness and judiciousness of their use (Heald, Livingston, Yung, & De Hert, 2017 [14]; Herr *et al.*, 2017 [15]; Warnock *et al.*, 2014 [13]).

The development and subsequent use of LAI antipsychotics emerged as a result of problems related to the use of oral forms of antipsychotics, principally, poor adherence to treatment. LAI antipsychotics were also considered as good options for patients who have swallowing difficulty, problems remembering to take medication regularly and those who prefer not having to take oral medications daily. Comparatively, oral antipsychotics are more frequently prescribed than long-acting preparations due to various reasons like tolerability and physicians related factors (Hamann, Kissling, & Heres, 2014) [16].

The use of LAI antipsychotics in clinical psychiatry continues due to their efficacy and the presence of patient-related characteristics. Many factors including but not limited to medical history, level of insight, risks to patients and the personal preferences of both patient and clinician are very relevant in deciding on the use of LAI antipsychotics (Wu, Baillargeon, Grady, Black, & Dunn, 2001) [17].

In an overview of available evidence justifying the comparative benefits of second-generation antipsychotics and LAI antipsychotics, long-acting agents are unequivocally superior to oral antipsychotics and that their use should be considered in all patients for whom long-term use is indicated (Fazel & Danesh, 2002) [18]. Research studies and reviews highlighted that second-generation antipsychotics do not improve medication adherence, however the concerns related to loss of autonomy by patients and lack of acceptance for long-acting antipsychotics are not well studied (Fazel & Danesh, 2002) [18]. Compliance with medications has been shown to improve with long term administration of long-acting antipsychotic injections (Baweja, Sedky, & Lippmann, 2012) [19]. Other possible benefits associated with the use of long-acting antipsychotic preparations include reduction in violence (Arango, Bombin, Gonzalez-Salvador, Garcia-Cabeza, & Bobes, 2006 [20]; Buckley, Noffsinger, Smith, Hrouda, & Knoll, 2003 [21]; Priebe *et al.*, 2009 [22]).

The older generation of LAI antipsychotics namely haloperidol decanoate, fluphenazine decanoate, fluspirilene, pipotiazine palmitate, zuclopenthixol decanoate and flupentixol decanoate have earned their place amongst antipsychotics in terms of clinical efficacy. Additionally, the new second generation LAI antipsychotics like Risperidone consta and Paliperidone palmitate, have become increasingly popular as very efficacious antipsychotics (Arnold, Giebe, Winnefeld, & Klein, 2002 [23]; Barnes, Shingleton-Smith, & Paton, 2009 [24]; Bobo & Shelton, 2010 [25]; Lasser, Bossie, Gharabawi, & Turner, 2004 [26]).

Studies have found LAI antipsychotic medication adherence rates ranged 24% - 90% for all antipsychotics (Cramer & Rosenheck, 1998 [27]; Graffino, Montemagni, Mingrone, & Rocca, 2014 [28]) and ranged 0% - 54% for LAI antipsychotics (Young, Spitz, Hillbrand, & Daneri, 1999) [29]. Overall, there is some consensus that LAI antipsychotics improve compliance, thus reducing hospitalization and relapse rates (Achilla & McCrone, 2013 [30]; Graffino *et al.*, 2014 [28]). Essentially, there are myriads of reasons as to why patients are prescribed long-acting antipsychotic injections and perhaps equally so, there are many reasons why patients' adherence to them remain very variable. In spite of their numerous advantages in terms of compliance with antipsychotics and consequent clinical improvements, the rate of prescriptions for LAI antipsychotics does not reflect the level of non-adherence to antipsychotics as there are many factors affecting prescription for long-acting antipsychotics.

Many studies have shown the rates of use of long-acting antipsychotics in various psychiatric populations nonetheless this study was intended to provide insight into the prevalence and use of LAI antipsychotics in three major psychiatric treatment facilities in Saskatchewan, Canada.

2. Setting and Methods

This one day cross-sectional study was conducted at three psychiatric treatment settings in Saskatchewan, Canada viz., Regional Psychiatric Centre (RPC-Forensic psychiatry), Dube Centre (DC-General psychiatry) and Saskatchewan Hospital North Battleford (SH-Forensic and general psychiatry). The RPC, located in Saskatoon, Saskatchewan, Canada, is a multi-level secure psychiatric hospital established with a capacity of 206 beds consisting of 194 for men and 12 for women (RPC, 2009) [31]. The RPC which is owned and operated by the Correctional Service of Canada serves the three Prairie Provinces although often admits patients that are federal prisoners from other regions in Canada. The RPC established in 1978 is an accredited psychiatric hospital operated in accordance with the provisions of the memorandum of agreements between the Government of Canada, the University of Saskatchewan and the Province of Saskatchewan. The RPC provides acute psychiatric care and rehabilitation programs for federally sentenced offenders. In addition, it admits Saskatchewan provincial inmates in need of psychiatric services in a maximum-security environment, individuals admitted for pre-trial psychiatric assessment and those found to be not criminally responsible on account of mental disorders. The RPC qualifies as a high-level secure hospital according to Thomson's criteria, and these imply that "these hospitals have a secure perimeter fence with powerful lighting, cameras and motion detectors. Security procedures vary in each institution but most have airport-style security measures such as X-ray screening and metal detectors. Personal alarms, air-lock entries to wards and security policies, for example on random searches, are routine" (Thomson, 2000) [32]. The DC is located on bank of South Saskatchewan River, near Royal University Hospital in Saskatoon, Saskatchewan. The DC has 54 beds for adults

plus 10 beds in a separate section for children and youth, including a dedicated adolescent unit. The DC provides an ideal environment for mental health patients and their families to receive care, including extended visiting hours and enhanced programming on evenings and weekends. The SH is a large pavilion-style mental institution located in North Battleford, Saskatchewan. The SH's total bed capacity is 178 beds, 25 of which are for forensic patients. It is the only psychiatric rehabilitation facility for the province of Saskatchewan in Canada.

