IJBPAS, August, 2021, 10(8): 2746-2759

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

AN OBSERVATIONAL COMPARATIVE STUDY OF EXTRAPYRAMIDAL SIDE EFFECTS IN PATIENTS TAKING TYPICAL AND ATYPICAL ANTIPSYCHOTICS

SONI P[1], SUDHEER KUMAR D[2] AND KISHORE P[1*]

1: Department of Pharmacy Practice, Care College of Pharmacy, Warangal rural - 506 006, Telangana

2: Department of Pharmaceutics, Care College of Pharmacy, Warangal rural - 506 006, Telangana

***Corresponding Author: Dr. P. Kishore: E Mail: kpcopsaz@gmail.com; Mob.: No.: +91-7569986361**

Received 5th Sept. 2020; Revised 9th Oct. 2020; Accepted 18th Nov. 2020; Available online 1st Aug. 2021

https://doi.org/10.31032/IJBPAS/2021/10.8.5585

ABSTRACT

The identification of Extra Pyramidal Side effects (EPS) like akathisia, rigidity, tremors and dystonic reactions in patients on antipsychotics is essential to determine the impact of extrapyramidal side effects on compliance. The present study included 277 patients attending a private psychiatric clinic and counselling centre. Prior to study initiation, approval was obtained from institutional ethical committee. All the necessary details were obtained from clinical records and by interacting with patients using data collection form. Patients were divided based on the use of atypical antipsychotics and combination of both typical and atypical antipsychotics. Details about drug characteristics like number of antipsychotics prescribed, use of anticholinergics, were recorded. The history and present occurrence of EPS was recorded from patient case sheets and using Simpson Angus Scale. 209 (75.5 %) patients were prescribed with atypical antipsychotics and 68 (24.5 %) patients were prescribed with combination of atypical and typical antipsychotics. Of 209 patients on atypical antipsychotics, 62 patients were on atypical mono therapy among which risperidone was most prescribed 15 (24 %) and least prescribed was clozapine 5 (8 %) and levosulpride 1 (2 %). We observed akathisia in 77 (65 %) patients, rigidity 36 (30 %), tremors in 43 (36 %) and dystonic reactions in 27 (23 %) patients. Side effects were found to be less in patients taking

atypical dual therapy compared to patients on atypical monotherapy. In our study, prevalence of antipsychotic use was mostly observed in rural patients. Side effects such as akathisia, tremor, rigidity and dystonic reactions were more prevalent in patients on combination of typical and atypical antipsychotics.

Keywords: Typical antipsychotics, atypical antipsychotics, Extrapyramidal Side effects, combination therapy

INTRODUCTION

Antipsychotics are the medications which are widely used in treating mental disorders like psychosis, schizophrenia, and bipolar disorder. These antipsychotics can be classified into two classes: Typical antipsychotics also called First generation or Conventional antipsychotics or neuroleptics and atypical or Second generation antipsychotics **[1]**. The term atypical refers to the lower likelihood of extrapyramidal symptoms to that of typical or conventional antipsychotics **[2]**. Drugs used in treating schizophrenia are antipsychotic drugs and often need long-term treatment **[3]**. The first generation antipsychotics, haloperidol was introduced in 1950s **[4]**. Chlorpromazine belonging to phenothiazines, promised the "psychopharmacological era" replacing the biological therapies such as electroconvulsive therapy, insulin coma, frontal lobotomy and simple sedation, leading to major changes in psychiatric practice **[5]**. The pathophysiology of schizophrenia mainly includes the decrease in dopaminergic activity in the prefrontal cortex resulting in deficit symptoms and cognitive impairment. In contrast the increased activity in the sub cortex region is associated with psychotic symptoms observed in schizophrenia **[6]**. The treatment of schizophrenia with first-generation antipsychotics though found to be effective in treating positive symptoms but they lack the efficacy towards negative symptoms. The serious drawbacks of first generation antipsychotics include Extrapyramidal Side effects which are associated with high dopamine (D_2) antagonism and low serotonin ($5\text{-}HT_{2A}$) antagonism **[7, 8]**. The second generation or atypical antipsychotic drugs acts by exhibiting the high-affinity for the serotonin receptor **[9]**. They exhibit lower affinity for dopamine D2 receptors and greater affinities for other neuroreceptors, like serotonin or 5-hydroxytryptamine (1A, 2A, 2C, 3, 6 and 7) and norepinephrine (a1 and a2) **[10]**. Neuroleptics bind more tightly to D2 receptor with dissociation constants lower than that for dopamine. Whereas, the atypical antipsychotics such as quetiapine, clozapine, olanzapine, sertindole, ziprasidone, and amisulpride bind more loosely than to D2 receptor and

