Asian Journal of Pharmaceutical Education and Research
Vol -11, Issue-2, April- June 2022
ISSN:2278 7496

RESEARCH ARTICLE Impact Factor: 7.014

DEMOGRAPHIC PROFILE AND MANAGEMENT STRATEGIES OF TREATMENT RESISTANT SCHIZOPHRENIA IN A TERTIARY CARE REFERRAL HOSPITAL

Balasubramanian T[1], Lina Elizabeth Cherian[1], Mumthas A.H[1], Jisna Jamal[1], Murshid C.P[1], B. Anandhi B[3], Balan P[2], A.R.Abdul Rasheed[1],Karthikeyan M*[4]

[1]Department of Pharmacology, Al Shifa College of Pharmacy, Perinthalmanna, Kerala, India

[2]Department of Pharmaceutical Chemistry, Al Shifa College of Pharmacy, Perinthalmanna, Kerala, India

[3]The Erode College of pharmacy and research institute, Erode, Tamilnadu, India

[4]Nirmala College of Pharmacy, Muvattupuzha, Ernakulam, Kerala, India

*Corresponding Author's E mail: karthikeyanpgt@gmail.com

Received 11 March 2022; Revised 23 March 2022; Accepted 2 April 2022, Available online 15 April 2022

Cite this article as: Balasubramanian T, Lina Elizabeth C, Jisna J, Murshid CP, Anandhi B, Balan P, Abdul Rasheed AR, Karthikeyan M. Demographic Profile and Management Strategies of Treatment Resistant Schizophrenia in A Tertiary Care Referral Hospital. Asian Journal of Pharmaceutical Education and Research. 2022; 11(2): 37-48
https://dx.doi.org/10.38164/AJPER/11.2.2022.37-48

ABSTRACT

Treatment resistance in schizophrenia is an emerging issue faced by physicians worldwide. This study was undertaken to evaluate the demographic profile and management of Treatment Resistant Schizophrenia (TRS) in psychiatric department of a tertiary care super-specialty hospital. In this prospective observational study, a total of 25 subjects diagnosed with TRS were enrolled. Treatment resistant cases in the hospital setting were identified by using positive and negative syndrome scale (PANSS). We evaluated the demographic profile, major adverse drug reactions, treatment provided for those patients and monitored for improvement of conditions. The demographic profile result shows that the gender doesn't have much influence on the occurrence of TRS. Family history had a strong correlation with the occurrence of TRS. Clozapine is used as a gold standard in treatment of TRS. Augmentation of clozapine with other antipsychotics has shown clinical improvement in patients. The major ADRs shown by TRS patients include weight gain, constipation, diabetes mellitus, extra pyramidal symptoms, sexual dysfunction and tachycardia. The study concluded that in this specific population of TRS patients who were unresponsive to previous treatment, a combination of clozapine with aripiprazole as well as other augmentation strategies were seen worthy for further exploration.

Keywords: Treatment Resistant Schizophrenia; Clozapine; Aripiprazole; ECT.

INTRODUCTION

A schizophrenic patient can be termed as resistant to treatment only after an inadequate response to trial of any two second generation antipsychotics or one first and one second generation antipsychotics for duration of 4 to 10 weeks [1]. The treatment resistance is as high as 15% even in first episode of

schizophrenic patient. Treatment resistant is one of the most important clinical challenges in the pharmacological management of schizophrenia. Therefore, the evaluation of the therapeutic options in case of treatment resistance is highly clinically relevant [2]. Treatment of Treatment Resistant Schizophrenia (TRS) includes management with clozapine, atypical antipsychotics (risperidone, olanzapine, quetiapine and amisulpiride), augmentation with antidepressants (fluoxetine, paroxetine and fluvoxamine) and mood stabilizers (valproate, carbamazepine, lamotrigine). Also, Electro convulsive therapy (ECT) has been used in combination with clozapine and has been found to be safe and clinically beneficial [3,15]. Moreover, no study had been conducted so far in this area in the topic chosen in the particular demographic group. The current study was aimed at evaluating the demographic profile and management of treatment resistant schizophrenia in psychiatric department of a tertiary care super-specialty hospital.

MATERIAL AND METHODS

Study design

This observational descriptive study was carried out over a duration of 6 months, commencing from November 2016 to April 2017 in psychiatric department of KIMS Al Shifa Hospital in order to determine the demographic profile and management strategies of TRS and to monitor the adverse drug events associated with drug therapy.