Data were collected from all the three sites on the same day using same data collection format. Data on clinical diagnoses and medication prescriptions for all the inpatients on that particular day were collected from the patient files. Data on the clinical variables and co-prescriptions were also collected. There was no direct contact with the patients in this study. Ethical approvals were obtained from the relevant authorities. All the patients in different treatment settings were grouped into four age groups (<25 years, 26 - 45 years, 46 - 65 years and >66 years) using quartile function in the IBM SPSS (SPSS, 2011) [33]. The patients were also grouped into gender (men and women). Those patients on LAI antipsychotic prescriptions were further analyzed to determine additional details of prescriptions. Patients with the diagnosis of schizophrenia and with prescription for LAI antipsychotics were matched for age with patients having same diagnosis but without prescription for LAI antipsychotics to study the similarities and differences between the two groups.

3. Results

3.1. Demographics

There were 381 patients consisting of 292 (76.6%) men and 89 (23.4%) women on admission at the three sites at the time of study. Only 33 (8.7%) were more than 66 years old, those between the ages of 26 and 65 constituted 76.6% (292) and those less than 25 years were 56 (14.7%).

3.2. Prescriptions

Out of the 381 patients on admission, 120 (31.4%) were on LAI antipsychotics and of the 176 patients with the diagnosis of schizophrenia, 84 (47.7%) were prescribed LAI antipsychotics. The prevalence of prescriptions for LAI antipsychotics in all the study sites ranged from 13.3 to 62.6 percent, Saskatchewan hospital being the highest compared to the other two sites (**Table 1**). Although there were more men patients than women yet the prescriptions for LAI antipsychotics were 42.7% and 28.1% amongst women and men (**Table 1**). There was an increase in the prescriptions for LAI antipsychotics with the age (**Table 1**). The study revealed that the there was a direct linear relationship between the mean age and percentage of patients on long-acting antipsychotics injections (R^2 = 0.69, **Figure 1**).

Overall, 120 patients (31.5%) were prescribed LAI antipsychotics and the proportions of patients varied widely between the study sites with SH having the highest proportion compared to DC and RPC (**Table 2**).

3.3. Diagnoses

There were 176 (68.7%) patients with the diagnosis for schizophrenia (Table 2). Among patients with schizophrenia, comparatively more were on LAI antipsychotics at SH followed by DC and RPC (Table 2). Only 5.2% (n = 20) of the patients in this study had diagnosis of bipolar disorder, highest being at RPC followed by DC and SH (Table 2). The proportion of patients with the diagnosis of bipolar disorder and having prescriptions for LAI antipsychotics were more at SH followed by RPC and DC (Table 2).

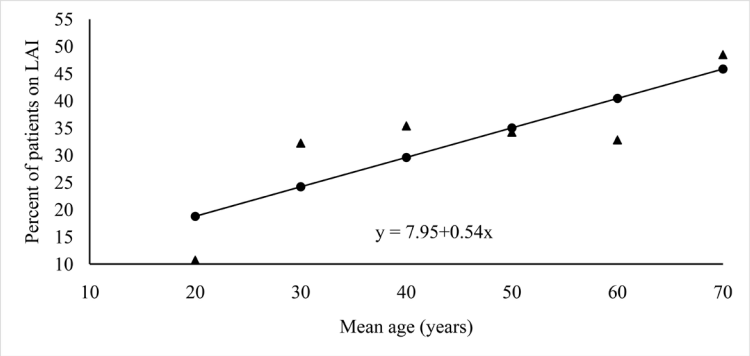

Figure 1. Relationship between mean age and percent of patients on Long Acting Injections.

Table 1. Demographic profile of patients on antipsychotics administered as LAI and through other routes at three different psychiatric treatment facilities.

Particulars		Route	Psychiatric treatment centres						Overall	
			RPC[a]		Dube[b]		Sask Hospital[c]			
			N	%	N	%	N	%	N	%
Gender	Female	LAI	1	9.0	5	15.6	32	69.6	38	42.7
		Other	10	91.0	27	84.4	14	38.4	51	57.3
	Male	LAI	23	13.5	4	13.8	55	59.1	82	28.1
		Other	147	86.5	25	86.2	38	40.9	210	71.9
Age groups (Years)	<25	LAI	2	7.7	0	0.0	4	40.0	6	10.7
		Other	24	92.3	20	100.0	6	60.0	50	89.3
	26 - 45	LAI	16	17.4	4	22.2	32	71.1	52	33.5
		Other	76	82.6	14	77.8	13	28.9	103	66.5
	46 - 65	LAI	6	10.3	4	23.5	36	58.1	46	33.6
		Other	52	89.7	13	76.5	26	41.9	91	66.4
	>66	LAI	0	0.0	1	16.7	15	68.2	16	48.5
		Other	5	100.0	5	83.3	7	31.8	17	51.5
	Total	LAI	24	13.3	9	14.8	87	62.6	120	31.5
		Other	157	86.7	52	85.2	52	37.4	261	68.5
Grand total			181		61		139		381	

[a]Regional Psychiatric Center (RPC), Saskatoon. [b]Inpatient facility at the University of Saskatchewan, Saskatoon (Dube). [c]Saskatchewan Hospital, North Battleford (Sask Hospital).

Table 2. Diagnoses of the patients on LAI antipsychotics at three different psychiatric treatment facilities.

Particulars		Psychiatric treatment centres						Overall	
		RPC[a]		Dube[b]		Sask Hospital[c]			
		N	%	N	%	N	%	N	%
Total		181	47.5	61	16.0	139	36.5	381	100
LAI		24	13.3	9	14.8	87	62.6	120	31.5
Schizophrenia	Total	70	39.8	20	11.4	86	48.9	176	100
	LAI	19	27.1	7	35.0	58	67.4	84	47.7
	Non-LAI	51	72.9	13	65.0	28	32.6	92	52.3
Bipolar disorder	Total	11	55.0	7	35.0	2	10.0	20	100
	LAI	4	36.4	1	14.3	2	100	7	35.0
	Non-LAI	7	63.6	6	85.7	0	00.0	13	65.0
Others*	Total	100	54.0	34	18.4	51	27.6	185	100
	LAI	1	01.0	1	02.9	27	52.9	29	15.7
	Non-LAI	99	99.0	33	97.1	24	47.1	156	84.3

*Depression, substance use, Borderline, Antisocial personality disorder. [a]Regional Psychiatric Center (RPC), Saskatoon. [b]Inpatient facility at the University of Saskatchewan, Saskatoon (Dube). [c]Saskatchewan Hospital, North Battleford (Sask Hospital).

