

Comparative Safety Profile of Single Versus Combination Antipsychotic Therapy by Using Glassgow Antipsychotic Side Effect Scale (Gass)

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Abstract

Background: The considerable controversies exist regarding the clinical safety of first and second-generation antipsychotics and their different combinations frequently prescribed for schizophrenia and bi-polar disorders.

Objective: The prime intent of the study was to compare the side effect profiles of first and second-generation antipsychotic drugs, either single or combination, in patients with schizophrenia and bipolar disorder.

Methods: In this cross-sectional observational study, Glassgow Antipsychotic Side effect Scale (GASS), a validated self-assessment and self-rating scale for determining side effects of antipsychotics, was used for grading purpose. The study was conducted by enrolling a total of 252 patients.

Results: Out of 252 patients, 21.83% were using first generation antipsychotics (FGAs), 44.04% were using second generation antipsychotics (SGAs) and 34.13% were using combination of the first and second generation antipsychotics. A total of 57.9% of patients suffered from mild and 42.06% patients experienced moderate side effects after using different antipsychotics. The findings indicated greater risk of side effects of antipsychotics in female gender based on GASS score (Male;18.82, Female; 22.00, $p=0.014$). On the other hand, demographic factors like age ($p=0.185$), marital status ($p=0.655$), education ($p=0.128$), family history of psychosis ($p=0.496$) and history of substance ($p=0.736$) were not significantly associated with overall side effects. However, patients doing exercise experienced fewer side effects as compared to those patients who were having sedentary life style (17.42 vs 20.51, $p=0.006$). Mean GASS score was least in case of combination therapy of FGAs and SGAs which showing that antipsychotic drugs were better tolerance when used in combination (FGAs: 20.51, SGAs: 20.05, Combination: 18.12).

Conclusion: This study manifested that the differences between antipsychotics were subtle, but precise and distinguishable. These findings depicted the general notion that risk of side effects significantly increased in patients on mono-therapy as compared to those who were using combination of FGA and SGA.

Keywords: Antipsychotic drugs; Safety; GASS; Monotherapy; Combination Therapy

Introduction

Schizophrenia is a cluster of different psychological disorder notable by disruptive thoughts and behaviours and characterized by hallucinations, delusions, aggression, hyperactivity and insomnia [1,2]. Bipolar disorder is generally characterized by mood variations with frequent episodes of depression, mania and mixed state [3]. Antipsychotic drugs act either by blocking dopaminergic or serotonin receptors and are used to treat symptoms of schizophrenia and bipolar disorder [4]. Most of the newer antipsychotic agents inhibit serotonin receptor [5]. Previously disease was treated with first generation antipsychotics (FGAs) but due to potential toxicity and side effects, lately, newer class of second generation antipsychotics (SGAs) were developed with lesser side effects [6]. FGAs affect basal ganglia and cortical areas of brain whereas second generation cause enlargement of thalamus [7]. Extra pyramidal side effects (EPS) include dystonia, akathisia, tardive dyskinesia and parkinson like symptoms which may lead to therapy related problems resulting in noncompliance among patients [8,9]. Antipsychotics-induced weight gain, endocrine imbalance and hyperlipidemia which may lead to diabetes mellitus, hyperprolactinemia, hypertension, orthostatic hypotension, coronary artery disease, seizures and stroke [10,11].

Newer SGAs have better control over negative symptoms [12] and extra pyramidal side effects along with more efficacious response to the delusions and hallucinations in those patients who don't reciprocate to other antipsychotics [13]. Nonetheless, the newer second generations are more likely to cause metabolic side effects [14]. Older conventional FGA which bind very tightly to dopaminergic receptors have more pronounced side effects linking with movement disorder, like haloperidol, as compared to those drugs that form weak bonds with dopaminergic receptors like Chlorpromazine [15]. Some of SGA have added side effects when compared with the rest of the class, therefore, in selecting the drug, physician should keep in mind treatment related disease symptoms together with efficacy [16]. Among these, olanzapine is

most notorious because of its side effects, such as weight gain and increment of blood glucose levels [17].

Polypharmacy of antipsychotic drugs in schizophrenia and bipolar disorder is being most commonly practiced from past many years [18]. Combination of first and second generation antipsychotics is comparatively condensing upon monotherapy in critically ill patients, however significant evidence regarding effectiveness of combination therapy is not present in literature and further clinical trials are needed in this respect [18,19]. The basic proposed working hypothesis of this study was to prove that monotherapy has rather more severe adverse effects as compared to combination of first and second generation antipsychotics. Therefore, we had done this observational study to compare the side effect profile of mono versus combination antipsychotic therapy among schizophrenic and bipolar disorder patients in Punjab Institute of Mental Health (PIMH) and Fountain House Lahore, Pakistan.

