Original Article

Adherence and Continuation of Treatment with First- and Second-generation Antipsychotics in Schizophrenia

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ABSTRACT

Background: Despite a large body of evidence, the issue of differences in adherence and continuation of treatment with first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) in schizophrenia remains unresolved. This study compared adherence and continuation of treatment between patients on SGAs and FGAs and examined the influence of several socio-demographic and clinical variables on adherence in the two antipsychotic groups. **Materials and Methods:** Two groups, one of 40 patients with schizophrenia on SGAs and the other with 30 patients on FGAs, were compared on clinician-rated and patient-rated measures of adherence over 6 months; a 3-month period prior to intake and a 3-month follow-up period. Mean scores on these measures and the proportion of adherent/non-adherent patients was estimated for both groups. **Results:** The two groups did not differ in the 3-month period prior to intake. Over the subsequent 3 months of follow-up, a-fifth of the patients on FGAs became non-adherent, while about 10% of those on SGAs became more adherent. These differences in continuation rates resulted in patients on SGAs being rated as significantly more adherent at the end of this 3-month follow-up period and over the entire 6 months of the study. Differences in adherence and continuation rates between the two groups were primarily driven by the differences between olanzapine and the FGAs. Supervision of treatment by relatives emerged as the only consistent determinant of adherence, but explained only 8% of the variance. **Conclusions:** Patients on certain SGAs, notably olanzapine, are more likely to continue with their treatment that those on FGAs.

Key words: *Adherence, antipsychotics, continuation, first-generation, second-generation*

INTRODUCTION

In the treatment of schizophrenia, poor treatment adherence is not only very common, but is also associated with relapses, rehospitalizations and increased costs of care.[1] Therapeutic gains obtained with conventional or first-generation antipsychotics (FGAs) are often offset by the burden of side-effects, especially extrapyramidal side-effects. This adversely affects treatment adherence. Atypical or second-generation antipsychotics (SGAs) have similar efficacy, but lesser propensity for extrapyramidal effects, than FGAs. In additional, some studies also indicate that SGAs are associated with improved subjective experience of treatment among patients.[2-4] The substantial influence these factors have on adherence led to the anticipation that SGAs would ensure better adherence.[3,4] However, the evidence regarding improved adherence with SGAs has been particularly inconclusive. While a number of studies

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have found patients on SGAs to adhere more with treatment, many others have not found any difference in adherence between FGAs and SGAs.[3-6] This debate has not been resolved by meta-analytic[7] and recent large-scale effectiveness studies.[5,8-11] Although some effectiveness trials have not found any differences in adherence between the two antipsychotic groups, others have found a clear advantage for SGAs with regard to adherence.[2,5,10-12] In contrast to the equivocal results on medication adherence, the results regarding persistence or continuation of treatment have been more consistent. The majority of efficacy trials have found that patients on SGAs are more likely to continue taking their medications[4,5] and this has been endorsed by the many of the effectiveness trials.[5,8,10,11]

Driven by these considerations, the current study attempted to compare adherence with treatment, as well as a continuation of treatment between patients on SGAs and FGAs. In addition, the influence of several socio-demographic and clinical variables on medication adherence was also examined in the two antipsychotic groups.

MATERIALS AND METHODS

The study-protocol was approved by the Research and Ethics committees of the institute. Written informed consent was obtained from all participants prior to inclusion; other ethical safeguards were also maintained during the study.

Participants

Patients aged between 18 and 60 years were included if they had a diagnosis of schizophrenia confirmed by the structured clinical interview for Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) axis-I disorders — clinical version I.[13] They had to be on treatment with the same antipsychotic for a minimum of 3 months prior to inclusion. They had to be living with and accompanied by a relative during assessments. Patients with organic brain syndromes or comorbid psychiatric illnesses and substance dependence (except nicotine) and patients on antipsychotic combinations or depot preparations were excluded.

