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Original Research Article

A clinical study on profile of the patients experiencing extra-pyramidal side-effects with the Usage of second generation antipsychotics Effects of second generation antipsychotics

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Abstract: There were claims that second generation antipsychotics (SGA) produce fewer extra-pyramidal symptoms (EPS) and their EPS profiles were compared. The aim is to compare the treatment emergent EPS and efficacy profile between olanzapine, risperidone, iloperidone and asenapine in people with psychoticdisorders. The clinical comparative study was undertaken at Department of Psychiatry, Sri Venkateshwara Ramnarayana Ruia Hospital, Tirupathi. Total 120 patients diagnosed to be suffering from psychotic disorders were enrolled in this study after obtainedwritten informed consent. They are treated alternately primarily with the 4 drugs i.e. olanzapine, risperidone, iloperidone and asenapine. They were regularly followed-up for 3 months for EPS and efficacy by using standardized rating scales.Patients were requested to attend regular follow-ups at 2 weeks, 4 weeks,8weeks and 12 weeks interval. Iloperidone dose was titrated over 6-10 days to reach its maximum dose. Specific instructions were given for asenapine in its sublingual administration. There were no significant differences in occurrence or changes in rating scales for parkinsonism, akathisia or tardive dyskinesia among the 4 drugs. There were also no significant differences in change in BPRS scores from baseline among the 4 drugs. The occurrence of treatment emergent EPS and changes in EPS rating scales indicated that all the 4 drugs were similar to each other in causing EPS. Regarding efficacy, this study concludes that all the 4 drugs were similar to each other in their efficacy profile in treatment of psychotic disorders.
Keywords: antipsychotics, olanzapine, risperidone, iloperidone.

INTRODUCTION:

Antipsychotics are drugs that specifically alleviate psychotic symptoms (i.e. not just by calming or tranquilizing the patient) (Deniker 1960). The first of these drugs, chlorpromazine, started a new era in psychiatry in the last half of the twentieth century, as for the first time psychotic symptoms could be managed by a drug, and many psychotic patients no longer required physical restraint or chronic hospitalization[1]. Different classes of antipsychotic drugs, categorized according to their structure or profile of action on different neurotransmitters, exist. The blockage of dopamine receptors is a key feature common to all antipsychotics. Antipsychotic drugs include dopamine receptor antagonists or typical (or conventional or FGA) antipsychotics (e.g. chlorpromazine, haloperidol), serotonindopamine antagonists or atypical antipsychotics or SGA (e.g. risperidone, clozapine) and dopamine partial agonists (e.g. aripiprazole). Antipsychotics are widely used drugs in psychiatric practice. Over the lastfew years second generation antipsychotics (SGA) are being increasingly used in pharmacological treatment of major psychotic disorders. Selection of the antipsychotic is mainly based on its potential to cause extra-pyramidal symptoms(EPS). But in comparison with first generation antipsychotics, the newer second generation antipsychotics have a lower liability for extra pyramidal symptoms[2**]**. Extra- pyramindal symptoms are group of neurological syndromes whichoccur following antipsychotic medication usage. These neuroleptic related symptoms can be divided according to time of onset in relation to starting medication (or) increasing the dose. For every set of neuroleptic related syndromes

have specific set of clinical criteria is defined and incorporated. They are mainly of5 types (APA, DSM, 4thed 2000).Neuroleptic induced Akathisia (NIA), Neuroleptic induced parkinsonism (NIP), Neuroleptic malignant syndrome (NMS), Neuroleptic induced acute dystonia, Neuroleptic induced tardive dyskinesia (NITD). The introduction of "atypical" or second generation antipsychotics (SGAs)was considered to be a milestone in treatment of people with psychotic disorders because the SGAs have a lower incidence of the "typical" extra-pyramidal side effects (EPS) such as parkinsonism, dystonia, dyskinesia and akathisia than highpotency FGAs but not eliminated[3,4,5,6,7]. The movement disorders associated with antipsychotics is disabling and distressing and result in behavioral disturbances (violence and aggression),non adherence, and exacerbation of psychosis. Some of the motor signs may bemisinterpreted as psychotic symptoms. The bradykinesia, limb stiffness, and masklikefacies seen in Parkinsonism are a social and functional handicap. The restlessness and agitation associated with akathisia have similar effects. Patients with tardive dyskinesia may not be distressed by their symptoms, but family and relatives may find them distressing. These movements are very obvious to the observer and add to the stigma of psychiatric illness. It is hence very important thata careful evaluation of these symptoms be made in all patients treated with antipsychotics, so that the balance between potential risks and benefits may beoptimized[8,9]. Extra pyramidal symptoms can adversely impact antipsychotics efficacy and tolerability and reduce compliance. They also have an impact on negative, cognitive and mood symptoms. If these syndromes are neglected in earlier stages they increase the risk of irreversible late-onset movement disorders. Sometimes they may also increase the risk of suicidality (i.e., ideation/behavior/completion)especially in persons with, tardive dyskinesia and akathisia[8,9,10]. Hence there is need to study extrapyramidal symptoms with second generation antipsychotics for detecting. Assessing, understanding and taking measures to prevent extra-pyramidal symptoms. This comparative study highlights about the development of extra pyramidal symptoms with the usage of second generation antipsychotics. Current study aims at frequencies, pattern, severity of extra pyramidal symptoms and also at dose and duration of treatment that induced extra pyramidal symptoms, which will help the psychiatrist in optimizing treatment regimens with second generation antipsychotics to avoid extra-pyramidal symptoms. This will further improvepatient compliance in long run. Primary objective measure is to study the profile of patients experiencingacute extra-pyramidal symptoms with the usage of second generation antipsychotics i.e., Olanzapine, Risperidone, Iloperidone, Asenapine and their comparison among them. Secondary objective measure is to study the efficacy of the treatment and their comparison.

Ethical clearance:

The study has been followed in accordance with the Institutional Ethical committee (IEC) guidelines and performed after IEC clearance only.