have dissociation constants higher than that for dopamine **[11]**. The risk of developing EPS increases when D2 receptor occupancy reaches 70 to 80% in the nigrostriatal system **[12, 13]**. The blockade of D2 and serotonin (5-HT2A) receptors by atypical antipsychotics exhibits less incidence of EPS and drug induced Parkinsonism. Therefore the main objectives of this study were to identify the Extrapyramidal Side effects associated with use of atypical antipsychotics and combination of typical and atypical antipsychotics along with the identification of prevalence of psychiatric disorders in urban and rural population, social habits, positive psychiatric family history, the index of an antipsychotic use in patients, the pattern of anticholinergic use in psychiatric patients.

MATERIALS AND METHODS

A six month, observational comparative study was carried out at a private psychiatric clinic and Counselling Centre. A total of 277 patients were included who fulfilled the inclusion criteria of study. Prior to study initiation, approval was obtained from the institutional ethical committee. Patients of age 10 - 90 years prescribed with both typical and atypical antipsychotics were included in the study. All the necessary details such as chief complaints, diagnosis, co morbidities, social history, family history and others were obtained from clinical records and by interacting with patients using data collection form. Patients were divided based on the use of atypical antipsychotics and combination of both typical and atypical antipsychotics. Details regarding drug characteristics like number of antipsychotics prescribed, use of anticholinergics, and dosage form of drug prescribed were recorded. The history and present occurrence of Extrapyramidal side effects was recorded from patient case sheets and using Simpson Angus Scale **[14]**. This scale consists of 10 items measuring gait (hypokinesia, one item), rigidity (six items), and glabella tap, tremor, and salivation (one item each). The items were scored on a five-point scale (0–4), which was developed for the assessment of Parkinsonism and related extrapyramidal adverse effects.

Statistics: Percentage calculations**,** Means and standard deviations (SD) were calculated for all possible variables. 95 % Confidence intervals was used to gain upper and lower limit around sample mean.

RESULTS

During the study period, a total of 277 psychiatric patients visiting out- patient department were identified. Male patients (57 %) were found to be more compared to female (43 %). Of 277 patients, 209 (75.5 %) patients with mean age of 35.05 (±13.34) were prescribed with atypical antipsychotics wherein male patients were

117 (55 %) followed by 92 (44 %) female patients. 68 (24.5 %) patients with mean age of 33.11 (±13.53) were prescribed with combination of atypical and typical antipsychotics. Among these, 40 (58 %) were male and 28 (42 %) were female patients. Out of 209 patients on atypical antipsychotics, 62 patients were on atypical mono therapy among which risperidone 15 (24 %) was prescribed in higher number of patients followed by olanzapine 13 (21 %), amisulpride 13 (21 %), quetiapine 8 (13 %), aripiprazole 7 (11 %), clozapine 5 (8 %) and levosulpride 1 (2 %). The mean age of patients taking atypical monotherapy was found to be 34.90 (± 14.10), dual therapy was observed to be 35.84 (± 13.4) and mean age of patients on polytherapy was 32.07(±11.18).

Development of Extrapyramidal effects in patients taking atypical monotherapy: Patients prescribed with atypical monotherapy also experienced side effects like akathisia, rigidity, tremor and dystonic reactions which were listed out in **Table 4**. Most of the patients experienced dystonic reactions like torticollis, retrocollis. Most of the side effects were observed in patients taking risperidone and amisulpride.