Study tools

Informed consent:

The nature, type or intention of the study was explained to the patients by direct patient interaction. Participants were then given time to decide their participation in the study. If they decided to participate, a written consent was obtained from them prior to their enrollment in the study by providing them with the consent letters in the local language.

Data collection form:

A data collection form was designed to collect information necessary for the study. It consists of the details like patient demographics, symptoms, final diagnosis, past medical and medication history, family history, medication chart, electroconvulsive therapy and adverse drug reactions.

Study procedure

A total of 25 patients in psychiatry department diagnosed with TRS were selected based on inclusion and exclusion criteria. Patients who can give informed consent with the age between 18-65 and satisfying the diagnostic criteria for TRS were included in this study. Patients with epilepsy, other substantial organic or neurologic disease, clinically relevant abnormal ECGs or laboratory tests, history of alcohol or drug abuse within the previous 12 months and psychiatric disorder as comorbid illness

were excluded from this study. Sources of data were patients case record, prescription and direct interactions with physician. Demographic profile of the patients was collected from their case files. The severity of symptoms of TRS patients were assessed using positive and negative syndrome scale (PANSS). Treatments were given to the patients according to their symptom's severity. Dose adjustments were done based on individual patient aspects. Effectiveness of the therapy was measured using PANSS scale scorings.

Statistical analysis

The collected data for the study were compiled, analyzed, categorized and entered into MS Excel format for drawing inferences employing statistical techniques. The test used was "Wilcoxon signed rank test".

RESULTS

Clinical demographics

Gender wise distribution of TRS patients:

Out of the data collected from 25 patients who visited the Psychiatry department, 13 patients (52%) were males and 12 patients (48%) were females (Fig.1A)

Age wise distribution of TRS patients:

The mean age=37.12±7.79 years (Range-26 to 57years). Age category: Below 25=0%, 26 to 30=24% (n=6), 31 to 35=20% (n=5), 36 to 40=28% (n=7), 41 – 45 =16% (n=4).and above 45 =12% (n=3) (Fig.1B).

Marital status in TRS patients:

In this study, out of the 25 patients 15 patients (60%) were married, 5 patients (20%) were single and 5 patients (20%) were divorcee (Fig.1C).

Family history of any psychiatric conditions in TRS patients:

In the studied 25 patients, about 72% (n=18) had a family history of any psychiatric conditions and 28% (n=7) had no family history (Fig.1D).

Figure 1: Clinical demographics of TRS Patients - (A) Gender wise distribution. (B) Age wise distribution. (C) Marital status (D) Family history

Management strategies

Choice of therapy in TRS patients:

Clozapine + Amisulpride combination (20%, n=5) was majorly used. Least consumption was Clozapine + Olanzapine + Amisulpride + Risperidone + Iloperidone combination and Clozapine + Haloperidol + Olanzapine + Risperidone combination (4%, n=1). Clozapine was given alone in one patient (4%) (Table 1).

Table 1: Choice of therapy in TRS patients

S. No.	DRUGS	Frequency	Percent
1.	Clozapine + Amisulpride	5	20.0%
2.	Clozapine + Aripiprazole	4	16.0%
3.	Clozapine + Olanzapine + Amisulpride	3	12.0%
4.	Clozapine + Risperidone	3	12.0%
5.	Clozapine + Haloperidol + Olanzapine + ECT	3	12.0%
6.	Clozapine + Olanzapine + Risperidone	2	8.0%
7.	Clozapine + Olanzapine + Amisulpride + ECT + Risperidone	2	8.0%
8.	Clozapine + Olanzapine + Amisulpride + Risperidone + Iloperidone	1	4.0%
9.	Clozapine	1	4.0%
10.	Clozapine + Haloperidol + Olanzapine + Risperidone	1	4.0%

Dose analysis in TRS patients:

Clozapine 100 mg was the mostly used (n=13) dose in this study. Clozapine 50 mg dose was also used widely (n=9). Olanzapine 20 mg was also used in many patients (n=6). Haloperidol 5mg, 20 mg, Olanzapine 210 mg, Aripiprazole 10mg, 30mg and Iloperidone 12mg were used rarely (Table 2).