METHODOLOGY:

120 subjects who are presenting with psychosis meeting the inclusion and exclusion criteria were chosen from outpatient and inpatient units of psychiatric unit of department of psychiatry at Sri Venkateshwara Medical College, which is a tertiary care teaching hospital in Tirupathi. The subjects in study population were given treatment primarily with 4 agents i.e. Olanzapine, Risperidone, Iloperidone, Asenapine according to patient profile, and underlying psychotic disorder. These drugs were allotted consecutively for every patient. Olanzapine started orally in 5-10mg, risperidone started orally in 4-6mg, iloperidone started orally in 4-8mg per day. Iloperidone dose was titrated over 7-10 days to reach maximum dose and to avoid orthostatic hypotension. Asenapine given sublingually at starting doses of 5-10mg per day and specific instructions pertaining to its administration were given to participant (i.e.asenapine must be taken after breakfast and tea, it must be taken after all other oral medicines, person administering wafer must have dry hands, place the wafer under tongue for few seconds and the wafer should not be chewed and swallowed. No food or drinks including water for 10 minutes after taking the wafer were advised. These participants were assessed in follow-ups at regular intervals for 3 months. During each visit patients who were taking drugs regularly and who were having good drug compliance were included in the study. Follow-up visits were scheduled at 2 weeks, 4 weeks, 8 weeks and 12 weeks. They were assessed for extra pyramidal side-effects and efficacy of treatment at each visit by using specific rating scales. Assessment of Extra pyramidal symptoms is assessed in all subjects to identify any of three NIMDs (NIA, NIP or TD) in accordance with DSM-IV. The participants were observed for abnormal movements in the sitting and standing position. The psychiatrist posed one subjective question to all patients concerning problems with movement: "Do you have troubles with movements, and if so, does it disturb you?" The answer was allocated to one of four categories a) No. b) Yes, but it does not disturb me. c) Yes, and it disturbs me. d) Yes, and it is very difficult to cope with. Then they are evaluated for postural tremor

in patients' outstretched hands. Rigidity was evaluated in upper limbs in the standing position. Rigidity in legs was evaluated with patients sitting on a table. Rigidity in the neck was evaluated in a lying position on a couch. Gait and posture were evaluated when the patient walked in the corridor or in evaluation room.

Scales for EPS Assessment:

The Barnes Akathisia Rating Scale (BARS) (Barnes 1989) was used for assessment of clinical akathisia (and pseudoakathisia), the Simpson–Angus Scale (SAS) for NIP, and the Abnormal Involuntary Movement Scale (AIMS) for TD. No rating scales have been developed specifically for acute dystonia as they are transitory with a rapid onset and respond well to treatment. Noted by clinical observation. The interrater reliability Cohen's kappa values have been as high as 0.738 in objective items, 0.827 in subjective awareness items, 0.901 in subjective distress and 0.955 in global clinical assessment (Barnes 1989) The scale has been widely used in recent phase III trials of new antipsychotics[15]. Because these medications are hypothesized to reduce akathisia in comparison with typical antipsychotics, the studies provide opportunities to assess the validity of BARS[11]. SAS contains ten items for assessing parkinsonian and related extrapyramidal side effects, each scored from 0 to 4, with higher scores indicative of more severe symptoms[12]. These original items are gait, arm dropping; shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor and salivation. The mean score is obtained by adding all of scores and dividing by 10. The mean interrater correlation coefficient between two raters was 0.87, with a range between 0.71 and 0.96, except for the salivation item, where it was between 0.16 and 1.0[12]. SAS has been criticized for its item choice (6 of 10 items concern rigidity) and the low mean interrater reliability coefficients for the gait, wrist rigidity, tremor and salivation items[13]. The intraclass correlation coefficients (ICC) for wrist rigidity, tremor and salivation items were below 0.34 in a study conducted in elderly patients [14]. SAS validity was obtained from a study involving two levels of haloperidol and placebo; the difference between the haloperidol group and the placebo group was statistically significant[12]. A mean score of 0.3 was cited as the upper limit for patients without NIP or related extra-pyramidal symptoms. The scale has been widely used in recent phase III trials of new antipsychotics[15]. Because these medications are hypothesized to have fewer extrapyramidal side-effects than typical antipsychotics, studies of these medications provide opportunities to assess the validity of SAS[11]. First-episode patients receiving olanzapine showed a statistically significant mean reduction of 1.2, and patients receiving haloperidol showed a statistically significant mean increase of 0.6 in SAS score compared with baseline[15]. Abnormal Involuntary Movement Scale (AIMS) is by far the most established scale for rating TD[11]. It has been used in several epidemio logical studies (McCreadie et al. 1992, van Harten et al. 1996, Halliday et al. 2002). The AIMS is a 12-item anchored scale (Guy 1976). Items 1–7 assess specific involuntary movements of the orofacial region, the extremities and the trunk. Items 8–10 deal with global severity, as judged by the examiner and the patients' awareness of the movements and associated distress. Items 11 and 12 are yes–no items concerning problems with teeth and/or dentures because such problems can lead to a mistaken diagnosis of dyskinesia Each item is scored on a scale from 0 to 4, with higher scores indicative of more severe movements. The AIMS total score is a sum of items 1–7. Item 8 (severity of abnormal movements) can be used as an overall severity index. Specific instructions are provided for asking the patient certain questions and having him/her perform certain manoeuvres. Score assignment is addressed well in an article by Munetz and Benjamin (1988). Smith et al. (1979) assessed test–retest reliability, which range was from 0.12 to 0.75. Interrater reliability (Pearson correlation coeffi cients) in the same study ranged from 0.66 to 0.82 for individual body area items. The correlation for overall severity was 0.75. An interrater reliability ICC of 0.91 for the seven body areas was found when rating ten elderly patients with AIMS (Sweet et al. 1993). Satisfactory levels of test–retest consistency have been achieved for 50 AIMS. However, the interrater variability often exceeds intra-rater variability, this has been shown also for AIMS and SAS. In terms of content validity AIMS seems to cover the commonly observed clinical features that accompany TD (i.e. facial, oral, buccal, lingual, jaw and extremity movements) and the less common truncal movements. It does not cover rare or more severe movements, e.g. pharyngeal and respiratory movements or tardive dystonias[11]. Use of a threshold, such as the Schooler and Kane criteria (1982), permits construct validity to establish a probable diagnosis of TD associated with antipsychotics[11]. AIMS has been used to assess TD in trials of the newer antipsychotic drugs. The ability of new medication to produce lower AIMS scores provides evidence of the validity of the scale[11]. Tollefson and colleagues (1997) compared 707 patients treated with olanzapine for a median of 237 days with patients treated with haloperidol for a median of 203 days. Using the total of AIMS items 1–7 as their dependent variable, they found that scores were reduced by an average of 0.13 scale points in the olanzapine