On comparing the EPS experienced by patients taking atypical monotherapy to that of patients on atypical dual therapy, we observed akathisia in 77 (65 %) patients, rigidity in 36 (30 %), tremors in 43 (36 %) and dystonic reactions in 27 (23 %) patients on dual therapy. In our study, patients on atypical polytherapy were found to be suffering more from side effects like akathisia 24 (86 %), rigidity 13 (46 %), tremors 15 (53 %) and dystonic reactions 19 (68 %) patients in comparison to that of patients on mono and dual therapy. In a similar way EPS were more observed in patients on combination therapy of typical and atypical antipsychotics including more than 2 drugs. On observing the occurrence of EPS in these patients akathisia was observed in 18 (72 %), tremors 14 (56 %), rigidity 11 (44 %) and dystonic reactions in 12 (48 %) patients. **Table 5** depicts the overall comparison of EPS observed in both treatment groups.

Table 1: Distribution of patients based on demographics

S. No.	Demographics	Atypical	Combination
	Diagnosis	*%*	*%*
1.	Schizophrenia	66	43
2.	Schizoaffective Disorder	20	29
3.	Bipolar Disorder	6	22
4.	Others	8	6
	Age	*%*	*%*
5.	≤ 18	4	7
6.	19 - 40	68	73
	Area	%	%
7.	Urban	33	53
8.	Rural	67	47
	Social habits	%	%
9.	Smoking	33	23
10.	Alcohol	36	16
11.	Both	30	60
	Marital status	%	%
12.	Married	44	38
13.	Unmarried	36	43
14.	Separated	16	16
15.	Widowed	4	3
	(+) Family history	%	%
16.	Male	68	62
17.	Female	32	38

Table 2: Prescription Pattern of antipsychotics

S. No.	Type of therapy	Number	%
	Atypical(209)		
1.	Mono	62	30
2.	Dual	119	57
3.	Poly	28	13
	Combination (68)		
1.	Mono	0	0
2.	Dual	25	37
3.	Poly	43	63
Total		277	

Table 3: Distribution of patients on atypical mono therapy based on drug prescribed

S. No.	Drug	No. of patients	%
1.	Amisulpride	13	21
2.	Aripiprazole	7	11
3.	Clozapine	5	8
4.	Levosulpride	1	2
5.	Olanzapine	13	21
6.	Quetiapine	8	13
7.	Risperidone	15	24
Total		62	100

Table 4: Development of Extrapyramidal effects (EPS) in patients taking atypical monotherapy

S. No.	Drug	Akathisia (%) n=33	Rigidity (%) n=17	Tremors (%) n=18	Dystonic reactions (%) n=14
1.	Amisulpride	12	23	21	21
2.	Aripiprazole	15	18	5	14
3.	Clozapine	12	6	11	0
4.	Levosulpride	3	0	5	0
5.	Olanzapine	21	6	17	7
6.	Quetiapine	12	6	11	14
7.	Risperidone	25	41	29	43
		Total	100		

Table 5: Overall comparisons of side effects among patients on atypical and combination treatment group

S. No.	Side effect	Atypical (%)	Combination (%)
1.	Akathisia	134 (64 %)	57 (84 %)
2.	Rigidity	66 (31 %)	35 (51 %)
3.	Tremors	76 (36 %)	41 (60 %)
4.	Dystonic reactions	60 (29 %)	31 (45 %)
Total	209		68

DISCUSSION

Although new generation or atypical antipsychotics are increasingly replacing conventional antipsychotics like chlorpromazine and haloperidol in some countries, many issues about these compounds need to be clarified Stefan Leucht *et al*., 2003 **[15]**.