Table 2: Dose analysis in TRS patients

Drug	Doses Given per Day	Number of Patients Treated
CLOZAPINE	25 mg	3
	50 mg	9
	100 mg	13
HALOPERIDOL	5 mg	1
	10 mg	2
	20 mg	1
AMISULPRIDE	10 mg	4
	20 mg	5
	50 mg	2

OLANZAPINE	7. 5 mg	3
	20 mg	6
	30 mg	2
	210 mg	1
RISPERIDONE	1 mg	3
	2 mg	3
	3 mg	3
ARIPIPRAZOLE	10 mg	1
	15 mg	2
	30 mg	1
ILOPERIDONE	12 mg	1

Drug use pattern in TRS patients:

Clozapine was given to all the patients treated (100%, n=25). Amisulpride was given in 44% (n=11) of patients. Olanzapine was used in 48% (n=12) and risperidone was used in 36% (n= 9) of patients. ECT was given for 50% (n=5) of the total patients. Aripiprazole was used in 16% (n=4) of patients. Iloperidone was given only to one patient (4%) (Fig.5).

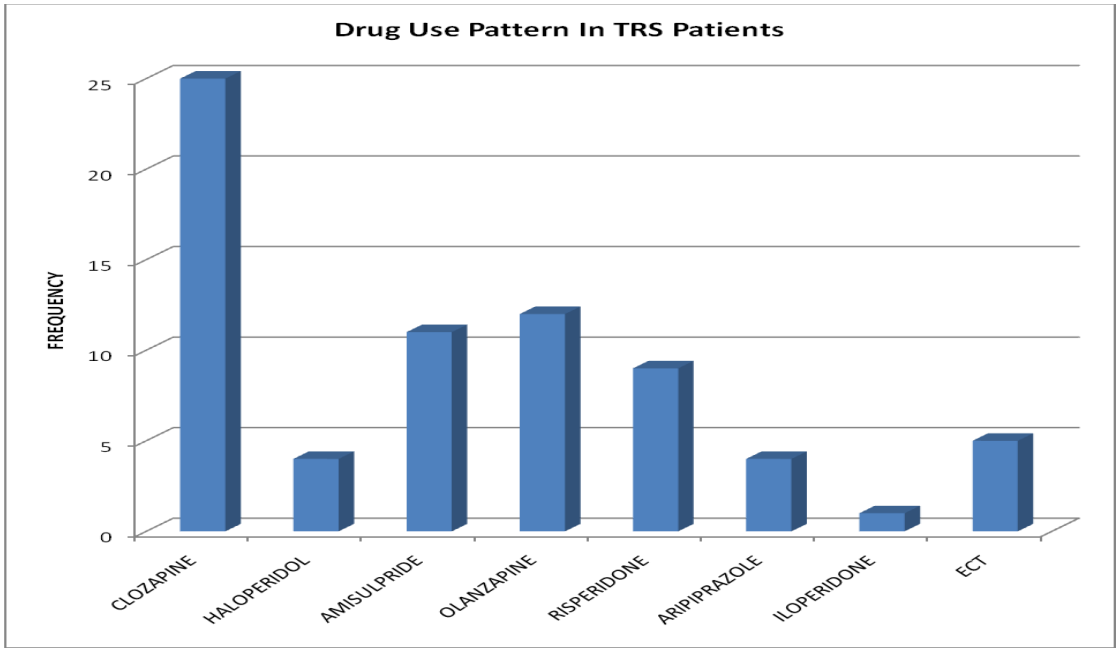

Figure 2: Management strategies - Drug use pattern in TRS patients

PANSS scoring for patients with TRS:

Initial PANSS score represents the severity of symptoms in TRS before the treatment and final PANSS score represents the symptoms severity after treatment. Here initial PANSS score had a mean of 107.64 ± 30.89 and final PANSS score had a mean of 83.96 ± 25.33. The mean difference was 23.68. Wilcoxon Signed Ranks Test was used to test the significance and the study was significant with Z=4.378 and p=0.001 at 1% level of significance.

Table 3: PANSS Score in TRS Patients

PANSS	***Mean***	***SD***	***Mean Difference***	***Wilcoxon Signed Ranks Test***	
				Z	***P Value***
Initial	***107.64***	***30.89***	***23.68***	***4.378***	***0.001****
Final	***83.96***	***25.33***			

Adverse reporting

Adverse effects observed in patients with TRS:

Weight gain (n=10), constipation (n=4), EPS (n=3), DM (n=3), sexual dysfunction (n=2) and tachycardia (n=1) were the observed ADRs in the 25 patients during the study period (Fig.3A).