The overall medication prescriptions per patient were 5.9, highest being at SH (7.1) followed by DC (5.3) and RPC (5.5). The prescription per patient for psychotropic medications were 2.3, 2.8 and 3.6, and for non-psychotropic medications were 3, 2.7 and 3.5 at RPC, DC and SH respectively.

3.4. Types of LAI Antipsychotics

Six different LAI antipsychotics, mostly first-generation antipsychotics namely; Zuclopenthixol decanoate, Flupentixol decanoate, Fluphenazine decanoate, Haloperidol decanoate, Pipotiazine palmitate and Risperidone consta were in use at the three study sites (**Figure 2**). The most frequently prescribed LAI antipsychotic was Zuclopenthixol decanoate constituting 44.1% (n = 53) of all prescriptions for LAI antipsychotics followed by Risperidone consta (20%, n = 24), Flupentixol decanoate (17.5%, n = 21), Fluphenazine decanoate (10%, n = 12), Haloperidol decanoate (5%, N = 6) and Pipotiazine palmitate (3.3%, N = 4). A comparison of the average dose prescribed and the Canadian Compendium of pharmaceuticals and specialties (CPS, 2018) [34] recommended maximum dose for the six different long acting antipsychotics used at the three study sites is presented in **Table 3**. The results revealed that all the LAI antipsychotic prescriptions were either equal to or lower than the maximum recommended doses except for one patient to whom Flupentixol decanoate was prescribed in excess of the recommended dose per week (**Table 3**).

The average doses for patients receiving LAI antipsychotics once in two weeks were, flupentixol decanoate 44.7 mg, fluphenazine decanoate 33 mg, haloperidol

decanoate 59.2 mg, pipotiazine palmitate 25.5 mg, Risperidone Consta 18.3 mg and zuclopenthixol decanoate 126.5 mg (Table 3).

Table 3. Prescription and dosage of LAI antipsychotics at three different psychiatric treatment centers.

Medications	Observed frequency of administration	Patients (N)	Number of Patients on LAI antipsychotics at study sites			Average Dose (mg)	Minimum Dose (mg)	Maximum Dose (mg)	Average prescribed doze per study site (mg/week)			Overall Average prescribed dose (mg/week)	Maximum recommended doze (mg/week) (CPS, 2018) [34]
			RPC	DC	SH				RPC	DC	SH		
Flupentixol decanoate	10 Days	1	1	0	0	100.00	100.00	100.00	70	-	19.35	44.7 ± 35.8	40
	1 month	1	0	0	1	20.00	20.00	20.00					
	2 weeks	13	0	0	13	43.08	20.00	100.00					
	3 weeks	2	0	0	2	60.00	60.00	60.00					
	4 weeks	4	0	0	4	43.75	20.00	75.00					
	Total	21	1	0	20								
Fluphenazine decanoate	2 weeks	7	2	1	4	77.14	25.00	175.00	30.47	50	18.62	33.0 ± 15.8	50
	3 weeks	2	0	0	2	62.50	25.00	100.00					
	4 weeks	3	2	0	1	17.00	1.00	25.00					
	Total	12	4	1	7								
Haloperidol decanoate	2 weeks	4	1	1	2	162.50	100.00	250.00	41.6	50	86.1	59.2 ± 23.6	100
	3 weeks	2	1	0	1	100.00	100.00	100.00					
	Total	6	2	1	3	141.67	100.00	250.00					
Pipotiazine palmitate	2 weeks	2	0	0	2	62.50	50.00	75.00	-	19.7	31.25	25.5 ± 8.2	83.3
	3 weeks	1	0	1	0	100.00	100.00	100.00					
	4 weeks	1	0	1	0	25.00	25.00	25.00					
	Total	4	2	0	2								
Risperidone consta	1 month	1	0	0	1	37.50	37.50	37.50	15.62	21.8	17.6	18.3 ± 3.2	25
	2 weeks	22	6	2	14	35.89	12.50	50.00					
	3 weeks	1	0	0	1	37.50	37.50	37.50					
	Total	24	6	2	16								
Zuclopenthixol decanoate	10 Days	1	0	1	0	350.00	350.00	350.00	97.7	165	116.9	126.5 ± 34.7	600
	1 month	1	0	0	1	200.00	200.00	200.00					
	1 weeks	1	1	0	0	100.00	100.00	100.00					
	2 weeks	42	10	2	30	245.83	75.00	400.00					
	3 weeks	4	0	0	4	187.50	150.00	200.00					
	4 weeks	4	0	0	4	325.00	200.00	400.00					
	Total	53	11	3	39								
Grand Total		120	24	9	87								

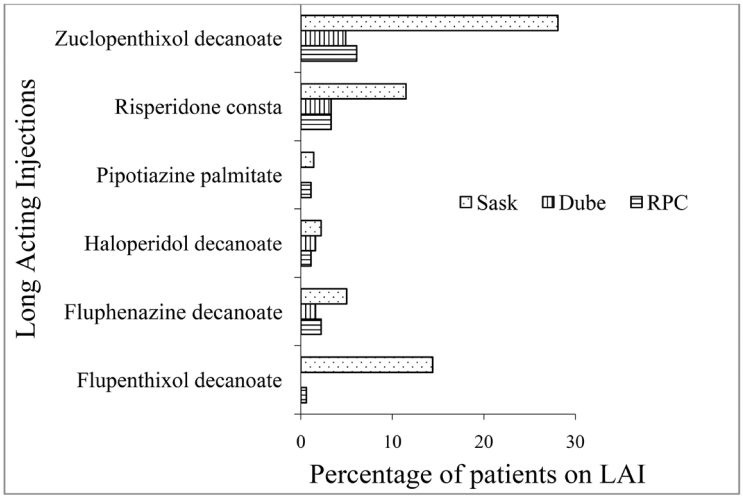

Figure 2. Use of long-acting antipsychotic injections at three different psychiatric treatment facilities (Percentage of patients on LAI antipsychotics).