group and increased by an average of 0.36 scale points in the haloperidol group, a statistically signifi cant difference (F = 9.02, df = 1.898, p = 0.003). 51 For research and clinical purposes, the following research criteria for diagnosing TD: 1. at least 3 months of cumulative exposure to neuroleptic medication, 2. the absence of other conditions that might cause the abnormal involuntary movements, and 3. movements of mild severity (score of 2 on the AIMS) in at least two discrete body parts or movements of moderate severity (score of 3 or more) in one body area. If these criteria are fulfilled, a diagnosis of probable TD is made. For case finding, the threshold value for NIA was a BARS global score of 2 or more (scale range 0–5), For NIP, SAS mean score of 0.3 or more (scale range 0–4). TD cases were defined by AIMS., which require at least moderate dyskinetic movements in one body area or mild dyskinetic movements in two body areas. B.Scale for assessment of Efficacy- (i) Brief Psychiatric Rating Scale- BPRS is a clinician based rating scale, first published in 1962 as a 16-construct tool by Drs. John Overall and Donald Gorham, the developers added two additional items, resulting in the 18-item scale used widely today to assess the effectiveness of treatment of psychotic disorders. It has proven particularly valuable for documenting the efficacy of treatment in patients who have moderate to severe disease. BPRS scored by summing the scores from the 18 items. Record the total score and compare the total score from one evaluation to the next as the measure of response to treatment (Overall, JE, Gorham DR 1988). Usually BPRS scores correlates to the severity of illness as follows. 52 Mildly ill- BPRS total score of 32 at baseline & 1week and 30 at 2 and 4 weeks. Moderately ill- BPRS total score of 44 at baseline, 40 at 1, 2, 4 weeks. Markedly ill- BPRS score of 55 at baseline, 53 at 1&2 weeks and 52 at 4weeks. Severely ill- BPRS total score of 70 at baseline, 68 at 1 week, 67 at 2 weeks and 65 at 4 weeks. Extremely ill- BPRS total score of 85 at baseline, 89 at 1 week, 84 at 2 weeks and 88 at 4 weeks. Improvement in response to treatment is measured as percentage of reduction in baseline score from one evaluation to the next. It is as follows. Minimal improvement- percentage (%) BPRS score reductions of 24, 27, 30 at 1, 2, 4 weeks respectively. Much improvement- percentage (%) BPRS score reductions of 44, 53, 58 at 1, 2, 4 weeks respectively. Very much improvement-percentage (%) BPRS score reductions of 71, 79, 85 at 1, 2, 4 weeks respectively. No change- percentage (%) BPRS score reductions of 5, 5, 8 at 1, 2, 4 weeks respectively. Efficacy of particular drug treatment is assessed at base line level, at 2weeks, 4 weeks, 8 weeks, 12 weeks intervals by using Brief psychiatric rating scale (BPRS). Statistics used comparison of total extra pyramidal symptoms occurrence for all 4 drugs and their distribution in age, sex and diagnosis categories were compared by chi-square test with p-value.

RESULTS:

One subject in risperidone group dropped out of the study because of acute dystonia (oculogyric crisis with torticollis) which is included in EPS results but excluded in BPRS results. Table.1 shows the distribution of socio-demographic variables in olanzapine, risperidone, iloperidone and asenapine groups. Results of age variables shows majority of subjects in this study were in range of 15-29 (58.3%) followed by in range of 30-44 years (32.5%). In results of sex variables 52.5% subjects were female and 47.5% subjects were males. In results of remaining socio-demographic variables indicate no major differences in distribution. Table 2 shows the 58.3% of subjects were schizophrenics and remaining 41.6% of subjects were with bipolar affective disorders currently in mania with psychosis. Results on comparison of clinical variables between 4 groups indicate no differences in distribution of precipitating factor in the three months preceding the onset of illness and no difference in the distribution of family history of psychosis.

Table. 3(Fig.1)shows the results for age distribution in EPS. On analysis of these results majority of subjects with EPS in risperidone group (33.3%), and asenapine group (20%) were in range of 15-29 years. Where as in olanzapine and iloperidone group it was 17.6% and 12.5% respectively. 15.3% subjects in risperidone group in range of 30-44 years shown EPS whereas it is 10% for olanzapine group and no subjects shown EPS in iloperidone and asenapine group. There were 40% of subjects of risperidone group in range of 45-59 years presented with EPS, whereas it is 100% for asenapine group. In total, 20% of subjects with the EPS were in range of 15-29 years, remaining 10% are in 35-59 years age group. Fig.2 (Table.4)analsys the results of comparision of age distributions in EPS among olanzapine, risperidone, iloperidone and asenapine group, statistically there was no significant difference present. (p value= 0.23, chisquare test value=4.30). Table 5(Fig.3)shows the results for sex distribution in EPS. On analysys of these results, majority of the subjects with EPS in risperidone group were males (40%). In asenapine group, majority of the subject with the EPS were females (27.7%). It is equally distributed in olanzapine (13.3%) and iloperidone (6.6%) group. Fig.3 shows a bar diagram for the analysis of results of sex distribution in EPS. (Table.5). Fig.4 shows distribution of sex in EPS(table.6). The presence of EPS slightly higher in