Over a 6-month period, 140 patients with schizophrenia on SGAs (including clozapine, olanzapine, risperidone, quetiapine, aripiprazole and ziprasidone) were approached. Of these 49 patients did not fulfill selection criteria, 10 patients refused consent and 26 did not complete their baseline assessments. Of the 55 remaining subjects, only 40 completed both baseline and 3-month follow-up assessments. Thus, 40 patients on SGAs formed the study group. Simultaneously, from a sample of 50 patients on FGAs, a comparison group of 30 patients on these medications, who fulfilled all selection criteria, were also recruited. The two groups were matched on age, gender, marital status, education of patients and the duration of their illnesses.

Assessments

The following assessments were carried out:

1. Psychopathology: The positive and negative syndrome scale (PANSS).[14]
2. Adherence: The compliance rating scale (CRS),[15] was used as a clinician-rated measurement of medication adherence. Patients with CRS scores of more than four were categorized as adherent. The drug attitude inventory-10 (DAI-10) item version[16] was used as a patient-report measure of adherence. Though the DAI-10 primarily measures subjective response and attitudes toward medication, scores on this scale are highly predictive of adherence.[17] For categorizing patients, the sum of the negative items on the DAI-10 was subtracted from the sum of the positive items; if the resulting score was less than or equal to zero, patients were considered to be non-adherent.[17]
3. Side-effects: Overall rating was carried out with the Udvalg for Kliniske Undersogelser side-effect rating scale (UKU);[18] the Barnes Akathisia Rating Scale (BARS)[19] was used to evaluate akathisia and the abnormal involuntary movements scale (AIMS)[20] for the assessment of dyskinesia.

All assessments were carried out twice. The baseline assessments performed at intake covered the preceding 3-month period. A second assessment after 3 months of follow-up covered the interim 3-month period between baseline and follow-up assessments. No attempt was made to intervene to improve adherence in the period between the two assessments.

Data analysis

Data were analyzed using the Statistical Package for Social Scientists, version 14 (SPSS Inc., Chicago, IL, USA). Chi-square, Student's-*t* and Mann-Whitney tests were used to compare the two groups on different parameters. Stepwise multiple regression analyses were carried out to determine the influence of socio-demographic and clinical variables on adherence for the whole sample and both groups.

RESULTS

Patient profiles

The demographic, clinical and treatment profiles of patients included in the study are depicted in Table 1.

Family incomes were significantly lower among patients on FGAs. Past severity of illness was greater in patients

Table 1: Demographic, clinical and treatment details†

Variables	SGAs *N*=40	FGAs *N*=30
Age-mean (SD)	35.8 (10.2) years	37.4 (8.8) years
Male/female	29/11	20/10
Married/single	25/15	19/11
≤8 years of schooling	13	14
>8 years of schooling	27	16
Employed	20	16 14
Unemployed/housewives	20	
Patients' income-mean (SD)	1832 (2562) Rs./month	817 (1240) Rs./month*
Family income-mean (SD)	12092 (13282) Rs./month	5157 (4034) Rs./month*
Urban/rural	31/9	21/9
Illness duration-mean (SD)	69.3 (35.7) months	78.9 (30.3) months
No. of hospitalizations in the past-mean (SD)	0.3 (0.5)	0.7 (.9)*
No. of relapses in the past-mean (SD)	15 (37.5)	19 (63.3)*
Type of antipsychotics		
Risperidone	14	—
Olanzapine	23	—
Quetiapine	03	—
Trifluoperazine	—	23
Chlorpromazine	—	07
Dose in chlorpromazine equivalents-mean (SD)	310 (172) mg/day	333 (86) mg/day
Duration of treatment with current medications-mean (SD)	12.3 (12) months	39.4 (30.8) months*
Total number of psychotropics-mean (SD)	1.5 (0.7)	2.3 (0.7)*
UKU scores-mean (SD)	17.7 (5.32)	20.0 (5.19)
BARS scores-mean (SD)	0.85 (1.09)	0.80 (0.91)
AIMS scores-mean (SD)		
Facial and oral movements	00.35 (00.95)	01.20 (2.01)*
Global movements	00.42 (01.25)	01.31 (2.06)*