3.5. Dosage Schedules

Overall, the dosage interval for all the LAI antipsychotics injections ranged from once a week to once in four weeks at all the study sites. The most common Interval of administration was once in two weeks (N = 90, 75%), other intervals of administrations were once a week (N = 1, 0.8%), once in 10 days (N = 2, 1.6%), thrice a week (N = 12, 10%) and every 4 weeks (N = 15, 12.5%). Noteworthy was the fact that 10 (83.3%) out of the recorded 3-weekly injection was in the SH. The proportion of each of the LAI antipsychotic injections given at 2 weeks intervals were Zuclopenthixol decanoate 79.2% (N = 42), Risperidone consta 91.6% (N = 22), Pipotiazine palmitate 50% (N = 2), haloperidol decanoate 66.7% (N = 4), Fluphenazine decanoate 58.3% (N = 7) and Flupentixol decanoate 69% (N = 13).

3.6. Polypharmacy

Co-prescriptions with other psychotropic medications were observed amongst patients on LAI antipsychotics. The 55.8% patients (N = 67) on LAI antipsychotic had prescriptions for antiparkinsonian medications ostensibly to control the extrapyramidal side effects of antipsychotics. A lower percentage (22.2%, N = 13) of co-prescription of antiparkinsonian agents was reported at DC, while comparatively higher percentages of 54.2% (N = 98) and 56.6% (N = 79) were reported for RPC and SH respectively. In terms of each LAI antipsychotic, Risperidone was associated with highest number of co-prescriptions with antiparkinsonian agent (45.8%, N = 11). Pipotiazine was associated with the least proportion of patients who had concomitant prescriptions for antiparkinsonian agents.

However, co-prescription with additional oral antipsychotics was observed in 107 (89.17%) patients. Out of the patients on additional antipsychotics 58 (48.3%) had additional prescriptions for one antipsychotic agent and 37 (30.8%)

and 12 (10%) had concomitant prescriptions for two and three oral antipsychotics respectively.

In terms of co-prescriptions with antidepressants, most patients on LAI antipsychotic (N = 86, 71.7%) did not have prescriptions for antidepressant medications. However, 29 (24.2%) and 5 (4.2%) had concomitant prescriptions for one and two antidepressant medications respectively. In the same vein, majority of the patients on LAI antipsychotics (N = 68, 56.7%) did not have prescriptions for mood stabilizers. Among those who had prescriptions for mood stabilizers, 42 (35%) had prescription for one, 9 (7.5%) for two and 1 (0.8%) for three additional mood stabilizers.

3.7. Comparison amongst Patients with Schizophrenia

Seventy-eight (78) patients with the diagnosis of schizophrenia who had prescriptions for LAI antipsychotics were matched for age and diagnoses with 78 patients without prescriptions for LAI antipsychotics but were on oral antipsychotics. The majority of patients in the LAI antipsychotics group (N = 42, 53.8%) also had prescriptions for antiparkinsonian medications whereas only 21.8% (N = 17) of the patients on only oral antipsychotics had prescriptions for antiparkinsonian agents. This trend was observed at each of the three study sites. Mood stabilizers were prescribed to 33.3% (N = 26) of the patients in the LAI antipsychotics group compared to 28.2% (N = 22) of patients in the non-LAI antipsychotics group. Of those without LAI antipsychotic prescriptions, 30.8% (n = 24) had prescriptions for antidepressants whereas in those who had prescription for LAI antipsychotics 26.9% (n = 21) had prescription for antidepressants.

The statistical analysis revealed that Flupentixol decanoate with two-weekly prescription interval at SH had a mean value (mg) of 43.1 ± 24.96 (N = 13) and those with four-weekly prescription interval had a mean value 43.8 ± 22.86 (N = 4). The two-weekly prescription interval for Fluphenazine decanoate at SH had a mean value of 41.3 ± 11.81 (N = 4). Risperidone Consta with two-weekly prescription interval at RPC had a mean value of 31.3 ± 10.45 (N = 6) but the mean value at SH was 37.5 ± 12.01 (N = 14), the difference was not statistically significant (P = 0.284). The two-weekly prescription interval for Zuclopenthixol decanoate at SH was significantly (P = 0.038) higher with a mean value of 262.5 ± 82.72 (N = 30) compared to RPC having a mean value of 195.0 ± 95.59 (N = 10).

4. Discussion

The prevalence for the use of LAI antipsychotics among psychiatric inpatients as demonstrated in this study was in line with that reported in another study (Rossi, Frediani, Rossi, & Rossi, 2012) [35]. The relatively high prevalence rate of 47.7% reported in this study for the use of LAI antipsychotics amongst patients suffering from schizophrenia falls within the range (4.8% to 66%) reported in another study (Rossi *et al.*, 2012) [35]. However, the rate reported in this study was comparatively higher and this was likely due to the combination of acute,

sub-acute and chronic care patients at two of the three study sites namely RPC and the SH which constituted 84% (N = 320) of the study population and 92.5% (N = 111) of the patients on LAI antipsychotics. The point prevalence of LAI antipsychotics used in this study mirrored the kind of patients admitted to these facilities. The SH has a lower turnaround of patients and more long-stay patients whereas the other two facilities have a lot of acute and sub-acute patients. Some predictors of LAI antipsychotic use like an earlier age of onset, a more significant history of suicide attempts, a history of violent behaviour and a family history of schizophrenia were recorded in another study (Albayrak, Unsal, & Beyazyuz, 2013) [36].