males (17.5%- 10 subjects in total of 57) than females (15.8%- 10 subjects in total of 63) in this study. On analsys of the results of comparision of sex distributions among olanzapine, risperidone, iloperidone and asenapine group, statistically there was no significant difference present. (p value= 0.8, chisquare test value=0.06). Table.7(Fig.5)is results for diagnosis distribution in EPS, majority of the subjects with schizophrenia in risperidone group (30%) and subjects with BPAD currently in mania with psychosis in asenapine group (23.5%) presented with the EPS. In the olanzapine group, all the EPS occurred in subjects with the schizophrenia (21%). In iloperidone group, the presence of eps is slightly higher in schizophrenic subjects than subjects with bipolar affective disorder. Figure 5 represents the results for diagnosis distribution in EPS. But Fig.6 on analsys of the results of comparision of diagnosis distributions among olanzapine, risperidone, iloperidone and asenapine group, statistically there was no significant difference present (p value= 0.439, chisquare test value=0.507) (Table.8). Table.9 shows the results for comparison of total number of subjects with EPS in olanzapine risperidone iloperidone and asenapine group. Statistically there was no significant difference was present in between the groups in occurrence of EPS. (p value=0.187, chisqure test value=4.8). Table 10 shows the results for mean dose for the subjects presented with the EPS for olanzapine, risperidone, iloperidone and asenapine groups. They were 18mg/day, 6.2mg/day, 16mg/day, 18.5mg/day respectively. Table 11 shows the results for comparision of means of BARS variables of all follow-up visits with four drug groups. Analysis of variance showed statistically no significant differences between BARS variables in olanzapine, risperidone, iloperidone and asenapine groups. (p value 0.188, F=1.624). Table 12 shows the results for comparision of means of SAS variables of all follow-up visits with four drug groups. Analysis of variance showed statistically no significant differences between SAS variables in olanzapine, risperidone, iloperidone and asenapine groups. (p value 0.56, F=2.609). Table 13 & 14 shows the results of comparision for use of medication between olanzapine, risperidone, iloperidone, asenapine groups on analysys of theses results indicate 26.08% of subjects in risperidone, 16.6 % of subjects in asenapine group required THP, whereas only 10% of the subjects in the olanzapine group, 3.3% of subjects in iloperidone group require THP in this study by the end of 8weeks of study. The results also indicate that more subjects in asenapine (13.3%), risperidone (10.3%) group required propranolol for akathisia in comparision to olanzapine (8.8%), iloperidone (3.3%). Table 14 shows comparision of BPRS score between the four groups at respective days of assessment and show that the rate of improvement is highly significant (p0.005) between day 14-28 in the four drug groups. Table.16 shows the comparision of BPRS means and their reduction from its basal means between on respective days of assessment in olanzapine, risperidone, iloperidone and asenapine groups. On analysys of these results, the distribution of basal means mean at 4 weeks and mean at 12 weeks was more are less similar across all the four groups. On Analysys of variance between reduction of means at 4 weeks and 12 weeks showed statistically no significant differences between olanzapine, risperidone, iloperidone and asenapine groups. (p value 0.08, F=2.26 & p value 0.217, F=1.50 respectively.