Causality of ADR in patients with TRS:

When analyzed on Naranjo ADR probability scale, majority of ADRs were rated as possible [n = 15 (65.22%)], followed by probable [n =8 (34.78%)] (Fig.3B).

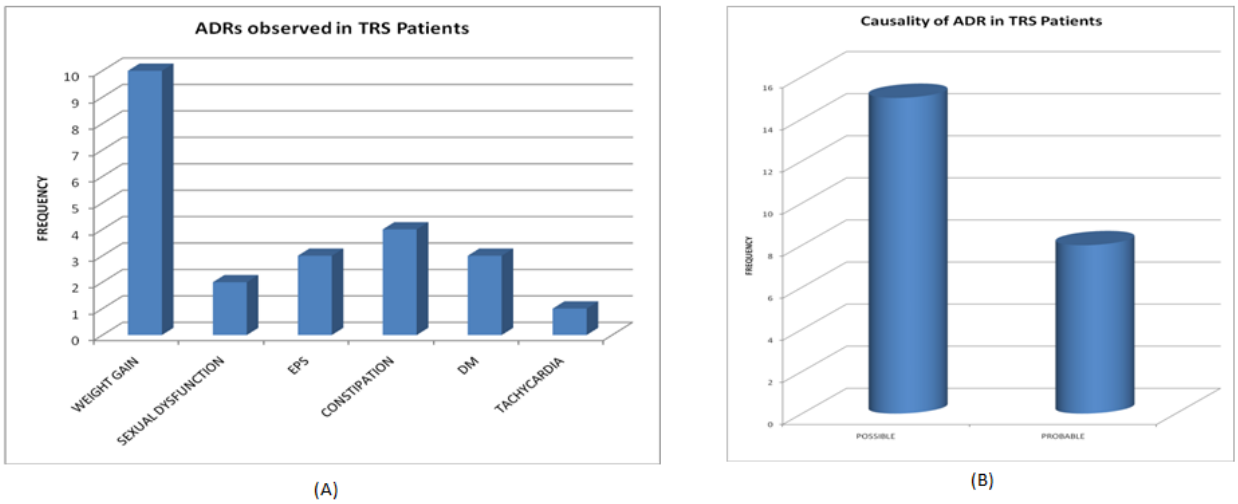

Figure 3: Adverse reporting of TRS Patients - (A) ADRs observed. (B) Causality of ADR

DISCUSSION

TRS is a major clinical challenge faced globally. Evaluation and updating the knowledge on TRS and the therapies help clinicians in their effective patient care. Our study investigated the demographic profile and management strategies of TRS in our hospital setting. Gender wise distribution of TRS was assessed here. The results of the study showed a small male predominance over female. One study reveals a same level of gender distribution in TRS patients [4]. Through the study, it was perceived that mean age of TRS was 37.12 ± 7.79 years (Range: 26-57). A study showed a mean age of 43 ± 12 years (Range: 24-72) for TRS [5]. Marital status of the patients was evaluated and it was found that out of 25 patients with TRS, 60% of patients were married, 20% of patients were single and 20% of patients were divorcee. A TRS study showed 73.4% patients (n=22) who are single which is contradictory to our study findings [4]. Family history of any psychiatric conditions in patients with TRS was assessed and out of the total 25 patients, about 72% (n=18) had a family history of a psychiatric condition.

In our study, clozapine was found to be the widely used drug in our hospital setting (100%). All the patients who had TRS was treated with clozapine with different doses and showed improvement in PANSS scores. A study suggest that clozapine emerges to be the gold standard in TRS patients [6]. The most consisting results regarding efficacy in their study group had been observed with clozapine. The data from studies showed superior effects of clozapine on positive and negative symptoms, compared to prior treatment with typical neuroleptics. Clozapine + amisulpride combination was used in 20% of