One of the interesting findings of this study was that prescriptions for LAI antipsychotics increased with age. Another study has also reported significant association between the use of Risperidone LAI and younger age group (Soleman, Lam, & Woo, 2017) [37]. Since this was a cross-sectional study involving only three centers with limited amount of data, the relationship between prescription for LAI antipsychotics and age needs to be studied further. Studies have also demonstrated association between prescription for LAI antipsychotics and co-prescription with anticholinergics (Rossi *et al.*, 2012 [35]; Sim *et al.*, 2004 [38]). In this study further analysis of patients suffering from schizophrenia on LAI antipsychotics and those without LAI antipsychotics matched for age did not show association with co-prescription for anticholinergic medications.

Polypharmacy of various types like antipsychotic drug polypharmacy and psychotropic drug polypharmacy as described in this study had indeed been demonstrated in other studies (Acquaviva, Gasquet, & Falissard, 2005 [39]; Tan *et al.*, 2008 [40]).

Evidence from Random Control Trials continues to buttress the lack of convincing relative advantage of new generation LAI antipsychotics over their oral preparations (Manchanda *et al.*, 2013) [41]. As with similar studies (Liu *et al.*, 2015 [42]; Samalin, de Chazeron, Vieta, Bellivier, & Llorca, 2016 [43]) this study indicated that first generation LAI antipsychotics were more frequently prescribed than the second-generation LAI antipsychotics. This probably reflects the comparative availability of first-generation LAI antipsychotics and their tested popularity with psychiatrists and patients. It remains to be studied if cost plays any role in the pattern of use of long-acting antipsychotic preparations. In this study Risperidone Consta was the only second-generation LAI antipsychotic prescribed and it could likely be due to the fact that it was the first atypical antipsychotic available as a LAI antipsychotic formulation and relatively more popular among patients and prescribers. Zuclopenthixol decanoate, a first generation LAI antipsychotic, was the most frequently prescribed in this study as was the case in some other studies where second-generation LAI were more commonly prescribed (Liu *et al.*, 2015 [42]; Samalin *et al.*, 2016 [43]). However, a study conducted by Lammers (Lammers, Zehm, & Williams, 2013) [44] reported flupentixol decanoate as the most frequently prescribed. A lot of factors

could have accounted for the difference and preference in the type of LAI antipsychotics prescribed and some of these may be related to prescribers, availability of LAI antipsychotics, patients' preference and cost. However, another study conducted in Europe had demonstrated that Paliperidone, a second generation LAI antipsychotic was the most commonly prescribed long-acting antipsychotic (Llorca *et al.*, 2018) [45], it may be due to the fact that this is a more recent study and prescribing second generation LAI antipsychotics is now more popular than before.This study with a 31.5% prevalence rate of LAI antipsychotics use at all the study sites, a sizable proportion of which was in forensic settings reflects what had been found in other studies with a range of 20% - 30%.

The average dose for Risperdal Consta in this study was similar to those found in the study conducted by Lambers in British Columbia on patients suffering from Schizophrenia (Lammers *et al.*, 2013) [44]. However, the average doses for zuclopenthixol decanoate and fluphenazine decanoate were higher in this study than what was reported by Lammers (Lammers *et al.*, 2013) [44]. Methodology and patient profile might have accounted for the observed differences.

Studies had shown a wide range of the prevalence of LAI antipsychotics prescription for patients suffering from schizophrenia and other psychotic disorders (Bossie *et al.*, 2015 [8]; Suzuki, 2016 [9]). This study indicated that prescribing LAI antipsychotics does not necessarily mean that the patients would be prescribed fewer oral antipsychotics as demonstrated in the study conducted by Armstrong (Armstrong & Temmingh, 2017) [46]. This study and other studies showed that patients on LAI antipsychotics were frequently prescribed additional psychotropic medications namely, antidepressants, mood stabilizers and antiparkinsonian agents. Another study also confirmed a relatively higher prevalence rate for multiple psychotropics especially antipsychotics for patients with schizophrenia, including co-prescription of first generation and second generation antipsychotics (Doshi, Pettit, Stoddard, Zummo, & Marcus, 2015) [47].

Some previous studies have demonstrated an association between prescription for LAI antipsychotics, oral antipsychotics and co-prescription with anticholinergic medications (Sim *et al.*, 2004) [38]. In this study, further analysis of patients diagnosed with schizophrenia and prescribed LAI antipsychotics and those without LAI antipsychotics, matched for age, did not show association with co-prescription for anticholinergics. However, this study as well as the study conducted by Lammers (Lammers *et al.*, 2013) [44] showed a concomitant prescription of antiparkinsonian agent for schizophrenic patients prescribed LAI antipsychotics compared to those not prescribed LAI antipsychotics. The reality of co-prescription of antipsychotics and anticholinergics, desirable as it may be, must be evaluated against the impact of such prescriptions on cognitive functions (Rehse *et al.*, 2016) [48] because these two classes of psychotropic medications have adverse side effects which may compound the debilitating consequences of severe and enduring mental illness for which they are primarily pre-

scribed.

Polypharmacy was observed in this study and has been demonstrated by other studies (Heald *et al.*, 2017 [14]; Yang *et al.*, 2018 [49]; Yoshio, 2012 [50]). Evidence from available literature from Random Control Trials continues to buttress the lack of convincing relative advantage of new generation LAI antipsychotics over their oral preparations (Yoshio, 2012) [50]. Continued high dose antipsychotic therapy as indicated by multiple prescriptions for antipsychotics is hardly supported by empirical evidence and in fact, available evidence suggests the opposite (Suzuki, 2016 [9]; Yamanouchi *et al.*, 2014 [51]).

Given that most prescriptions for LAI antipsychotics were below the recommended maximum doses and all the patients were on additional oral antipsychotics, further studies are necessary to fully determine the clinical impact of prescribing maximum doses of long-acting alone as opposed to the concomitant use of oral antipsychotic agents and submaximal doses of LAI antipsychotics.