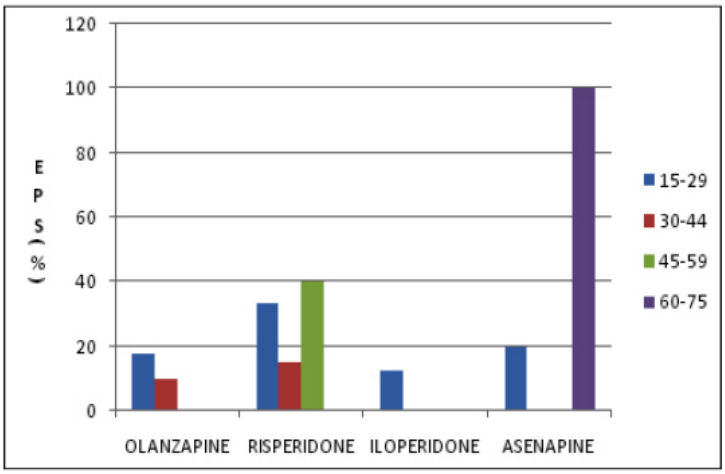

Fig.1 Bar diagram for age distribution in EPS

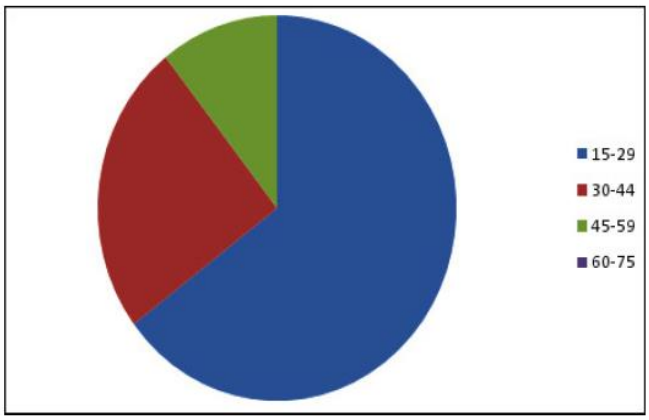

Fig.2 Pie diagram for age wise distribution of total EPS

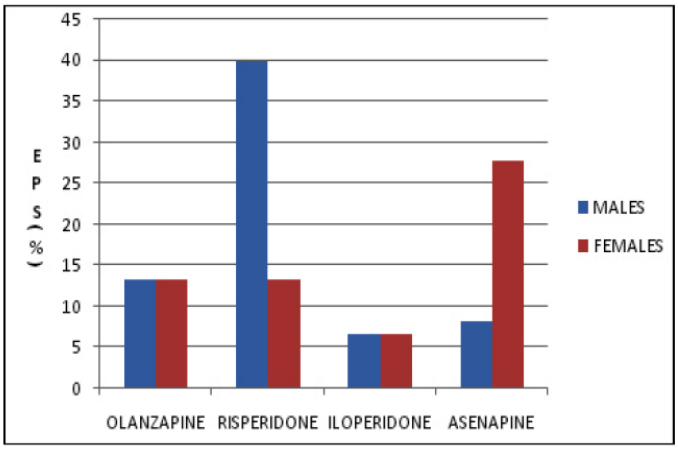

Fig.3 Bar diagram for sex distribution in EPS

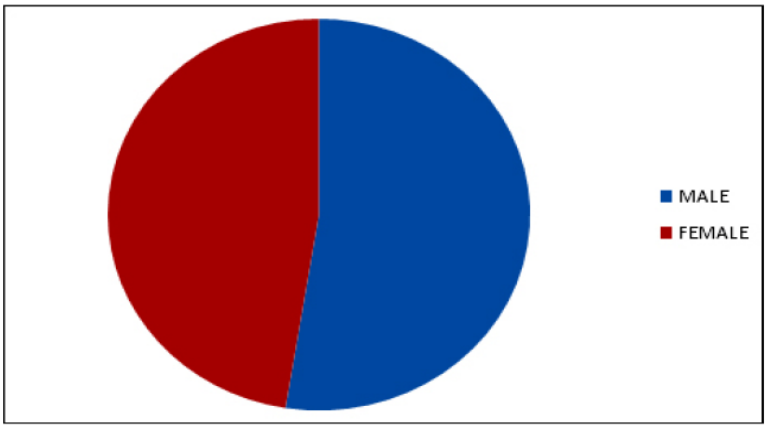

Fig.4 Pie diagram for sex wise distribution of total EPS

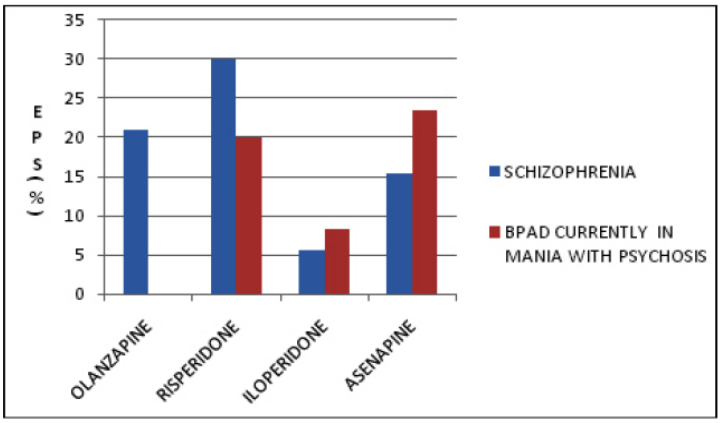

Fig.5 Bar diagram for diagnosis distribution in EPS

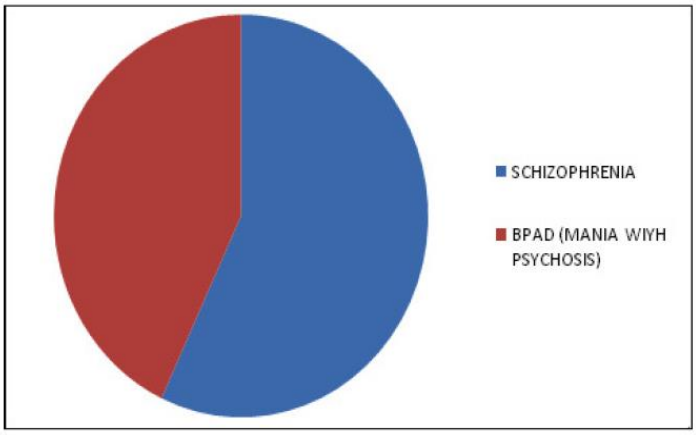

Fig.6 Pie diagram diagnosis wise distribution of total EPS

Table-1: Distribution of Sociodemographic Variables in Olanzapine, Risperidone, Iloperidone and Asenapine Groups

Socio Economic variables	Olanzapine n=30	Risperidone n=30	Iloperidone n=30	Asenapine n=30	Total n=120
Age (Yrs)					
15-29	17 (56.6)	12 (40)	16 (53.3)	25 (83.3)	25 (83.3)
30-44	10 (33.3)	13 (43.3)	12 (40)	4 (13.3)	4 (13.3)
45-5	92 (6.6)	5 (16.6)	2 (6.6)	1 (3.3)	1 (3.3)
60-7	51 (3.3)	Nil	Nil	Nil	Nil
Sex					
Male	15 (50)	15 (50)	15 (50)	12(40)	57 (47.5)
Female	15(50)	15 (50)	15 (50)	18 (60)	63 (52.5)
Education level					
Illiterate	6 (20)	3(10)	3 (10)	1 (3.3)	13 (10.8)
Upto primary	6 (20)	5 (16.6)	4 (13.3)	6 (20)	21 (17.5)
Upto high school	10 (33.3)	15 (50)	18 (60)	19 (63.3)	62 (51.6)
College level	8 (26.6)	7 (23.3)	5 (16.6)	4 (13.3)	24 (20)

Occupational status					
Student	3 (10)	2 (6.6)	6 (20)	4 (13.3)	15 (12.5)
Unemployed	4 (13.3)	4 (13.3)	6 (20)	7 (23.3)	21 (17.5)
Dailywage Earner	7 (23.3)	5 (16.6)	2 (6.6)	2 (6.6)	16 (13.3)
Housewife	9 (30)	7(23.3)	8 (26.6)	6 (20)	30(25)
Cultivator	2 (6.6)	3 (10)	4 (13.3)	4 (13.3)	13 (10.8)
Skilled labour	3 (10)	4 (13.3)	1 (3.3)	3 (10)	11(9.1)
Business	2 (6.6)	5 (16.6)	3 (10)	4 (13.3)	14(11.6)
Marital status					
Married	16 (53.3)	16 (53.3)	18 (60)	11 (36.6)	61(50.8)
Unmarried	13 (43.3)	8 (26.6)	11 (36.6)	18 (60)	50(41.6)
Widowed	1 (3)	6 (20)	1 (3.3)	1 (3.3)	9(7.5)
Place of locality					
Rural	13 (43.3)	10 (33.3)	13 (43.3)	13 (43.3)	49(40.8)
Urban	7 (23.3)	10 (33.3)	5 (16.6)	7 (23.3)	29(24.1)
Semi-urban	10 (33.3)	10 (33.3)	12 (40)	10 (33.3)	42(35)
Religion					
Hindu	26 (86.6)	22 (73.3)	25 (83.3)	23 (76.6)	96(80)
Muslim	2 (6.6)	6 (20)	2 (6.6)	3 (10)	13(10.8)
Christian	2 (6.6)	2 (6.6)	3 (10)	4 (13.3)	11(9.1)

Figure in parenthesis indicate percentage

Table 2: Distribution of Diagnostic Categories (Icd-10) and Clinical Variables in Olanzapine, Risperidone, Iloperidone and Asenapine Groups

Socio Economic variables	Olanzapine n=30	Risperidone n=30	Iloperidone n=30	Asenapine n=30	Total n=120
Diagnostic Categories					
Schizophrenia	19 (63.3) (F 20)	20 (66.6)	18 (60)	13 (43.3)	70 (58.3)
Bipolar Affective	11 (36.6)	10 (33.3)	12 (40)	17 (56.6)	50 (41.6)
Disorder currently In mania with Psychosis	(F30.2,31.2)	-	-	-	-
Clinical variables					
i. Precipitating factors (in preceding 3months)					
Present	13 (43.3)	14 (46.6)	12 (40)	13 (43.3)	52 (43.3)
Absent	17 (56.6)	16 (53.3)	18 (60)	17 (56.6)	68 (56.6)
ii. Family history of psychosis (first and second degree relative)					
Present	6 (20)	7 (23.3)	4 (13.3)	7 (23.3)	24 (40)
Absent	24 (80)	23 (76.6)	26 (86.6)	23 (76.6)	96 (60)