In our study male patients were more in number and total of 84 (57 %) were male receiving polytherapy in atypical treatment group and 40 (59 %) were among polytherapy in combination treatment group. The mean age of the patients in atypical treatment group and in combination treatment group was 35.05 (±13.34; 95 % CI: 33.2 to 36.9) and 33.11 (±13.53; 95 % CI: 31.3 to 34.9). Most of the patients in our study were suffering from schizophrenia followed by schizoaffective disorder. The most commonly used atypical antipsychotic as monotherapy in our study was risperidone 15 (24 %) and least prescribed was clozapine 5 (8 %). The most commonly used typical antipsychotics in polytherapy was haloperidol. Around (60 %) patients among atypical treatment group were from rural areas and around (33 %) patients were from urban areas. Occurrence of akathisia and tremors were observed more with risperidone among patients on atypical monotherapy. The overall occurrence of akathisia and tremors was predominately observed more in patients on combination therapy of atypical and typical antipsychotics. Rigidity among patients on atypical monotherapy was observed in (41 %). Of 62 patients treated with atypical antipsychotics, risperidone induced dystonic reactions were observed in 6 (43 %) patients. The overall occurrence was observed more in patients treated with combination therapy (60 %). The use of anticholinergics in atypical group was observed in 188 (90 %) patients and combination group was 65 (95 %).

In consistent to the study done by Annica Bergendal *et al.,* **[16]** who stated that men used antipsychotic drugs more often than women in our study male patients were more in number. In contrast to our findings, study conducted by Jamie Karagianis *et al.,* **[17]** found more women patients than male. A total of 84 (57 %) were male receiving polytherapy in atypical treatment group and 40 (59 %) were among polytherapy in combination treatment group, as the women

with psychotic disorders have better outcomes, possible reasons could include genetic factors, higher rates of marriage among women, lower rates of substance abuse as stated by Grossman *et al.,* **[18]**. The mean age of the patients in atypical treatment group and in combination treatment group was 35.05 (±13.34; 95 % CI: 33.2 to 36.9) and 33.11 (±13.53; 95 % CI: 31.3 to 34.9) which were found to be similar to the results of Siranesh Tesfaye *et al.,* **[19]** where mean age was 35.28 (±10.35). The mean age of patients on monotherapy was 34.90 (±14.10; 95 % CI: 33 to 36.8) and that of polytherapy was found to be 35.84 (±13.40; CI 95% 34 to 37.7) which were consistent to the results of Ric M Procyshyn *et al.,* **[20]**, where mean age was found to be 35.7 (11.2) and 36.9 (10.7) for monotherapy and polytherapy groups respectively. Most of the patients in our study were suffering from schizophrenia followed by schizoaffective disorder. Our findings were similar to the results of Fisher *et al.,* **[21]**, where bipolar disorder was observed in (6 %) of the patients on monotherapy and schizoaffective disorder was observed (24.7 %) of patients. Polytherapy (70 %) in atypical treatment group was possibly used to improve suboptimally controlled symptoms of psychiatric disorder. Our results were found to be similar to results of work done by Douglas Faries *et al.,* **[22]**, where monotherapy was observed in (34 %) of patients and (66 %) of patients were on polytherapy. Polytherapy can be due to switching of antipsychotics during its failure to exhibit therapeutic efficacy, switching is done gradually rather than abruptly to avoid symptom exacerbation and other rebound phenomena as stated by T. Scott Stroup *et al.,* **[23]**. The most commonly used atypical antipsychotic as monotherapy in our study was risperidone 15 (24 %) and least prescribed was clozapine 5 (8 %) which might be due to the repetitive haematological test associated with prescribing of clozapine. The results were almost similar to observations made by Fisher *et al.,* **[21]** risperidone (24 %), clozapine (6.3 %). The most commonly used typical antipsychotics in polytherapy was haloperidol 48 (71 %), where as Flupenthixol and Zuclopenthixol accounted for about 20 (29 %) of patients. The clozapine along with conventional antipsychotic was used in around (20.5 %) of patients which was within the range of (18.5 %) to (56 %) stated by W.J.Broekema **[24]**. Around (60 %) patients among atypical treatment group were from rural areas and around (33 %) patients were from urban areas. In contrast to our findings, Jordan E. De Vylder *et al.,* **[25]** stated, the risk of developing schizophrenia is approximately 2.37 times greater in urban compared with rural settings. This