Based on the pharmacokinetics of the LAI antipsychotics, their recommended dosage intervals range from 1 to 4 weeks in this study as it was so reported in another study (Spanarello & La Ferla, 2014) [52]. The dosage interval though in keeping with established recommendations needs to be assessed in relation to patients' preferences and desires even if only to improve adherence to treatment. Direct clinical patient care experience seems to suggest that most patients prefer longer intervals of administration of LAI antipsychotics.

5. Conclusion

It can be concluded from this study that the use of LAI antipsychotics was common among psychiatric inpatients and most of such prescriptions were accounted for by first generation LAI antipsychotics. All prescriptions except one were below recommended maximum dose. There were both intra-class and inter-class polypharmacy amongst psychiatric patients on admission. Co-prescription of oral antipsychotics and LAI antipsychotics was common practice. It was not possible to determine the stability and duration of the prescriptions for LAI antipsychotics and their benefits over time because of the cross-sectional nature of this study. Further follow-up studies would be needed to get additional clinical information regarding the use of LAI antipsychotics. It remains to be seen if there are advantages that accrue to patients in terms of reduction in overall quantity of oral antipsychotic prescriptions which are attributable to their prescriptions for LAI antipsychotics.

Acknowledgements

The authors are grateful to the Correctional service of Canada, the Regional Psychiatric Center, Saskatoon, the Dube Center at the University of Saskatchewan and the Saskatchewan Hospital, North Battleford. The grant provided by Alfred E. Molstad is very much appreciated and so is the secretarial support provided by our able administrative assistant, Fay Nochowny, at the RPC.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Song, W.S., Cha, J.H., Yoon, S.H., Cho, Y.S., Park, K.Y. and Kim, M.H. (2017) The Atypical Antipsychotic Olanzapine Disturbs Depotentiation by Modulating mAChRs and Impairs Reversal Learning. *Neuropharmacology*, **114**, 1-11. https://doi.org/10.1016/j.neuropharm.2016.11.012

[2] Bond, D., Pratoomsri, W. and Yatham, L. (2007) Depot Antipsychotic Medications in Bipolar Disorder: A Review of the Literature. *Acta Psychiatrica Scandinavica*, **116**, 3-16. https://doi.org/10.1111/j.1600-0447.2007.01054.x

[3] De Risio, A. and P Lang, A. (2014) History and Therapeutic Rationale of Long Acting Antipsychotics. *Current Clinical Pharmacology*, **9**, 39-52. https://doi.org/10.2174/15748847113089990057

[4] Malempati, R.N., Bond, D.J. and Yatham, L.N. (2008) Depot Risperidone in the Outpatient Management of Bipolar Disorder: A 2-Year Study of 10 Patients. *International Clinical Psychopharmacology*, **23**, 88-94. https://doi.org/10.1097/YIC.0b013e3282f2b4c5

[5] Chang, W.C., Wong, C.S.M., Chen, E.Y.H., Lam, L.C.W., Chan, W.C., Ng, R.M.K., Bebbington, P., *et al.* (2017) Lifetime Prevalence and Correlates of Schizophrenia-Spectrum, Affective, and Other Non-Affective Psychotic Disorders in the Chinese Adult Population. *Schizophrenia Bulletin*, **43**, 1280-1290. https://doi.org/10.1093/schbul/sbx056

[6] Nørgaard, A., Jensen-Dahm, C., Gasse, C., Hansen, E.S. and Waldemar, G. (2017) Psychotropic Polypharmacy in Patients with Dementia: Prevalence and Predictors. *Journal of Alzheimer's Disease*, **56**, 707-716. https://doi.org/10.3233/JAD-160828

[7] Weber, S.R., Wehr, A.M. and Duchemin, A.M. (2016) Prevalence of Antipsychotic Prescriptions among Patients with Anxiety Disorders Treated in Inpatient and Outpatient Psychiatric Settings. *Journal of Affective Disorders*, **191**, 292-299. https://doi.org/10.1016/j.jad.2015.11.031

[8] Bossie, C.A., Alphs, L.D. and Correll, C.U. (2015) Long-Acting Injectable versus Daily Oral Antipsychotic Treatment Trials in Schizophrenia: Pragmatic versus Explanatory Study Designs. *International Clinical Psychopharmacology*, **30**, 272-281. https://doi.org/10.1097/YIC.0000000000000082

[9] Suzuki, T. (2016) A Further Consideration on Long-Acting Injectable versus Oral Antipsychotics in the Treatment of Schizophrenia: A Narrative Review and Critical Appraisal. *Expert Opinion on Drug Delivery*, **13**, 253-264. https://doi.org/10.1517/17425247.2016.1115479

[10] Doey, T., Handelman, K., Seabrook, J.A. and Steele, M. (2007) Survey of Atypical Antipsychotic Prescribing by Canadian Child Psychiatrists and Developmental Pediatricians for Patients aged under 18 Years. *The Canadian Journal of Psychiatry*, **52**, 363-368. https://doi.org/10.1177/070674370705200605

[11] Larose, D.S., Landry, C. and Collerette, C. (1999) Overuse of Psychotropic Drugs in Seniors. *Canadian Nurse*, **95**, 45-50.