Figure in parenthesis indicate percentage

Table 3: Age Distribution In Eps

Age in years	Olanzapine n=30	Risperidone n=30	Iloperidone n=30	Asenapine n=30	Total n=120
15-29	3 (17.6) (n=17)	4 (33.3) (n=12)	2 (12.5) (n=16)	5 (20) (n=25)	14 (20) (n=70)
30-44	1 (10) (n=10)	2 (15.3) (n=13)	NIL (n=12)	NIL (n=4)	3 (7.6) (n=39)
45-59	NIL (n=2)	2 (40) (n=5)	NIL (n=2)	1 (100) (n=1)	3 (2.5) (n=10)
60-75	NIL (n=1)	NIL (n=0)	NIL (n=0)	NIL (n=0)	NIL (n=1)
Mean age ± SD	30.33 ±9.9	33.3 ±9.6	29.2 ±7.61	24.73 ±7.27	29.4 ±3.56
Mean age of patiens with EPS	25.72 ±10.2	31.82 ±13.1	6 1.41	26.6 ±11.8	25.5 ±2.89

Figure in parenthesis indicate percentage

Table 4: Comparison of age distribution in eps in 4 drug Groups.

Age in years	EPS	NO EPS	CHISQURE TEST	SIGNIFICANCE (p value)
15-29	14	56	4.30	0.23 (not significant)
30-44	03	36		
45-59	03	07		
60-75	0	01		

Table 5: Sex distribution in eps

Drugs	Male	Female
Olanzapine (n=30)	2 (13.3) (n=15)	2 (13.3) (n=15)
Risperidone (n=30)	6 (40) (n=15)	2 (13.3) (n=15)
Iloperidone (n=30)	1 (6.6) (n=15)	1 (6.6) (n=15)
Asenapine (n=30)	1 (8.3) (n=12)	5 (27.7) (n=18)
Total	10 (17.5) (n=30)	10 (15.8) (n=30)

Table 6: Comparison of sex distribution in eps in 4 drug groups.

SEX	EPS	NO EPS	CHISQURE TEST	SIGNIFICANCE (p value)
Male	10	47	0.06	0.8
Female	10	53		

Table 7: Diagnosis Distribution In Eps

Drugs	Schizophrenia	BPAD
Olanzapine (n=30)	4 (21) (n=19)	NIL (n=11)
Risperidone (n=30)	6 (30) (n=20)	2 (20) (n=10)
Iloperidone (n=30)	1 (5.5) (n=18)	1 (8.3) (n=12)
Asenapine (n=30)	2 (15.3) (n=13)	4 (23.52) (n=17)
Total (n=120)	3 (18.5) (n=70)	7 (14) (n=50)

Table 8: Comparison of diagnosis distribution in eps in 4 drug groups.

Diagnose	EPS	NO EPS	CHISQURE TEST	SIGNIFICANCE (p value)
Schizophrenia	13	57	0.439	0.507 (Not Significant)
BPAD	07	43		

Table 9: Comparison Of Occurrence Of EPS 4 Drug Groups

Diagnose	EPS	NO EPS	CHISQURE TEST	SIGNIFICANCE (p value)
Olanzapine	04	26	4.8	0.187 (Not Significant)
Risperidone	08	22		
Iloperidone	02	28		
Asenapine	06	24		

Table 10: Mean Dose Of Eps Occurred

Drugs	Mean dose	Chlorpromazine 100mg/day dose equivalents
Olanzapine	18 mg/day	5 mg/day
Risperidone	6.2 mg/day	2 mg/day
Iloperidone	16 mg/day	6 mg/day
Asenapine	18.5 mg/day	5 mg/day

Table 11: Comparison of bars variables in eps in 4 drug groups.

Diagnose	MEAN±SD	F	SIGNIFICANCE (p value)
Olanzapine	0.36±0.38	1.624	0.188 (Not Significant)
Risperidone	0.57±0.46		
Iloperidone	0.39±0.32		
Asenapine	0.52±0.42		

Table 12: Comparison of sas variables in eps in 4 drug groups.

Diagnose	MEAN±SD	F	SIGNIFICANCE (p value)
Olanzapine	0.13±0.13	2.609	0.55 (Not Significant)
Risperidone	0.21±0.6		
Iloperidone	0.11±0.06		
Asenapine	0.16±0.14		

Table 13: Requirement of adjunct medication for eps.

Adjunct Medication For EPS	Olanza-Pine (n=30)	Risper-Done (n=29)	Iloper-Done (n=30)	Asena-Pine (n=30)	Chi-Squre Test	Signi-ficance
THP (2 mg)						
Received	3 (10)	6 (26)	1 (33)	5 (16.6)	2.82	0.42
Not received	27 (90)	23 (74)	29 (96.7)	25 (83.4)		(NS)
Propranolol (40mg)						0.83
Received	2 (6.6)	3 (10.3)	1 (3.3)	4 (13.3)	0.868	(NS)
Not received	28 (93.4)	26 (89.7)	29(96.7)	26 (86.7)		

Table 14: comparative use of adjunct medication between olanzapine, risperidone, iloperidone and asenapine grooups.

MEDICATION	OLANZAPINE				Risperidone				Iloperidone				Asenapine			
	2 wk	4 wk	8 wk	12 wk	2 wk	4 wk	8 wk	12 wk	2 wk	4 wk	8 wk	12 wk	2 wk	4 wk	8 wk	12 wk
THP (2 mg/day)	Nil	Nil	33 (10)	33 (10)	Nil	2 (6.6)	4 (26.6)	6 (26.6)	Nil	Nil	1 (3.3)	1 (3.3)	Nil	1 (3.3)	4 (16.6)	5 (16.6)
Propranolog (402 mg/day)	1 (3.3)	1 (3.3)	1 (3.3)	Nil	3 (10)	3 (10)	2 (6.6)	Nil	Nil	1 (3.3)	Nil	Nil	Nil	3 (10)	1 (16.6)	4 (16.6)

Olanzapine											
Day 0 Mean ±SD	Day 14 Mean ±SD	p value	Day 0 Mean ±SD	Day 28 Mean ±SD	p value	Day 0 Mean ±SD	Day 84 Mean ±SD	p value	Day 14 Mean ±SD	Day 28 Mean ±SD	p value
63.16 ±4.53	36.2 ±7.44	p<0.001	63.16 ±4.53	29.3 ±6.13	p<0.001	63.16 ±4.53	27.4 ±7.34	p<0.001	36.2 ±7.44	29.3 ±6.13	p<0.30

Table.15: comparision of changes in bprs scores between respective days of assessment in olanzapine, risperidone, iloperidone and asenapine groups.