the patients and was the mostly used combination. The patients also showed improvement in their PANSS score after the treatment. A case series study, showed improvement in previously treatment resistant symptoms following a combined treatment strategy of clozapine and amisulpride [7,16]. An open trial of amisulpride augmentation in a long term (52 weeks) study showed a significant improvement in most of the patients with no additional side effects [8]. Clozapine + aripiprazole combination was used in 16% of the patients with TRS and an improvement in the psychotic symptoms were observed in them. Studies also showed that using aripiprazole augmentation in TRS with clozapine effectively reduced the symptoms in most of the patients[9]. Augmentation therapy of clozapine with other antipsychotics such as risperidone, olanzapine, haloperidol and iloperidone were given for many patients with TRS and showed significant improvement in their symptoms. This is correlated with the study results which shows the effectiveness of using first generation and second generation antipsychotics in combination with clozapine in their study [10,17]. Another study, revealed the results of a meta-analysis indicating that clozapine augmentation with atypical and typical antipsychotics improve the symptoms of TRS in majority of the studied cases [11]. Electro convulsive therapy was given as augmentation with clozapine and other antipsychotics in many patients (20%) and shown improvement in their symptoms. The results were also similar to the previous study which implicated the improvement in symptoms when ECT was given along with antipsychotics.

In this study, the significance of the PANSS score difference suggested the effectiveness of treatment given. Large scale studies shows the significant reduction in TRS symptoms and effectiveness of treatment when PANSS initial and final scores differ significantly. The adverse drug reactions that occurred in the patients during the study were evaluated and causality assessment was done using Naranjos scale. Out of the 25 patients, 40% had an ADR of weight gain (n=10), 16% had the incidence of constipation (n=4), 12% had the episodes of EPS (n=3), 12% had incidence of DM (n=3), 8 had an ADR of sexual dysfunction (n=2) and 4% had tachycardia (n=1) during the study period. A study showed the incidence of weight gain and increased glucose level in patients who were taking clozapine and other second generation antipsychotics [12]. Researchers studied the frequency of sexual dysfunction in patients using risperidone, olanzapine and haloperidol and found out high frequency of sexual dysfunction with these drugs [13]. A recent study about clozapine with ECT found out the occurrence of supraventricular and sinus tachycardia in some patients [14]. When analyzed on Naranjo ADR probability scale, majority of ADRs were rated as possible [n = 15 (65.22%)], followed by probable [n =8 (34.78%)].

CONCLUSION

A prodigious degree of treatment resistance was shown by many schizophrenic patients in the psychiatric department of our hospital. From the evaluation of the demographic profile, it was concluded that the gender doesn't have much influence on the occurrence of TRS. Furthermore, family history had a strong correlation with the occurrence of TRS. The study also illustrates that for this specific population unresponsive to previous treatment, a combination of clozapine with aripiprazole, as well as other augmentation strategies for clozapine, seen worthy of further exploration. Thus, the study offered greater benefit to these patients by optimizing the treatment strategy and proper monitoring of adverse effects of the drug. So, we hope this study may contribute something new to the health care professionals, thereby helps improve patient care.

RECOMMENDATIONS

Expanding the study to include larger sample in different regions would more accurately identify characteristic demographics, treatment strategies, adverse effect of the drug and improve the quality of the results yielded in data analysis.

ACKNOWLEDGEMENTS

We acknowledge the valuable comments and suggestions by Dr. Jishnu Narayanan, Consultant Neuropsychiatrist, during this project. The authors would like to thank the Staff, Department of Psychiatry, Kims Al Shifa Hospital and Department of Pharmacy Practice, Al Shifa College of Pharmacy for supporting this work.

CONFLICT OF INTEREST

The authors declare no relevant conflicts of interest.

SOURCE OF FUNDING

Funding for the research project was provided by Al Shifa College of Pharmacy, Shifa Institute of Medical Sciences, Shifa Medicare Trust, Perinthalmanna, Kerala, India.

ETHICS STATEMENT

The study was approved by the Hospital Human Ethics Committee, vide reference number KAS/ADMN/AC/EC/154/2016 dated 20-12-2016. Informed consent was obtained from participants.