[12] Martin, K., Arora, V., Fischler, I. and Tremblay, R. (2017) Descriptive Analysis of Pro Re Nata Medication Use at a Canadian Psychiatric Hospital. *International Journal of Mental Health Nursing*, **26**, 402-408. https://doi.org/10.1111/inm.12265

[13] Warnock, C.A., Ferguson, I.D. and Lam, J. (2014) Psychotropic Drug Prescribing Survey in a Canadian Rehabilitation and Complex Care Facility. *Consultant Pharmacist*, **29**, 387-399. https://doi.org/10.4140/TCP.n.2014.387

[14] Heald, A., Livingston, M., Yung, A. and De Hert, M.A. (2017) Prescribing in Schizophrenia and Psychosis: Increasing Polypharmacy over Time. *Human Psychopharmacology Clinical and Experimental*, **32**, e2579. https://doi.org/10.1002/hup.2579

[15] Herr, M., Grondin, H., Sanchez, S., Armaingaud, D., Blochet, C., Vial, A., Ankri, J., *et al.* (2017) Polypharmacy and Potentially Inappropriate Medications: A Cross-Sectional Analysis among 451 Nursing Homes in France. *European Journal of Clinical Pharmacology*, **73**, 601-608. https://doi.org/10.1007/s00228-016-2193-z

[16] Hamann, J., Kissling, W. and Heres, S. (2014) Checking the Plausibility of Psychiatrists' Arguments for Not Prescribing Depot Medication. *European Neuropsychopharmacology*, **24**, 1506-1510. https://doi.org/10.1016/j.euroneuro.2014.06.015

[17] Wu, Z., Baillargeon, J., Grady, J., Black, S. and Dunn, K. (2001) HIV Seroprevalence among Newly Incarcerated Inmates in the Texas Correctional System. *Annals of Epidemiology*, **11**, 342-346. https://doi.org/10.1016/S1047-2797(01)00210-1

[18] Fazel, S. and Danesh, J. (2002) Serious Mental Disorder in 23000 Prisoners: A Systematic Review of 62 Surveys. *The Lancet*, **359**, 545-550. https://doi.org/10.1016/S0140-6736(02)07740-1

[19] Baweja, R., Sedky, K. and Lippmann, S. (2012) Long-Acting Antipsychotic Medications. *Current Cancer Drug Targets*, **13**, 555-560. https://doi.org/10.2174/138945012799499785

[20] Arango, C., Bombin, I., Gonzalez-Salvador, T., Garcia-Cabeza, I. and Bobes, J. (2006) Randomised Clinical Trial Comparing Oral versus Depot Formulations of Zuclopenthixol in Patients with Schizophrenia and Previous Violence. *European Psychiatry*, **21**, 34-40. https://doi.org/10.1016/j.eurpsy.2005.07.006

[21] Buckley, P.F., Noffsinger, S.G., Smith, D.A., Hrouda, D.R. and Knoll, J.L. (2003) Treatment of the Psychotic Patient Who Is Violent. *Psychiatric Clinics of North America*, **26**, 231-272. https://doi.org/10.1016/S0193-953X(02)00029-1

[22] Priebe, S., Burton, A., Ashby, D.R.A., Burns, T., David, A., McCabe, R., *et al.* (2009) Financial Incentives to Improve Adherence to Anti-Psychotic Maintenance Medication in Non-Adherent Patients—A Cluster Randomised Controlled Trial (FIAT). *BMC Psychiatry*, **9**, 61. https://doi.org/10.1186/1471-244X-9-61

[23] Arnold, R., Giebe, W., Winnefeld, K. and Klein, A. (2002) An Initially Unexplained Death during Prison Sentence. Diagnostic Verification by Atomic Absorption Spectrometry. *Archiv fur Kriminologie*, **209**, 14-19.

[24] Barnes, T.R., Shingleton-Smith, A. and Paton, C. (2009) Antipsychotic Long-Acting Injections: Prescribing Practice in the UK. *The British Journal of Psychiatry*, **195**, s37-s42. https://doi.org/10.1192/bjp.195.52.s37

[25] Bobo, W.V. and Shelton, R.C. (2010) Risperidone Long-Acting Injectable (Risperdal Consta®) for Maintenance Treatment in Patients with Bipolar Disorder. *Expert Review of Neurotherapeutics*, **10**, 1637-1658. https://doi.org/10.1586/ern.10.143

[26] Lasser, R.A., Bossie, C.A., Gharabawi, G.M. and Turner, M. (2004) Patients with Schizophrenia Previously Stabilized on Conventional Depot Antipsychotics Experience Significant Clinical Improvements Following Treatment with Long-Acting Risperidone. *European Psychiatry*, **19**, 219-225. https://doi.org/10.1016/j.eurpsy.2003.11.007

[27] Cramer, J.A. and Rosenheck, R. (1998) Compliance with Medication Regimens for Mental and Physical Disorders. *Psychiatric Services*, **49**, 196-201.

https://doi.org/10.1176/ps.49.2.196

[28] Graffino, M., Montemagni, C., Mingrone, C. and Rocca, P. (2014) Long Acting Injectable Antipsychotics in the Treatment of Schizophrenia: A Review of Literature. *Rivista di Psichiatria*, **49**, 115-123.

[29] Young, J.L., Spitz, R.T., Hillbrand, M. and Daneri, G. (1999) Medication Adherence Failure in Schizophrenia: A Forensic Review of Rates, Reasons, Treatments, and Prospects. *Journal of the American Academy of Psychiatry and the Law Online*, **27**, 426-444.

[30] Achilla, E. and McCrone, P. (2013) The Cost Effectiveness of Long Acting/Extended-Release Antipsychotics for the Treatment of Schizophrenia: A Systematic Review of Economic Evaluations. *Applied Health Economics and Health Policy*, **11**, 95-106. https://doi.org/10.1007/s40258-013-0016-2

[31] RPC (2009) Overview of Regional Psychiatric Centre.

[32] Thomson, L.D. (2000) Management of Schizophrenia in Conditions of High Security. *Advances in Psychiatric Treatment*, **6**, 252-260. https://doi.org/10.1192/apt.6.4.252

[33] SPSS, I. (2011) SPSS Statistics for Windows. IBM Corp., Armonk.

[34] CPS (2018) Compendium of Pharmacist and Specialist. Canadian Pharmacists Association, Ottawa.