discrepancy might be due to the difference in the degree of urbanicity among our region and their region. This can also be attributed to the superstitious believes of the patient associated with poor literacy rate in rural areas in our region and social stigma regarding the occurrence of psychiatric disorders. This may also be affected by the higher number of consanguineous marriages as stated by Aideen Maguire *et al.,* **[26]** that a child of consanguineous parents is at increased risk of common mood disorders and psychoses. Occurrence of akathisia in patients on atypical monotherapy was mostly observed with risperidone 8 (25 %) which was similar to the findings of Maria Juncal-Ruiz *et al.,* **[27]** where akathisia induced by risperidone was observed in (20 %) of patients. The overall occurrence of akathisia was observed more in patients on combination therapy of atypical and typical antipsychotics which accounted for (84 %), among which most of the patients were treated with haloperidol and risperidone which carried a higher risk of akathisia as stated by lieberman, tollefson, tohen, *et al.,* **[28]**. Out of all patients treated with atypical monotherapy, tremors were predominately observed in patients treated with risperidone 5 (29 %), which was possibly due to its higher affinity to dopamine receptors causing blockade of dopamine. These results were found to be in line with the results of Y.C. Yen *et al.,* **[29]**, where tremors with risperidone were observed in (38 %) patients. Our results also found to be similar with the findings of Bobes *et al.,* **[30]** where tremors were observed in (25.5 %) patients treated with risperidone. Tremors were observed more in male patients (66 %) with the mean age of 35.16±13.48. The overall occurrence of tremors was observed more in patients treated with combination therapy 41 (60 %), among these patients 23 (56 %) were on haloperidol along with other antipsychotic and 11 (29 %) were using haloperidol and risperidone, the higher affinity of this antipsychotics to dopamine receptors could possibly lead to occurrence of tremors when compared to other antipsychotics. Among patients treated with atypical antipsychotics alone, rigidity among patients on atypical monotherapy was observed in (41 %) of patients which found to be similar to the results of Bobes *et al.,* **[30]** where rigidity with risperidone was observed in (32.3 %) of patients. Study conducted by Y.C. Yen *et al.,* **[29]** found that (50 %) patients treated with haloperidol were affected by rigidity, similarly in our study (77 %) of patients affected with rigidity were treated haloperidol along with other antipsychotic with synergizes the dopamine antagonizing affect in the body increasing the effect of rigidity. Of 62 patients treated with atypical

antipsychotics, risperidone induced dystonic reactions were observed in 6 (43 %) patients. The overall occurrence was observed more in patients treated with combination therapy (60 %). This may be attributed to (32.2 %) patients being treated with IM form of Zuclopenthixol, as this dosage form may result in EPS, which was in consonance to the statement that some studies point out that the incidence of EPS was significantly higher in patients receiving depot preparations, by Altamura *et al.,* **[31]** and (61 %) patients were treated with risperidone and haloperidol or both. The study conducted by kapur, zipursky, jones, *et al.,* **[32]** explained that 65 % –70 % D2 occupancy was obtained with 2.5 mg/ day of haloperidol in a majority of the patients. In our study (48 %) patients were on 5 mg of haloperidol, which may enhance the dopamine occupancy leading to extrapyramidal effects. The observed use of anticholinergics in atypical group was 188 (90 %) and combination group was 65 (95 %), which was similar to the observations made by Seunghyong Ryu, **[33]**. Among 188 patients (64 %) patients were prescribed with anticholinergic drugs before the onset of extrapyramidal side effects. The prophylactic use of anticholinergic drugs may worsen the tardive dyskinesia and may cause other side effects like blurred vision, constipation, whereas in older patients it may lead to severe cognitive impairment. Trihexyphenidyl was used in 49 % and combinations like trihexyphenidyl + procyclidine, trihexyphenidyl + Glycopyrrolate were used in 45 % patients taking atypical treatment alone. Whereas 35 % of patients were on trihexyphenidyl and 57 % were on combinations like trihexyphenidyl + procyclidine, trihexyphenidyl + Glycopyrrolate in combination treatment group. (65 %) patients treated with polytherapy, where atypical antipsychotics were augmented with typical antipsychotics were non-adherent to their medications. It was observed that patients non-adherent to medications were affected with EPS during study period, which was in line to the conclusions made by Sultan *et al.,* **[34]** that experiencing motor side effects was associated with nonadherence. Patients of younger age, male sex, lack of social activities, side-effects, symptom control may also lead patients to stop taking medication. Apart from these factors, achieving symptom relief may also affect adherence by believing that it is no longer necessary to continue medications M. Narasimhan *et al.,* **[35]**. When Simpson Angus Scale (SAS) was used to assess the parkinsonian symptoms like rigidity, tremor and sialorrhea the mean score of these patients was found to be (1.67 ±1.16). Most of the patients were observed to be