Methodology

A cross sectional observational study was designed to assess the side effects of antipsychotics in schizophrenia and bipolar patients presenting to two major hospitals of Lahore including Punjab Institute of Mental health and Fountain House. Ethical approval for the study was obtained from Ethical committee on human research, University of the Punjab and medical directors of both the hospitals. Selection criteria were majorly inclusive and were least exclusive. A total of 252 patients, willing to give their information and stable on medication for the last one year irrespective of age, gender, education and ethnic background, were enrolled in the study. Diagnosis of patients was being done by qualified physicians of both hospitals based on DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition Text Revision). Manual describes the diagnostic criteria for this disease which states that ailment is present if pertinacious dysfunction persists longer than 6 months and more than two symptoms like delusions, hallucination and negative symptoms exist for at least

the month [20]. Patients with epilepsy and concomitant disease of other organs were excluded from the study. A group of six final professional Pharm.D graduates collected the data, having thorough knowledge of the disease. Informed consent was obtained from all the enrollees as per hospital policy.

In this study Glasgow Antipsychotic Side effect Scale (GASS), a validated self-assessment and self-rating scale for determining side effects of antipsychotics, was used for grading purpose. Total GASS scoring from 0-21 indicates mild side effects, 22-42 indicates moderate side effects and 43 or more than this indicates severe side effects. There are several antipsychotic side effect rating scales that were used previously, majority of them are extensive, time taking and focussing on merely akathisia or extra pyramidal side effects [21]. It is relatively new, convenient, handy, time saving and patient friendly scale that is covering all aspects. A comprehensive questionnaire along with the 22 items GASS, fulfilling the project needs and objectives was prepared.

Data and Statistical Analysis

The data was analysed using the SPSS software (IBM, version 22) to estimate the side effects of first generation, second generation and their combination. Descriptive statistics was performed using SPSS. Chi square test was applied for nominal data, kruskal-wallis for ordinal data and independent sample t-test and analysis of variance (ANOVA) for continuous data. A p-value less than 0.05 was considered significant.

Results

As per the data, out of 252 patients, 21.83% were using FGA, 44.04% were using SGA and 34.13% were using combination, both first and second-generation.

Patient Demographics and Clinical Characteristics

Patient demographics and clinical characteristics are summarized in (Table 1). The occurrence of schizophrenia was more frequent in males as per antipsychotic usage (FGAs; 76.4%, SGAs; 82.9%, Combination; 75.5%) compared to females, and more likely to affect unmarried (FGAs; 63.6%, SGAs; 63.1%, Combination; 52.3%). Out of total 252 patients, 70.9% educated people were on different types of antipsychotics ($p=0.604$). Overall 45.3% patients were unemployed taking combination treatments ($p=0.496$). Moreover, 67.4% patients that were on combination drugs didn't have any of the psychiatric diseases in their families including blood relations i.e. in their parents, grandparents and siblings. This study also revealed that 58.2% patients taking first generation antipsychotics were not addicts, while 76.6% people taking combination of neuroleptics were normotensive before starting antipsychotics. A total of 56 patients out of 252 patients were diagnosed with bipolar disorder and among them 20.9% were on combination of Antipsychotics along with other medications.

Parameters	FGAs (n=55)	SGAs (n=111)	Combination (n=86)
Gender_no. (%)			
Male	42 (76.4%)	92 (82.9%)	65 (75.5%)
Female	13 (23.6%)	19 (17.1%)	21 (24.4%)
Marital Status_no. (%)			
Married	20(36.4%)	41(36.9%)	41(47.7%)
Single	35(63.6%)	70(63.1%)	45(52.3%)
Education_no. (%)			
Educated	36(65.5%)	81(73%)	61(70.9%)
Uneducated	19(34.5%)	30(27%)	25(29.1%)
Occupation_no. (%)			
Govt.job	2(3.6%)	2(1.8%)	0 (0%)
Private	8(14.5%)	23(20.7%)	13(15.1%)
Self	19(34.5%)	44(39.6%)	34(39.5%)
Unemployed	26(47.3%)	42(37.8%)	39(45.3%)
Family history_no. (%)			
No	31(56%)	70(63.1%)	58(67.4%)
Yes	24(43.6%)	41(36.9%)	28(32.6%)
Drugabuse_no. (%)			
Non Abusers	32(58.2%)	53(47.7%)	42(48.8%)