SD – Standard deviation; SGAs – Second-generation antipsychotic medications; FGAs – First-generation antipsychotic medications; UKU – Udvalg for kliniske undersogelser side effects rating scale; BARS – Barnes akathisia rating scale; AIMS – Abnormal involuntary movements scale; †Doses of antipsychotics and scores on the UKU, BARS and AIMS represent averages of the scores at baseline and after 3 months of follow-up; *$P<0.05$ (Mann Whitney U or *t* values)

on FGAs based on the significantly higher number of past relapses and hospitalizations. Patients on FGAs had been on treatment for a longer period and were on a higher number of psychotropics. There were no differences in the UKU and BARS scores, but patients on FGAs had significantly higher scores on two of the five subscales of the AIMS, indicating greater prevalence of dyskinesia.

Adherence with and continuation of treatment

Mean scores on the CRS and the DAI-10 were used to evaluate adherence. Patients were also categorized as adherent or non-adherent based on these scores. The average CRS and DAI-10 scores of both intakes covering the entire 6-month study-period, as well as the numbers that were adherent/non-adherent over this period are depicted in Table 2.

There were no differences between the two antipsychotic groups at baseline on both their mean CRS and DAI-10 scores and in the proportion of patients who were categorized as adherent/non-adherent according to these scores. However, over the 3-month follow-up period five patients (17%) in the FGA group became non-adherent based on their CRS scores, while one patient in the SGA group moved from the non-adherent to the adherent category. Similarly, six patients (20%) in the FGA group became non-adherent based on the DAI-10 categorization in the same period, while five patients (12%) in the SGA group moved from the non-adherent to the adherent category. Consequently, at the end of the 3-month period, patients on SGAs were rated to be significantly more adherent based on the their mean CRS and DAI-10 scores, as well the proportion of patients who were categorized as adherent/non-adherent based on these scores. The significantly higher mean CRS and DAI-10 scores over the entire 6-month study-period in the SGA group reflected this change, which occurred over 3 months of follow-up. The proportion of adherent patients over 6 months was also greater in the SGA group, but this difference was significant only for the CRS categorization and not according to the DAI-10.

Analysis of adherence and continuation with individual medications in the SGA group revealed that the differences obtained between the two antipsychotic groups were primarily driven by olanzapine. Accordingly, patients on olanzapine differed significantly from those on FGAs in terms of their mean CRS and DAI-10 scores at 3 months, as well as over the 6-month study-period. The proportion of patients categorized as adherent according to both the CRS and the DAI-10 was significantly greater in the olanzapine group at the end of 3 months. In addition, the proportion of adherent patients over 6 months was also greater in the olanzapine than the FGA group, but this difference was significant only for the CRS and not the DAI-10 categorization. The risperidone group differed significantly from the FGA group only with regard to the significantly higher DAI-10 scores at baseline and over the 6-month study period. There were no significant differences between olanzapine and risperidone on any of the above parameters.

Table 3 includes other details pertaining to adherence with appointments and supervision of treatment by relatives. Though there were a few significant differences between the two antipsychotic groups