affected with tremors and mild to moderate rigidity. The occurrence of side effects like akathisia, rigidity and tremor were found to be high in these patients even though these patients were on anticholinergic medication. Typical antipsychotics trigger the occurrence or worsen existing EPS. On the other hand the (47 %) patients were non-adherent in atypical treatment group. In addition to the above factors polytherapy of antipsychotics increases the cost burden on patients affecting the adherence.

CONCLUSION

In our study, prevalence of antipsychotic use was mostly observed in rural patients. Most of the patients had positive family history for psychiatric disorders. Risperidone was observed to be the most commonly prescribed atypical antipsychotics and haloperidol was prescribed more often than other typical antipsychotics. More than half of the patients were prescribed with prophylactic anticholinergic drugs. Patient treated with combination therapy had significant social habits compared to atypical therapy. Side effects such as akathisia, tremor, and rigidity and dystonic reactions were more prevalent in patients on combination of typical and atypical antipsychotics compared to patients on atypical antipsychotics alone. Overall decrease in compliance was observed in patients treated with combination of typical and atypical antipsychotics. Pharmacist plays pivotal role in counselling about disease, creating awareness about side effects and the importance of medication adherence for better quality of life.

REFERENCES:

[1] Shah A, Verma R, Yadav P, Patel J. Drug utilization study of antipsychotic drugs in the psychiatry outpatient department of a tertiary care hospital. Natl J Physiol Pharm Pharmacol 2019; 9 (11): 1111-1116.

[2] Jonathan R. Scarff, MD; and David A. Casey. Newer Oral Atypical Antipsychotic Agents: A Review. P&T, 2011; Vol. 36 No. 12, 382-341.

[3] Oommen S, Elango P, Alwar MC, Solomon S. Assessment of drug prescribing pattern in schizophrenia in a tertiary care hospital in South India. Natl J Physiol Pharm Pharmacol 2019; 9(8): 709-713.

[4] DE Adkins, K A berg, JL McClay, J Bukszar, Z Zhao, P Jia, TS Stroup, D Perkins, JPMcEvoy, JA Lieberman, PF Sullivan and EJCG van den Oord. Genomewide pharmaco-genomic study of metabolic side effects to antipsychotic drugs. Molecular Psychiatry, 2011, 16, 321–332

[5] Chaitra T. Ramachandraiah, Narayana Subramaniam, Manuel

Tancer. The story of antipsychotics: Past and present. Indian J Psychiatry 2009; 51: 324-6.

[6] Larry J. Siever, Kenneth L. Davis. The Pathophysiology of Schizophrenia Disorders: Perspectives from the Spectrum. Am J Psychiatry 2004; 161: 398–413.