Abusers	23(41.8%)	58(52.3%)	44(51.2%)
Exercise_no. (%)			
Yes	15(27.3%)	41(36.9%)	27(31.4%)
No	40(72.7%)	70(63.1%)	59(68.6%)
Blood Pressure_no. (%)			
Normotensive	47(85.5%)	94(84.7%)	66(76.7%)
Hypertensive	8(14.5%)	17(15.3%)	20(23.3%)
Diagnose no. (%)			
Schizophrenia	48(87.27%)	80(72.07%)	68(79.07%)
Bipolar Disorder	7(12.72%)	31(20.12%)	18(20.9%)

Table 1: Patient Demographics, Personal Information and Clinical Presentation.

Grading of Side Effects of Antipsychotic Drugs Based on GASS

The frequencies of side effects in all three arms, FGAs, SGAs and combinations, are summarized in (Table 2 & Figure 1). When data was segregated based on mild and moderate side effects as per GASS criteria, in FGAs group, fluphenazine exhibited higher frequencies of side effects, mild (42.4%) and moderate (36.4%), followed by flupentixol (mild; 24.3%, moderate; 31.8%) and haloperidol (mild; 18.2%, moderate; 27.3%) (Table 2). When SGAs group was examined for side effects,

risperidone demonstrated higher frequencies of side effects (mild; 67.8%, moderate; 75%) followed by olanzapine (mild; 20.4%, moderate; 13.4%), quetiapine (mild; 6.8%, moderate; 9.6%) and clozapine (mild; 3.4%, moderate; 1.9%) (Table 3). More interestingly, combination group, FGAs + SGAs, demonstrated significantly lower frequencies of side effects except for risperidone + fluphenazine group (mild; 66.7%, moderate; 50%), followed by some observations in risperidone + haloperidol group (mild; 13%, moderate; 12.5%) (Table 2).

Drugs	Mild Side Effect	Moderate Side Effects	Total
FGAs			
Haloperidol_no. (%)	6/33(18.2%)	6/22(27.3%)	12/55(21.8%)
Fluphenazine_no. (%)	14/33(42.4%)	8/22(36.4%)	22/55(40%)
Flupentixol_no. (%)	8/33(24.3%)	7/22(31.8%)	15/55(27.3%)
Trifluoperazine_no. (%)	3/33(9.1%)	1/22(4.5%)	4/55(7.3%)
Zuclopenthixoldihydrochloride_no. (%)	2/33 (6.1%)	0	2/55(3.6%)
SGAs			
Risperidone_no. (%)	40/59(67.8%)	39/52(75%)	79/111(71.2%)
Olanzapine_no. (%)	10/59(20.4%)	7/52(13.4%)	17/111(15.3%)
Quetiapine_no. (%)	4/59(6.8%)	5/52(9.6%)	9/111(8.1%)
Clozapine_no. (%)	2/59(3.4%)	1/52(1.9%)	3/111(2.7%)
Aripiprazole_no. (%)	3/59(1.7%)	0	3/111(2.7%)
Combination of FGAs & SGAs			
Risperidone+ Fluphenazine_no. (%)	36/54(66.7%)	16/32(50%)	52/86(60.5%)
Fluphenazine+ Olanzapine_no. (%)	1/54(1.9%)	3/32(9.4%)	4/86(4.7%)
Risperidone +quetiapine+ Flupentixol_no. (%)	1/54(1.9%)	2/32(6.3%)	3/86(3.5%)
Olanzapine+ Risperidone+ Fluphenazine_no. (%)	2/54(3.7%)	0	2/86(2.3%)
Risperidone+ quetiapine+ Fluphenazine_no. (%)	1/54(1.9%)	0	1/86(1.2%)
Risperidone+ Zuclopenthixol_no. (%)	1/54(1.9%)	1/32(3.1%)	2/86(2.3%)
Risperidone + Flupentixol_no. (%)	2/54(3.7%)	2/32(6.3%)	4/86(4.7%)
Haloperidol+ quetiapine_no. (%)	1/54(1.9%)	0	1/86(1.2%)
Fluphenazine+ haloperidol+ Olanzapine_no. (%)	1/54(1.9%)	3/32(9.4%)	4/86(4.7%)
Fluphenazine+ Risperidone +zuclopenthixol_no. (%)	1/54(1.9%)	1/32(3.1%)	2/86(2.3%)
Risperidone + haloperidol_no. (%)	7/54(13%)	4/32(12.5%)	11/86(12.8%)

Table 2: Side Effects of Fgas, Sgas and Combinations Based on Gass.