Table 2: Adherence with and continuation of treatment

Variables	Baseline assessments covering 3 months prior to intake	Assessments after 3 months of the follow-up	Average of both intakes (over 6 months)[†]
SGAs (*N*=40)			
CRS scores-mean (SD)	5.03 (1.75)	5.33 (1.54)	5.17 (1.60)
CRS-adherent patients[§]	26	27	27
CRS-non-adherent patients	14	13	13
DAI-10 scores-mean (SD)	1.83 (1.71)	2.20 (2.15)	2.01 (1.60)
DAI-adherent patients	29	34	33
DAI-non-adherent patients	11	6	7
FGAs (*N*=30)[‡]			
CRS scores-mean (SD)	4.33 (1.67)	3.90 (1.54)***	4.12 (1.52)*
Patients who were adherent	13	08***	10*
Patients who were non-adherent	17	22***	20*
DAI-10 scores-mean (SD)	0.97 (1.87)	0.90 (1.24)**	0.93 (1.21)**
DAI-adherent patients	21	15**	20
DAI-non-adherent patients	9	15**	10
Olanzapine (*N*=23)[@]			
CRS scores-mean (SD)	5.22 (1.76)	5.48 (1.50)***	5.27 (1.57)*
Patients who were adherent	16	17***	16*
Patients who were non-adherent	7	6***	7
DAI-10 scores-mean (SD)	1.48 (1.78)	2.52 (2.21)**	2.00 (1.68)*
DAI-adherent patients	18	19*	19
DAI-non-adherent patients[¶]	5	4*	4
CRS scores-mean (SD)	4.57 (1.79)	4.86 (1.56)	4.79 (1.68)
Patients who were adherent[$]	8	8	8
Patients who were non-adherent	6	6	6
DAI-10 scores-mean (SD)	2.57 (1.40)*	1.86 (2.11)	1.96 (1.68)*
DAI-adherent patients	14	9	11
DAI-non-adherent patients	0	5	3

SGAs – Second-generation antipsychotic medications including olanzapine (*n*=23), risperi done (*n*=14) and Quetiapine (*n*=3); FGAs – First-generation antipsychotic medications including trifluoperazine (*n*=23) and chlorpromazine (*n*=7); CRS – Compliance rating scale-Kemp *et al*.;[15] DAI-10 – Drug attitude inventory-10 item version; SD – Standard deviation; [†]Total period of assessment was 6 months, including a 3-month period prior to intake and 3 months of follow-up; [§]Patients with CRS scores of >4 were rated as adherent; those with CRS scores ≤4 were rated as non-adherent [¶]DAI-10: The sum of the negative items was subtracted from the sum of the positive items. If the resulting score was less than or equal to zero, patients are considered to be non-adherent; [‡]SGAs versus FGAs: significant differences; CRS scores at 3 months $t=3.56$; $P<0.001$; CRS adherent/non-adherent patients at 3 months-$\chi^2=11.43$; $P<0.001$; CRS scores averaged over 6 months $t=2.79$; $P<0.05$; CRS adherent/non-adherent patients averaged over 6 months-$c^2=6.88$; $P<0.05$; DAI-10 scores at 3 months $t=2.96$; $P<0.01$; DAI adherent/non-adherent patients at 3 months-$c^2=10$; $P<0.01$; DAI-10 scores averaged over 6 months $t=3.09$; $P<0.01$; [@]Olanzapine versus FGAs: significant differences, CRS scores at 3 months $t=3.74$; $P<0.001$; Adherent/non-adherent patients at 3 months $c^2=11.66$; $P<0.001$; CRS scores averaged over 6 months $t=2.69$; $P<0.05$; CRS adherent/non-adherent patients averaged over 6 months $c^2=6.84$; $P<0.05$ DAI-10 scores at 3 months $t=3.38$; $P<0.01$; Adherent/non-adherent patients at 3 months-$c^2=4.68$; $P<0.05$; DAI-10 scores averaged over 6 months $t=2.69$; $P<0.05$; [#]Risperidone versus FGAs: significant differences DAI-10 scores at baseline $t=2.86$; $P<0.05$; DAI-10 scores averaged over 6 months $t=2.32$; $P<0.05$; *$P<0.05$; **$P<0.01$; ***$P<0.001$

on some of these parameters, there was no clear pattern to these differences. On the other hand, the PANSS scores in both groups demonstrated a trend, which mirrored the differences in adherence and continuation rates. Accordingly, at intake the PANSS scores did not differ significantly between the two groups, apart from the significantly higher positive scores of the FGA group. However, over the next 3 months, there was a significant decline ($P < 0.05$) in all subscale scores and the total PANSS scores among patients on SGAs, while patients on FGAs registered only minimal and non-significant declines in their PANSS scores. Thus, at the end of 3 months of follow-up the FGA group had significantly higher total scores and higher scores on all three subscales of the PANSS. A similar difference emerged between the two groups when the PANSS scores over the 6-month study period were compared.