Resperidone											
Day 0 Mean ±SD	Day 14 Mean ±SD	p value	Day 0 Mean ±SD	Day 28 Mean ±SD	p value	Day 0 Mean ±SD	Day 84 Mean ±SD	p value	Day 14 Mean ±SD	Day 28 Mean ±SD	p value
63.75 ±5.79	38.68 ±8.98	p<0.001	63.75 ±5.79	29.86 ±7.49	p<0.001	63.75 ±5.79	27.62 ±7.91	p<0.001	38.68 ±8.98	29.86 ±7.49	p<0.34
Iloperidone											
Day 0 Mean ±SD	Day 14 Mean ±SD	p value)	Day 0 Mean ±SD	Day 28 Mean ±SD	t (p value)	Day 0 Mean ±SD	Day 84 Mean ±SD	t (p value)	Day 14 Mean ±SD	Day 28 Mean ±SD	t (p value)
64.0 ±4.57	40.0 ±7.62	p<0.001)	64.0 ±4.57	31.53 ±8.12	19.08 (p<0.001>	64.0 ±4.57	28.4 ±7.63	19.08 <p0.001>	40.0 ±7.62	31.53 ±8.12	4.16 (p<0.73)
Asenapine											
Day 0 Mean ±SD	Day 14 Mean ±SD	t (p value)	Day 0 Mean ±SD	Day 28 Mean ±SD	t (p value)	Day 0 Mean ±SD	Day 84 Mean ±SD	t (p value)	Day 14 Mean ±SD	Day 28 Mean ±SD	t (p value)
63.56	38.5 ±4.83	16.95 (p<0.001)	63.56 ±4.83	30.36 ±7.17	21.03 (p<0.001)	63.56 ±4.83	28.93 ±7.96	20.37 (p<0.001)	38.5 ±4.83	30.36 ±7.17	4.60 (p<0.60)

Table 16: Comparision Of BPRS Means And Their Reduction From Its Basal Means Between Respective Days Of Assessment In Olanzapine, Risperidone, Iloperidone And Asenapine Groups.

Drug	Baseline (BL) Mean±SD	Mean at 4 weeks Mean±SD	Mean at 12 weeks Mean±SD	Reduction of Mean at 4 wks(BL - mean at Mean 4wks)	Reduction of Mean at 12 wks(BL - mean at Mean 12wks)	F(for reduction of mean at 4 weeks)	F(for reduction of mean at 4 weeks)
Olanzapine	63.16 ±4.53	29.3 ±6.13	27.4 ±7.34	33.86	35.7	2.26 (p=0.08) (NS)	1.50 (p=0.217) (NS)
Risperidone	63.75 ±5.79	29.86 ±7.49	27.62 ±7.91	33.89	36.13		
Iloperidone	64.0 ±4.57	31.53 ±8.12	28.4 ±7.63	32.47	35.6		
Asenapine	63.56 ±4.83	30.36 ±7.17	28.93 ±7.96	33.2	34.63		

DISCUSSION:

Using variety of measures of dystonia, parkinsonism, akasthisia and tardive dyskinesia the analysys of incidence rates and continuous rating scale measures from this study shows no consistent substantial or stastically significant differences between all 4 drugs i.e. olanzapine, risperidone, iloperidone and asenapine. Currently there are little number of studies in comparing the EPS and the efficacy of asenapine & iloperidone, olanzapine & risperidone. But evidence from various trails discussed here indicate these SGAs appear to have a lower propensity to induce motor symptoms. In this study 30 participants were allocated for each drug and comparisions are madeout between olanzapine, risperidone, iloperidone and asenapine. Total 4 (13.3%) participants were presened with EPS with olanzapine, among them one with NIA, two with NIP and one with NIA&NIP. There were no TD and acute dystonias are found with olanzapine in this study. For risperidone total 8 participants (26.6%) were presented with EPS, among them one with NIA, 4 with NIP, 2 with NIA&NIP and one case of dystonia involving eyes & neck (ie. Oculogyric crisis). There were no TD are found with risperidone in this study For iloperidone only 2 cases (6.6%) of EPS are found. One with NIA another one with NIP. For asenapine total 6 participants (20%) were presened with EPS, among them two subjects with NIA, 3 subjects with NIP and 1 subject with NIA&NIP. There were no TD and acute dystonias are found with iloperidone in this study. On statistical analysys there were no significant differences found in BARS SAS variables among four drugs and also in between olanzapine & risperidone and iloperidone & asenapine. All are similar to each other in EPS profile. In this study EPS is more commonly occurred in age group in range of 15- 29 years, majority of subjects were with schizophrenia, almost equal occurrence in either sex. But statistically no significant difference is present in these distributions among the four groups. Overall in yhis study 10 subjects (8.3%) were presented with NIA, 13 subjects (10.8%) were presented with NIP, one subject presented with acute dystonia (1%) and no subject presented with tardive dyskinesia in this 12 week study. the total EPS constitutes for 20%. EPS more common in elderly females those with pre-existing neurological damage[16,17,18] reported that acute akathisia occurs approximately in 25% of patients treated with an atypical antipsychotics. Whereas data from CATIE trails shows that akathisia occurs in 10- 20% of patients treated with SGAs which was less than 20-52% when FGAs were used. But there was no significant age and gender such as a predisposing factor has been found[18,19,20], found that acute dystonias were 2-3% in subjects treated with neuroleptics, in first few days after the treatment. But they were more common in young males, in neuroleptic naïve, with high potency drugs like haloperidol than SGAs. (APA 1997) APA task force study (1993) corell et al., (2004) reported that TD found 5% of patients per year of antipsychotic exposure, more common in elderly women, those with affective illness. Those who had acute EPS early on in 73 treatment. According to Corell Et Al. (2004) study TD with atypical antipsychotics treatment incidence is significantly lower than FGA. When risperidone and olanzapine used the incidence becomes the same as (0.5-1%) spontaneous TD in patients with schizophrenia. In this study, 26.08% of subjects in risperidone group, 16.6 % of subjects in asenapine group required THP, whereas only 10% of the subjects in the olanzapine group, 3.3% of subjects in iloperidone group required THP by the end of 8weeks of study and the more subjects in asenapine (13.3%), risperidone (10.3%) group required propranolol for akathisia in comparision to olanzapine (8.8%), iloperidone (3.3%). In this study BPRS is taken as measure of efficacy which is applicable to all psychotic disorders. Initially the total score is recorded at baseline this score is