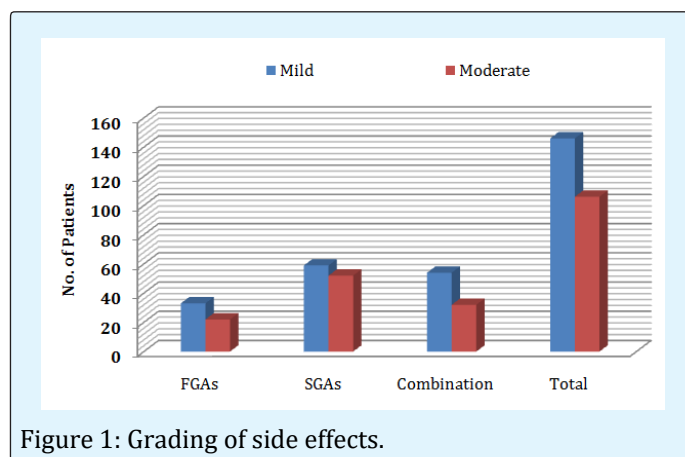


Figure 1: Grading of side effects.

Parameters	No. (%)	Mean±S.D	p-value
Gender			
Male	199 (78.9%)	18.82±8.19	0.014*
Female	53 (21%)	22.00±8.61	
Age			
<30	116(46.03%)	20.25±8.20	0.185
>30	136(53.97%)	18.84±8.42	
Marital Status			
Married	102(40.5%)	19.21±8.28	0.655
Unmarried	150(59.5%)	19.69±8.44	
Education			
Educated	178(70.6%)	19.07±8.25	0.218
Uneducated	74(29.4%)	20.50±8.61	
Family history			
No	159(63.1%)	19.77±8.71	0.496
Yes	93(36.9%)	19.02±7.77	
Substance abuse			
Non Abusers	127(50.4%)	19.31±8.74	0.736
Abusers	125(49.6%)	19.67±7.80	
Exercise			
Yes	83(32.9%)	17.42±8.97	0.006*
No	169(67.1%)	20.51±7.88	
Blood Pressure			
Normotensive	207(82.1%)	19.25±8.21	0.318
Hypertensive	45(17.9%)	20.62±9.08	
Type of Antipsychotic Drug			
FGA	55(21.8%)	20.51±9.34	0.036*
SGA	111(44.1%)	20.05±7.93	
Combination	86(34.1%)	17.45±7.28	

Table 3: GASS score classified by demographic and clinical characteristics.

GASS Score Classified by Demographic Characteristics

As shown in table 3, gender was found to be more significantly associated with GASS score. The finding indicated that females were having higher GASS score as compared to male patients which was indicating greater risk of side effects of antipsychotics in female gender. As shown in (Table 3), mean GASS score for male and female gender were 18.82 and 22.00 respectively ($p=0.014$). On the other hand, demographic factors like age ($p=0.185$), marital status ($p=0.655$), education ($p=0.128$), family history of mental illnesses ($p=0.494$) and history of drug substance abuse ($p=0.736$) were not significantly associated with overall GASS score. However, patients doing exercise experienced fewer side effects as compared to those patients who were having sedentary life style (17.42 vs 20.51 $p<0.05$ i.e. $p=0.006$). On the whole, there was non-significant association among the type of antipsychotic drugs and GASS. However, mean GASS score was least in case of combination therapy of FGAs and SGAs which showing that antipsychotic drugs were better tolerance when used in combination (FGAs: 20.51, SGAs: 20.05, Combination: 17.45).

Discussion

There are numerous antipsychotic side effect rating scales that were used previously like Simpson-Angus Scale (SAS), Barnes Akathisia Scale, Abnormal Involuntary Movement Scale (AIMS), Extrapyramidal Side Effect Rating Scale (ESRS), Antipsychotic Non-Neurological Side-effect Rating Scale (ANNSERS), Liverpool University Neuroleptic Side-Effect Rating Scale (LUNERS) and many others [22]. In this study, a new self-assessment Glasgow Antipsychotic Side Effect Scale (GASS) was used which was relatively easy, time saving, patient friendly and covers all side effects including metabolic along with extra pyramidal side effects. Several assessment scales have certain advantages and disadvantages like Simpson Angus Scale and Extra pyramidal Side Effect Rating Scale were rather easy to conduct but solely used for determination of extra pyramidal side effects. Barnes Akathisia Rating Scale and Hillside Akathisia Scale only concentrate on Akathisia. Liverpool University Neuroleptic Side Effect Rating Scale covers many areas of side effects but it is slightly lengthy and symptoms can only to be described in single word that is quite arduous for patients suffering from mental illness. Another Abnormal Involuntary Movement Scale is used that is quick to perform but only considering on abnormal movements. Side Effects Rating