Correlates of adherence

Multiple regression analyses were carried out to examine the associations between demographic variables, scores on the PANSS, DAI, UKU, BARS and AIMS, proportions of appointments attended, of visits with relatives and medication intakes supervised by relatives as independent variables and the average CRS scores as the dependent variable.

For the whole group, only higher family income, the proportion of supervised intakes and proportion of outpatient visits accompanied by a relative, emerged as significant correlates of adherence. Together these

Table 3: Adherence with treatment: Related details

Variables	Baseline assessments covering 3 months prior to intake mean (SD)	Assessments after 3 months of follow-up mean (SD)	Average of both intakes (over 6 months)† mean (SD)
SGAs (*N*=40)			
Percentage of medication intakes supervised by relatives‡	48.5 (41.3)	53.1 (35.9)	50.8 (35.5)
No. of visits per month	3.2 (1.6)	2.95 (1.22)	3.1 (1.3)
Percentage visits accompanied by a relative§	85.6 (22.6)	76.9 (22.9)	81.2 (18.1)
Percentage of appointments attended	80 (23.4)	72.5 (24.6)	76.2 (18.9)
PANSS positive scores	15.8 (3.1)	12.7 (3.3)	14.3 (2.1)
PANSS negative scores	15.8 (4.8)	14.6 (3.8)	15.2 (4.1)
PANSS GP scores	29.5 (5.2)	27.0 (5.7)	28.2 (5.0)
PANSS total scores	61.1 (11.2)	54.3 (10.6)	57.7 (10.2)
FGAs (*N*=30)			
Percentage of medication intakes supervised by relatives	49.2 (44.8)	45.0 (40.7)	47.1 (41.3)
No. of visits per month	3.3 (0.9)	3.5 (0.6)*	3.4 (0.6)
Percentage visits accompanied by a relative	72.5 (29.6)*	72.5 (23.1)	72.5 (21.4)
Percentage of appointments attended¶	80.8 (23.3)	78.3 (20.4)	79.6 (18.4)
PANSS positive scores	17.7 (3.4)*	17.2 (4.03)***	17.4 (3.4)*
PANSS negative scores	17.1 (3.9)	17.1 (3.8)*	17.1 (3.5)*
PANSS GP scores	31.2 (6.1)	31.03 (8.1)*	31.1 (6.8)*
PANSS total scores	66.03 (10.9)	65.3 (14.3)***	65.7 (11.9)*

SD – Standard deviation; SGAs – Second-generation antipsychotics medications; FGAs – First-generation antipsychotic medications; PANSS – Positive and negative syndrome scale; GP – General psychopathology; †Total period of assessment was 6 months, including a 3-month period prior to intake and 3 months of follow-up; ‡Percentage of supervised intakes/total number of intakes for each patient; §Percentage of outpatient visits with a relative/total number of visits; ¶Percentage of appointments attended/total number of appointments; *Significant difference between SGAs and FGAs; $P<0.05$; ***Significant difference between SGAs and FGAs; $P<0.001$

variables explained about 8.5% of the variance in adherence scores ($r^2 = 8.53$; $F = 3.5$; $P < 0.05$). However, in the FGA group higher DAI scores demonstrated a significant association with CRS scores and explained about 25% of the variance ($r^2 = 0.25$; $F = 3.8$; $P < 0.05$).