[35] Rossi, G., Frediani, S., Rossi, R. and Rossi, A. (2012) Long-Acting Antipsychotic Drugs for the Treatment of Schizophrenia: Use in Daily Practice from Naturalistic Observations. *BMC Psychiatry*, **12**, 122. https://doi.org/10.1186/1471-244X-12-122

[36] Albayrak, Y., Unsal, C. and Beyazyuz, M. (2013) Relationships between Use of Long Acting Antipsychotics and Sociodemographic and Clinical Characteristics of Patients with Schizophrenia. *Bulletin of Clinical Psychopharmacology*, **23**, 171-179. https://doi.org/10.5455/bcp.20130408021412

[37] Soleman, M., Lam, N. and Woo, B. (2017) Ethnic and Age Disparities in Patients Taking Long-Acting Injectable Atypical Antipsychotics. *Cureus*, **9**, e1772. https://doi.org/10.7759/cureus.1772

[38] Sim, K., Su, A., Ungvari, G.S., Fujii, S., Yang, S.Y., Chong, M.Y., Tan, C.H., *et al.* (2004) Depot Antipsychotic Use in Schizophrenia: An East Asian Perspective. *Human Psychopharmacology*, **19**, 103-109. https://doi.org/10.1002/hup.571

[39] Acquaviva, E., Gasquet, I. and Falissard, B. (2005) Psychotropic Combination in Schizophrenia. *European Journal of Clinical Pharmacology*, **61**, 855-861. https://doi.org/10.1007/s00228-005-0034-6

[40] Tan, C.H., Shinfuku, N., Sim, K., Tan, C.-H., Shinfuku, N. and Sim, K. (2008) Psychotropic Prescription Practices in East Asia: Looking Back and Peering Ahead. *Current Opinion in Psychiatry*, **21**, 645-650. https://doi.org/10.1097/YCO.0b013e32830e6dc4

[41] Manchanda, R., Chue, P., Malla, A., Tibbo, P., Roy, M.-A., Williams, R., Banks, N., *et al.* (2013) Long-Acting Injectable Antipsychotics: Evidence of Effectiveness and Use. *The Canadian Journal of Psychiatry*, **58**, 5S-13S. https://doi.org/10.1177/088740341305805s02

[42] Liu, C.-C., Shan, J.-C., Chiang, C.-L., Hsieh, M.H., Liu, C.-M., Chien, Y.-L., Hwang, T.-J., *et al.* (2015) Initiating Long-Acting Injectable Antipsychotics during Acute Admission for Patients with Schizophrenia—A 3-Year Follow-Up. *Journal of the Formosan Medical Association*, **114**, 539-545. https://doi.org/10.1016/j.jfma.2013.01.004

[43] Samalin, L., de Chazeron, I., Vieta, E., Bellivier, F. and Llorca, P.M. (2016) Residual Symptoms and Specific Functional Impairments in Euthymic Patients with Bipolar Disorder. *Bipolar Disorders*, **18**, 164-173. https://doi.org/10.1111/bdi.12376

[44] Lammers, L., Zehm, B. and Williams, R. (2013) Risperidone Long-Acting Injection in Schizophrenia Spectrum Illnesses Compared to First Generation Depot Antipsychotics in an Outpatient Setting in Canada. *BMC Psychiatry*, **13**, 155. https://doi.org/10.1186/1471-244X-13-155

[45] Llorca, P.M., Bobes, J., Fleischhacker, W.W., Heres, S., Moore, N., Bent-Ennakhil, N., Patel, M.X., *et al.* (2018) Baseline Results from the European Non-Interventional Antipsychotic Long Acting Injection in Schizophrenia (ALTO) Study. *European Psychiatry*, **52**, 85-94. https://doi.org/10.1016/j.eurpsy.2018.04.004

[46] Armstrong, K.S. and Temmingh, H. (2017) Prevalence of and Factors Associated with Antipsychotic Polypharmacy in Patients with Serious Mental Illness: Findings from a Cross-Sectional Study in an Upper-Middle-Income Country. *Revista Brasileira de Psiquiatria*, **39**, 293-301. https://doi.org/10.1590/1516-4446-2016-2015

[47] Doshi, J.A., Pettit, A.R., Stoddard, J.J., Zummo, J. and Marcus, S.C. (2015) Concurrent Oral Antipsychotic Drug Use among Schizophrenia Patients Initiated on Long-Acting Injectable Antipsychotics Post-Hospital Discharge. *Journal of Clinical Psychopharmacology*, **35**, 442-446. https://doi.org/10.1097/JCP.0000000000000353

[48] Rehse, M., Bartolovic, M., Baum, K., Richter, D., Weisbrod, M. and Roesch-Ely, D. (2016) Influence of Antipsychotic and Anticholinergic Loads on Cognitive Functions in Patients with Schizophrenia. *Schizophrenia Research and Treatment*, **2016**, Article ID: 8213165. https://doi.org/10.1155/2016/8213165

[49] Yang, S.Y., Chen, L.Y., Najoan, E., Kallivayalil, R.A., Viboonma, K., Jamaluddin, R., Lin, S.K., *et al.* (2018) Polypharmacy and Psychotropic Drug Loading in Patients with Schizophrenia in Asian Countries: Fourth Survey of Research on Asian Prescription Patterns on Antipsychotics. *Psychiatry and Clinical Neurosciences*, **72**, 572-579. https://doi.org/10.1111/pcn.12676

[50] Yoshio, T. (2012) The Trend for Megadose Polypharmacy in Antipsychotic Pharmacotherapy: A Prescription Survey Conducted by the Psychiatric Clinical Pharmacy Research Group. *Seishin Shinkeigaku Zasshi*, **114**, 690-695.

[51] Yamanouchi, Y., Sukegawa, T., Inagaki, A., Inada, T., Yoshio, T., Yoshimura, R. and Iwata, N. (2014) Evaluation of the Individual Safe Correction of Antipsychotic Agent Polypharmacy in Japanese Patients with Chronic Schizophrenia: Validation of Safe Corrections for Antipsychotic Polypharmacy and the High-Dose Method. *International Journal of Neuropsychopharmacology*, **18**, pyu016. https://doi.org/10.1093/ijnp/pyu016

[52] Spanarello, S. and La Ferla, T. (2014) The Pharmacokinetics of Long-Acting Antipsychotic Medications. *Current Clinical Pharmacology*, **9**, 310-317. https://doi.org/10.2174/1574884713089990051