Scale for the Registration of Unwanted Effects of Psychotropics and Antipsychotic Non-Neurological Side Effect Rating Scale covers several arms of side effects but slightly burdensome as it have oodles of questions. Most of these scales are quick to conduct and they differ only in covering different adverse effects. The disadvantage in using GASS is that it is self-rating scale which can account to overstate patient's symptoms [21]. The purpose of this study was to compare side effects of different types of antipsychotics by using this scale. This study portrayed that movement disorder was commonly observed in patients who were using FGAs – probably caused by the blockade of nigrostriatal dopamine tracts that results in the increase in cholinergic activity especially in the elderly [23]. A fewer people treated with clozapine, compared to risperidone, suffer from movement disorders, dry mouth, insomnia and impotence but the occurrence of extra pyramidal side effects is minimal with SGAs as compared to FGAs [24]. According to another study, SGAs are associated with fewer adjuvant use of antiparkinson drugs than FGAs [25]. Among SGAs, risperidone presented with least favorable EPS profile as compared to new atypical drugs. In our study, this clinical difference between extra pyramidal side effects (EPS) of different treatment groups was not statistically significant [26]. In a randomized trial, no significant difference in the treatment emergent EPS rating was proved when comparing between FGA and SGA and even between SGAs [27]. Antipsychotics-induced acute Extra Pyramidal side-effects are more visible in patients having Bipolar Disorder as compared to Schizophrenic patients when in depressive state. Atypical antipsychotics are least markedly to produce acute Extra Pyramidal side-effects in Bipolar Disorder as compared to typical antipsychotics, although every antipsychotic has a distinctive burden [28]. This study showed that SGAs caused more weight gain as compare to FGAs and combination of antipsychotics. Clozapine and olanzapine are more frequently associated with weight gain problems [29,30].

The use of Olanzapine, risperidone and quetiapine were also associated with weight gain, however risperidone cause least weight gain in comparison to the other two [31]. Altered normal carbohydrates and lipids is one of the major reason behind this complication [32]. In this study, it was also found that both FGAs and SGAs have equal tendencies to cause cardiovascular adverse events as per literature evidence [33]. Seemingly, cardiac disease associated death – the main reason of mortality in CHD patients, has been shown to be caused by antipsychotic side effects risk profile [34]. Sleep disturbance along with restless legs syndrome (RLS),

sleep related breathing disorder and night eating syndrome was due to use of both FGAs and SGAs [35]. Studies also demonstrated that SGAs significantly increases stage 2 sleep and total sleep time, whereas FGAs significantly decreases the stage 2 sleep latency but enhances the sleep efficacy [36]. According to another data, second generation aripiprazole caused minimum side effects in comparison to first generation haloperidol [37]. There was no significance difference in the side effect profile of all first and second generation drugs in the response of remaining questions of GASS in this study.

When the GASS score was classified by treatment arms, there was significant reduced risk of side effects in combination therapy as compared to monotherapies of FGAs and SGAs. Data obtained from this study suggested that there was prominent reduction in the frequency of mild and moderate adverse events when risperidone combined with fluphenazine. A meta-analysis of randomized controlled trails has suggested that co-treatment of different classes of antipsychotics are far better than the monotherapy [19]. However, likelihood of getting benefit out of this augmentation with co treatment is still controversial [38-40]. Patients clinical characteristics play a pivotal role in making decision to start with either monotherapy or co-treatment with FGA and SGA [41]. A paucity of data also highlighted that discontinuing one of two drugs from combination therapy was followed by more quickly and more often treatment discontinuation owing to non-adherence [42]. According to another meta-analysis, patients who have partially responded to clozapine get benefit after adding another antipsychotic [43].

Limitation of study

The only limitation observed during study was that few questions related to sex life were not replied by patients properly due to sociocultural perspectives of region. So most of the patients replied “Never” in few questions of questionnaire or didn't respond entirely.

Conclusion

This study manifested that the differences between antipsychotics were subtle, but precise and distinguishable. According to the GASS scoring, risk of side effects significantly increased in patients on monotherapy as compared to those who were using combination of FGA and SGA.

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