DISCUSSION

Two related constructs of adherence and persistence are often used to describe medication taking behavior by patients. Adherence or compliance is usually defined as the "extent to which a person's behavior in terms of taking medications, following diets or executing life-style changes, coincides with the clinical prescription."[21] Persistence or continuation of treatment is defined as "the duration of time from initiation to discontinuation of therapy."[22] It has been proposed that adherence captures the cross-sectional compliance with a medication regime while persistence is an index of long-term commitment to treatment.[4] However, it is not clear whether both indices measure the same thing, or whether they are independent parameters mediated by two different sets of factors.[4,5,23]

In this study, patients on SGAs and FGAs did not differ over a 3-month period prior to intake on both clinician-rated and patient-rated measures of adherence. However, during the subsequent 3 months of follow-up, about a-fifth of the patients on FGAs became non-adherent, while about a-tenth of those on SGAs moved from being non-adherent to adherent. These differences in continuation rates among patients of the two groups resulted in patients on SGAs being rated as significantly more adherent at the end of this 3-month follow-up period and over the 6-month study period. Moreover, the differences between the two antipsychotic groups were mainly because of higher adherence and continuation rates of olanzapine and not risperidone, which was the other principal constituent of the SGA group. Finally, these differences in medication taking behavior between the two groups was paralleled by a change in symptom-severity; the FGA group registered a worsening of symptoms over the 3-month follow-up period while patients in the SGA group improved with regular treatment.

These results reflect the major trends in research on adherence and persistence among SGAs and FGAs. Much of this inconsistency between studies has concerned adherence with treatment among these two antipsychotic groups. While many studies have found better adherence among patients on SGAs, an almost equal number of studies have not found any differences in medication adherence between the two classes of antipsychotics.[3-6,8-12] The findings of the current study suggest that since the assessment of adherence often involves a shorter timeframe, the results may vary depending on the point of time when the assessments are carried out as they did between the baseline and follow-up assessments of this study.

This could explain some of the discrepancy in results of previous studies.[5] On the other hand, estimation of persistence or continuation of treatment usually involves longitudinal assessments over longer periods. This could account for the greater consistency among studies focusing on continuation rates, most of which have found that patients on SGAs are more likely to continue with their treatment.[3,5,7,8,10-12] In the present study, differences in adherence after 3 months resulted from the differences in continuation rates between SGAs and FGAs during this period of follow-up. A similar relationship or overlap between the two parameters has been found in some studies,[5] but not in others.[11,23] In addition, in the current study, differences in adherence and continuation rates between the two antipsychotic groups were clearly driven by the differences on these measures between olanzapine and the FGAs. This was in keeping with much of the literature on differential adherence and persistence among SGAs. In contrast to the less convincing evidence favoring better adherence with specific SGAs such as olanzapine,[3,5] results of efficacy trials[4,5] meta-analytic studies[7] and effectiveness trials[2,12] have consistently indicated that patients on olanzapine and clozapine are more likely to continue with their treatment. However, what determines the better persistence with certain SGAs is far from clear. Treatment adherence and persistence are complex behaviors and can be potentially influenced by a multitude of factors.[1,3,6] In this study, supervision of treatment and medication intake by relatives emerged as the only meaningful correlates of adherence, but explained only a small part of the variance in adherence. Incidentally, a few other studies have also indicated that supervision of treatment by relatives and caregivers is associated with better adherence among patients.[1,24,25] Attitudes toward medications and subjective responses as measured by the DAI have also shown a consistent association with adherence,[16] but this was only true for the FGA group of the current study. Finally, the finding of worsening symptoms among patients with poorer adherence and higher discontinuation rates is a common finding in many of the studies,[6,26] which serves to emphasize the adverse consequences of non-adherence.

The findings of the present study were limited by the small numbers in both groups, the relatively short period of prospective follow-up and the fact that the patients were drawn from a single center. Moreover, assessments of adherence were not blind and not as comprehensive as they could have been. Therefore, the results can only be considered tentative and cannot be readily generalized. Nevertheless, they provide some support for the notion that patients on certain SGAs, notably olanzapine, are more likely to continue with their treatment that those on FGAs; this could result in differences in adherence between these two antipsychotic groups depending on the timing of the adherence assessments. It would be worthwhile to examine the reasons for these differences between antipsychotics, because such research might not only yield clues to the determinants of adherence, but also suggest ways of improving non-adherence among patients with schizophrenia.

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