AUTHOR'S CONTRIBUTIONS

BT conceived the original idea, supervised the work and approved the final manuscript. **LEC** and **MAH** were responsible for conceptualization and design of the study, data analysis and interpretation, drafting of the manuscript, approval of the final manuscript. **JJ** and **MCP** were responsible for critical review of the manuscript and approval of the final manuscript. **AB, BP & AR** analyzed the data, and took the lead in writing the manuscript as well. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

REFERENCES

1. Bustillo R, Lauriello J, Horan P, Keith J. The psychosocial treatment of schizophrenia: An Update. Am J Psychiatry. 2001;158(2):163-175. https://doi.org/10.1176/appi.ajp.158.2.163
2. Havaki-Kontaxaki BJ, Ferentinos PP, Kontaxakis VP, Paplos KG, Soldatos CR. Concurrent administration of clozapine and electroconvulsive therapy in clozapine-resistant schizophrenia. Clin Neuropharmacol. 2006; 29(1):52-56. https://doi.org/10.1097/00002826-200601000-00012
3. Conley R, Buchanan R. Evaluation of treatment-resistant schizophrenia. Schizophrenia Bulletin. 1997;23(4):663-672. https://doi.org/10.1093/schbul/23.4.663
4. Uriel HL, Marina E, Bronia Q, Michael L. Treatment resistant schizophrenia and staff rejection. Schizophrenia Bulleti. 1999;25(3):457-465. https://doi.org/10.1093/oxfordjournals.schbul.a033393
5. Antonio TL, Paul G, Mehdi V, Shamir P. Management of treatment resistant schizophrenia in medium secure care. Prog Neurol Psychiatry. 2014;18(5):27-28. https://doi.org/10.1002/pnp.349
6. Solanki RK, Paramjeet S, Deepti M. Current perspectives in the treatment of resistant schizophrenia. Indian J Psychiatry. 2009;51(4):254-260. https://www.indianjpsychiatry.org/text.asp?2009/51/4/254/58289
7. Mathias Z, Udo K, Fritz AH, Johannes T. Combination of clozapine and amisulpride in treatment-resistant schizophrenia: case reports and review of the literature. Pharmacopsychiatry. 2004;37(1):26-31. https://doi.org/10.1055/s-2004-815471
8. Rob WK, Anusha B. Management of clozapine-resistant Schizophrenia. Adv Psychiatr Treat. 2005;11:101-106. http://apt.rcpsych.org/cgi/eletter-submit/11/2/101
9. Nilufar M, Rainer MK. Role of aripiprazole in treatment-resistant schizophrenia. Neuropsychiatric Dise Treat. 2012;8:235-244. https://doi.org/10.2147/ndt.s13830
10. Chakos M, Lieberman J, Hoffman E. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia:A review and meta-analysis of randomized trials. Ame Jr of Psychiatr. 2001;158:518-526. https://doi.org/10.1176/appi.ajp.158.4.518.

11. Lévyrueff M, Gourevitch R, Lôo H. Maintenance electroconvulsive therapy: An alternative treatment for refractory schizophrenia and schizoaffective disorders. Psychiatry Res. 2010;175(3):280-283. https://doi.org/10.1016/j.psychres.2008.10.012.
12. Krakowski M, Czobor P, Citrome L. Weight gain, metabolic parameters and the impact of race in aggressive inpatients randomized to doubleblind clozapine, olanzapine or haloperidol. Schizophr Res. 2009;110(3):95-102. https://doi.org/10.1016/j.schres.2009.02.006
13. Bobes J, Garc MP, Rejas J. Frequency of sexual dysfunction and other reproductive side effects in patients with schizophrenia treated with risperidone, olanzapine, quetiapine or haloperidol:The results of the EIRE study. Schizo Bulletin. 2010;159(7):125-147. https://doi.org/10.1080/713847170
14. Kupchik M, Spivak B, Mester R. Combined electro eonvulsive-clozapine therapy. Clin Neuropharmacol. 2000;23(1):14-16. https://doi.org/10.1097/00002826-200001000-00003
15. Braga RJ, John M, Schooler NR, Bailine SH, Malur C, Mendelowitz A, et al. Continuation Electroconvulsive Therapy for Patients With Clozapine-Resistant Schizophrenia-A Pilot Study. The Journal of ECT. 2019;35(3):156-160. https://doi.org/10.1097/yct.0000000000000588
16. Kudva GK, Gupta DK. Strategies in clozapine-resistant schizophrenia: A literature review. J Mental Health Hum Beha. 2016;21:6-15. https://www.jmhhb.org/text.asp?2016/21/1/6/182096
17. Oh S, Lee TY, Kim M. Kim SH, Lee S,Cho S, et al. Effectiveness of antipsychotic drugs in schizophrenia: a 10-year retrospective study in a Korean tertiary hospital. npj Schizophr.2020;6,32. https://doi.org/10.1038/s41537-020-00122-3