[7] Krishna R. Patel, Jessica Cherian, Kunj Gohil, Dylan Atkinson. Schizophrenia: Overview and Treatment Options. P&T 2014; Vol. 39 No. 9: 638-645

[8] Nevena Divac, Milica Prostran, Igor Jakovcevski, and Natasa Cerovac. Second-Generation Antipsychotics and Extrapyramidal Adverse Effects. BioMed Research International 2014; Volume 2014: 1-6

[9] Mona M Boules, Paul Fredrickson, Amber M Muehlmann and Elliott Richelson. Elucidating the Role of Neurotensin in the Pathophysiology and Management of Major Mental Disorders. Behavioural sciences. . 2014, 4, 125–153

[10] Jeffrey A. Lieberman, T. Scott Stroup, Joseph P. McEvoy, Marvin S. Swartz, Robert A. Rosenheck, Diana O. Perkins, Richard S.E. Keefe, Sonia M. Davis, Clarence E. Davis, Barry D. Lebowitz, Joanne Severe and John K. Hsiao, Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia, The New England Journal of Medicine. September 22, 2005, 353: 1209-23.

[11] Seeman P, Atypical antipsychotics: mechanism of action. Canadian journal of psychiatry, 2002 Feb; 47(1):27-38.

[12] Arshia A. Shirzadi and S. Nassir Ghaemi. Side Effects of Atypical Antipsychotics: Extrapyramidal Symptoms and the Metabolic Syndrome. Harv Rev Psychiatry Volume 14, Number 3 152-164

[13] B Thanvi, S Treadwell. Drug induced Parkinsonism: a common cause of Parkinsonism in older people. Post grad Med J 2009; 85: 322–326.

[14] https://wbma.cc/wp-content/uploads/2018/01/Simpson_Angus_scale.pdf

[15] Stefan Leucht, Kristian Wahlbeck, Johannes Hamann, Werner Kissling. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. Lancet, 2003; 361: 1581–89.

[16] Annica Bergendal, Helena Schiöler, Bjorn Wettermark, Karin Sparring Bjorksten. Concomitant use of two or more antipsychotic drugs is common in Sweden. Therapeutic

Advances in Psychopharmacology, 2015; Vol. 5(4): 224–231.

[17] Jamie Karagianis, Richard Williams, Lori Davis, Ric Procyshyn, Neerav Monga, James Hanley, Ranjith Chandrasena, Aruna Thakur and Ruth Dickson. Antipsychotic switching: results from a one-year prospective, observational study of patients with schizophrenia. Current Medical Research and Opinion, 2009; Vol. 25, No. 9: 2121–2132.

[18] Linda S. Grossman, Martin Harrow, Cherise Rosen, Robert Faull, B.S Gregory P. Strauss M.A. Sex Differences in Schizophrenia and Other Psychotic Disorders: A 20-Year Longitudinal Study of Psychosis and Recovery. Compr Psychiatry, 2008; 49(6): 523–529.

[19] Siranesh Tesfaye, Nigussie Debencho, Teresa Kisi and Minale Tareke. Prevalence of Antipsychotic Polypharmacy and Associated Factors among Outpatients with Schizophrenia Attending Amanuel Mental Specialized Hospital, Addis Ababa, Ethiopia. Hindawi Publishing Corporation, Psychiatry Journal, 2015; Volume 2016: 1-7.

[20] Ric M Procyshyn, Nathan B Ken needy, Gore don Tse, Barbara Thompson. Antipsychotic Polypharmacy: A Survey of Discharge Prescriptions from a Tertiary Care Psychiatric Institution. Can J Psychiatry, 2001; 46: 334–339.

[21] Maxine D Fisher, Kathleen Reilly, Keith Isenberg and Kathleen F Villa. Antipsychotic patterns of use in patients with schizophrenia: polypharmacy versus monotherapy. BMC Psychiatry 2014; 14: 341.

[22] Douglas Faries, Haya Ascher-Svanum, Baojin Zhu, Christoph Correll& John Kane. Antipsychotic monotherapy and polypharmacy in the naturalistic treatment of schizophrenia with atypical antipsychotics. BMC Psychiatry, 2005; Page 1-11

[23] T. Scott Stroup, Neil Gray. Management of common adverse effects of antipsychotic medications. World Psychiatry, 2018; 17: 341–356.