compared from one evaluation to the next as the measure of response to the treatment. In our study baseline BPRS means are 63.16 for olanzapine, 63.75 for risperidone, 64 for iloperidone and 63.56 for asenapine. So the severity of illness is more or less similar to all 4 drugs. After the treatment with concerning drug for 12 weeks the change in BPRS mean is also similar to each other. It is 27.46 for olanzapine, 27.62 for risperidone, 28.4 for iloperidone and 28.93 for asenapine. The percentage of change in BPRS score after the treatment for 12 weeks is similar to each other, i.e. 65.5% for olanzapine, 56.67% for risperidone, 55.62% for iloperidone and 54.48% for asenapine. But stastically there was no significant difference present among them. This gives the inference that all the 4 drugs had similar efficacy in controlling psychotic symptoms. Currently there were no studies comparing directly the EPS and efficacy profile of asenapine and iloperidone with olanzapine and risperidone. Many of the studies were placebo controlled. Potkin et al. (2007) compared asenapine with risperidone found significantly more recovery with asenapine and risperidone in terms of PANSS & CGI in schizophrenia. Peter j weiden et al. (2008) compared iloperidone with risperidone in their EPS and efficacy profile in treatment of schizophrenia and the results were consistent with this study. The compared asenapine and olanzapine in bipolar affective disorder mania & mixed episodes, reported statistically significant remission in terms of YMRS score. compared asenapine, olanzapine in schizophrenia and bipolar I disorders, they reported that the treatment emergent EPS with asenapine however had been found to be higher than that with olanzapine. Asenapine was more likely to cause akathisia than olanzapine. The compared iloperidone and risperidone in an hospitalized schizophrenia patients, shown similar efficacy rates in BPRS which were similar to this study. EPS rates were 5% with iloperidone and 10% with risperidone. Arpi minassianjaved W young et al. (2010) compared asenapine with risperidone in treatment of schizophrenia, they reported that rates of EPS with asenapine treatment lower or equivalent risperidone. There was increase in rates of akathisia with 10mg BD dose of asenapine than 5mg BD dose of asenapine. They found that asenapine and risperidone were similar in reducing positive symptoms in schizophrenia. The compared iloperidone with risperidone in schizophrenia, changes in BPRS score were consistent with this study, stated that both iloperidone and risperidone were similar in their efficacy. The compared iloperidone with risperidone in treatment of schizophrenia, they found that iloperidone had low EPS rates than with risperidone. The EPS rates were more or less similar to this study for risperidone (29.9% with 4-8 mg/day) but for iloperidone EPS rates were higher than this study (18% 8-24mg/day). The BPRS scores shown statistically significant improvement from their baseline scores with iloperidone and risperidone. Roger S mcintyre et al. (2012) compared olanzapine with asenapine in bipolar mania and schizophrenia and they found that EPS rates of 15% with asenapine and 13% with olanzapine which were similar to this study. Ludovic samalin et al. (2013) compared asenapine and olanzapine in bipolar I disorders. They reported treatment emergent EPS are10% with asenapine, 9.4% with olanzapine and 5% with placebo, which were similar to this study. Greatest incidence occurred with the highest dose of asenapine (10mg twice daily).

CONCLUSIONS:

The present study a total number of 120 patients suffering from psychotic disorder were treated primarily with 4 agents in single i.e. olanzapine, risperidone, iloperidone and asenapine for 12 weeks. They are followed-up at regular intervals for EPS and efficacy profile by using various standardized rating scales. Total EPS observed is 13.3% for olanzapine, 26.6% for risperidone, 6.6% for iloperidone and 20% for asenapine. Overall EPS in this study is 20% for four drug groups in subjects of 120. The percentage of change in BPRS scores were 65.5% for olanzapine, 56.67% for risperidone, 55.62% for iloperidone and 54.48% for asenapine. According to this study all the 4 drugs were similar to each other in inducing EPS and in their efficacy profile in treatment of psychotic disorders. The increasing awareness of this ascociation among clinicians will help to prevent, detect and treat EPS which interferes with the compliance of the treatment regimen. The occurrence of treatment emergent EPS and changes in EPS rating scales indicated that all the 4 drugs were similar to each other in causing EPS. And it also concluded that iloperidone & asenapine were similar to olanzapine & risperidone in their EPS profile. Regarding efficacy profile, this study concludes that all the 4 drugs and iloperidone & asenapine and olanzapine & risperidone were similar to each other in treatment of psychotic disorders.

Conflicts of interest:

No conflicts of interest from any author regarding the publication of this article.

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List of Abbrevations:

5HT : 5 Hydroxy Tryptamine
AIMS : Abnormal Involuntary Movement Scale
ANOVA : Analysis Of Variance
BARS : Barnes Akathisia Rating Scale
BPRS : Brief Psychiatric Rating Scale
D2 : Dopamine Receptor Subtype
DSM IV : Diagnostic Statistical Manual 4th Edition
EPS : Extrapyramidal Symptoms/ side-effects
GABA : Gama Amino Butyric Acid
ICD-10 : International Classification Of Diseases 10th Edition
NIA : Neuroleptic Induced Akathisia
NIMD : Neuroleptic Induced Movement Disorder
NIP : Neuroleptic Induced Parkinsonism
NITD : Neuroleptic Induced Tardive Dyskinesia
NMS : Neuroleptic Malignant Syndrome
PsA : Pseudoakathisia
PD : Parkinsons Disease
RCT : Randomised Control Trails
SAS : Simpson Angus Scale
SGA : Second Generation Antipsychotics
TD : Tardive Dyskinesia

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