[24] W. J. Roukema, I. W. de Grout, P. N. van Herten. Simultaneous prescribing of atypical antips-ychotics, conventional antipsy-chotics and anticholinergics—a European study. Pharm.D World Sic (2007) 29: 126–130

[25] Jordan E. DeVylder**,** Ian Kelleher, Monique Lalane, Hans Oh, Bruce G. Link, Ai Koyanagi. Association

of Urbanicity with Psychosis in Low- and Middle-Income Countries. JAMA Psychiatry, 2018; 75(7): 678-686.

[26] Aideen Maguire, FoteiniTseliou, Dermot O'Reilly. Consanguineous Marriage and the Psychopathology of ProgenyA Population-wide Data Linkage Study. JAMA Psychiatry. 2018;75(5): 438-446

[27] Maria Juncal-Ruiz**,** Mariluz Ramirez-Bonilla, Jorge Gomez-Arnau, Victor Ortiz-Garcia de la Foz, Paula Suarez-Pinilla, Obdulia Martinez-Garcia, Karl David Neergaard, Rafael Tabares-Seisdedos, Benedicto Crespo-Facorro. Incidence and risk factors of acute akathisia in 493 individuals with first episode non-affective psychosis: a 6-week randomised study of antipsychotic treatment. Psychopharmacology, 2017; volume 234: 2563–2570.

[28] Jeffrey A. Lieberman**,** Gary Tollefson, Mauricio Tohen, Alan I. Green, Raquel E. Gur, Rene Kahn, Joseph McEvoy, Diana Perkins, Tonmoy Sharma, Robert Zipursky, Hank Wei, Robert M. Hamer. Comparative Efficacy and Safety of Atypical and Conventional Antipsychotic Drugs in First-Episode Psychosis: A Randomized, Double-Blind Trial of Olanzapine Versus Haloperidol. Is J Psychiatry, 2003; 160: 1396–1404?

[29] Yung-Chieh Yen, For-Wey Lunga, Mian-Yoon Chong. Adverse effects of risperidone and haloperidol treatment in schizophrenia. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 2004; Volume 28: 285–290.

[30] J. Bobes, J. Rejas, M. Garcia-Garcia, F. Rico-Villademoros, M.P. Garcia-Portilla, M. Madrigal and G. Hernandez, on behalf of the EIRE Study Group. Frequency of Extrapyramidal Adverse Reactions in Schizophrenic Outpatients Treated with Risperidone, Olanzapine, Quetiapine or Haloperidol. Clin Drug Invest, 2002; 22 (9): 609-622.

[31] A. Cario Altamura, Francesca Sassella, Annalisa Santini, Clauno Montresor, Sara Fumagalli, Emanuela Mundo. Intramuscular Preparations of Antipsychotics. Adis International Limited. Drugs, 2003; 63 (5): 493-512.

[32] Shitij Kapur, Robert Zipursky, Corey Jones, Gary Remington, Sylvain Houle. Relationship between Dopamine D2 Occupancy, Clinical Response, and Side Effects: A Double-Blind PET Study of First-

Episode Schizophrenia. Is J Psychiatry, 2000; 157:514–520.

[33] Seunghyong Ryu**,** Jae Hyun Yoo, Joo Hyun Kim, Ji Sun Choi, Ji Hyun Baek, and Kyooseob Ha, Jun Soo Kwon, Kyung Sue Hong: Tardive Dyskinesia and Tardive Dystonia with Second-Generation Antipsychotics in Non-Elderly Schizophrenic Patients Unexposed to First-Generation Antipsychotics: A Cross-Sectional and Retrospective Study. Journal of Clinical Psychopharmacology, 2015: 35(1): 13–21.

[34] Mara Abdel-Raman Sultan, Ream El Sayad Hashem, Nesreen Mohamed Mohsen, Doaa Helmy Barakat, Ramy Ali Ryad and Afaf Hamed Khalil. Studying medication adherence in patients with schizophrenia: focus on antipsychotic- related factors. Middle East Current Psychiatry, 2016; Volume 23: 27–34.

[35] Meera narasimhan, chi yunpae, Natasha masand & prakash masand. Partial compliance with antipsychotics and its impact on patient outcomes. International Journal of Psychiatry in Clinical Practice, 2007; 11(2): 102-111.