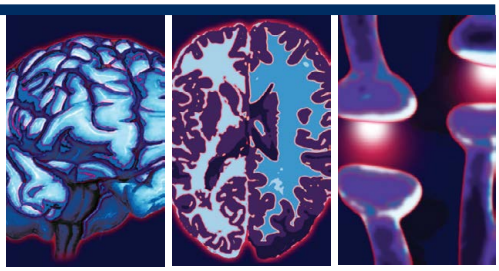

Comparison of pre-treatment clinical characteristics and post-treatment outcomes of patients treated with Clozapine and long acting antipsychotics

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ABSTRACT

Introduction:

Clozapine is a cornerstone in the treatment of resistance schizophrenia, whereas long-acting antipsychotics (LAA) are central in the care of patients with poor compliance. Both populations represent daunting challenges. We aim to compare pre-treatment disease severity and treatment outcome of patients receiving clozapine and LAA.

Methods:

Medical records of patients who attend an outpatient schizophrenia clinic were randomized and examined retrospectively. Demographics and psychiatric history prior hospitalizations and suicide attempts were reviewed. Additionally, the Positive and Negative Symptom Scale (PANSS) and Medication Adherence Rating Scale (MARS) were administered to patients during their last visit.

Results:

Preliminary results from 27 patients show that those on LAA had more hospitalizations (p=0.021) and suicide attempts (75% *vs*. 11%, p=0.034) than patients on clozapine before initiation of treatment. There were no differences in frequency of visits, MARS or PANSS scores between the two groups. Negative symptoms were more predominant among the patients on long-acting antipsychotics than in those on clozapine, although the difference was borderline significant.

Discussion:

Patients on LAA had a more severe disease course prior to the initiation of LAA, reflected in more hospitalizations and suicide attempts, possibly due to persistent non-compliance with oral treatment in the past. Patients on clozapine had more recent hospitalizations, perhaps due to suboptimal dosing. Treatment adherence and symptom burden were similar in both patient groups. There was an expected trend of patients on long acting antipsychotics to display poorer negative symptom control than those on clozapine.

Keywords

Schizophrenia, Clozapine, Long-acting antipsychotics, Treatment adherence

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Introduction

Clozapine and long acting antipsychotics (LAA) have a prominent role in the management of challenging subpopulations of patients with schizophrenia, such as those treatment resistant and those with poor treatment adherence, respectively. Unfortunately, both treatment options are underutilized [1]. Even though 30% of patients with schizophrenia are treatment resistant, only 4.4% receive clozapine [2]. Non-adherence in schizophrenia can exceed 60%; however, less than 1 in 5 individuals with poor adherence receive LAA [3].

Clozapine is associated with several adverse effects, including sedation, tachycardia and sialorrhea [4], as well as potentially fatal adverse reactions such as agranulocytosis; myocarditis and metabolic syndrome [5] which limits its use as a first-line agent. However, medication compliance is greater in clozapine when compared to first generation antipsychotics, partly due to greater symptom improvement and reduced side effects [6]. LAA have a number of pharmacokinetic advantages over oral antipsychotics. LAA are not influenced by first-pass metabolism, decreasing the potential for drug-drug interactions [7]. Furthermore, LAA can reduce the risk of relapse when combined with psychosocial interventions [8].

On the other hand, patients treated satisfactorily with clozapine or LAA need active treatment compliance due to scheduled laboratory monitoring and regular visits for injections, respectively. There is a relative dearth of information comparing pre-treatment clinical characteristics and post-treatment outcomes of patients on clozapine and LAA treatment. Most long term studies analyzing both treatments focus on symptom resolution and side effect burden but neglect long term factors such as treatment adherence, life skills and patient's functionality [9,10]. The rationale for the present study is to compare two underused treatment strategies that are proven to be effective in symptom control in difficult populations, and might influence clinician decisions regarding treatment.

In the present study, our main hypothesis was that patients who receive clozapine have a more severe pretreatment clinical course compared with those receiving LAA. A secondary hypothesis was whether on a cross sectional view, patients stable on clozapine or LAA treatment will have comparable clinical and functional outcomes.

Methods

■ Participants

A randomized retrospective review of the medical records of patients seen at the outpatient schizophrenia clinic at University of Miami who were either receiving clozapine or LAA therapy between January 2014 and June 2014 was completed for 30 individuals. All procedures were approved by the University of Miami Institutional Review Board. This clinic is part of a tertiary care referral center, accepting all patients older than 18 years of age from the greater Miami area, which includes an elevated number of Hispanic patients.

Inclusion criteria were: with a) diagnosis of schizophrenia, b) age 18-65 years, c) attending the outpatient schizophrenia clinic at University of Miami between January 1, 2014 and June 31, 2014, and d) receiving active monotherapy treatment with clozapine or LAA. The only exclusionary was a history of traumatic brain injury or the presence of co-morbid intellectual disability or autism spectrum disorder.

■ Procedures

For those patients meeting inclusion but not exclusion criteria demographic, laboratory, and clinical data were collected from the medical records going back 6 years from the time of review. Demographic data included age, gender, and race.

Clinical data included: primary diagnosis as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition [11], length of current treatment, number of prior hospitalizations and suicide attempts were reviewed. Additionally, the Positive and Negative Symptom Scale (PANSS), Medication Adherence Rating Scale (MARS), Clinical Global Impression-Severity Index (CGI-S), and the Life Skills Profile-39 (LSP) were rated in person by one rater from the last visit of the patients. The rater was blind to the treatment received by the patients.

■ Data Analysis

Descriptive statistics were calculated for both groups. T-student and Chi square were used to compare the different variables between the two study groups. Significance level was set at 0.05. All analyses were performed using SPSS 22.0.

Results

Three of the 30 randomized patients were

excluded because of incomplete documentation. In our sample of 27 patients with schizophrenia, nine were receiving LAA, (five haloperidol decanoate, two fluphenazine decanoate and two risperidone long-acting injections) with a mean dose of 630 mg of chlorpromazine equivalent/month. Eighteen patients were receiving clozapine (mean dose of 400 mg/day, equivalent to 800 mg of chlorpromazine a day). Because the equivalences were calculated in a different time period (days versus months) no comparison was done. As seen in **Table 1**, a higher number of patients had been on current treatment with LAA for more than 5 years compared with those receiving clozapine. Prior to the initiation of current pharmacological therapy, more patients in the LAA had had more than five hospitalizations (χ^2=3.9; *df*=1; *P*=0.04). A significant proportion (P=0.034) of patients in the LAA had attempted suicide compared with the clozapine group prior to initiation of treatment.

Although no hospitalizations occurred while patients were receiving LAA, 21% of patients were hospitalized while taking clozapine (P=0.021). The most common side effects were tremors (44%) and akathisia (22%) in the LAA group, and sedation (39%) and sialorrhea (33%) in the clozapine group. As seen in **Table 2**, current clinical severity assessed with the CGI-S reflected adequate symptom control, with more severe current symptoms in the LAA (mildly ill) than in the clozapine group (borderline mentally ill) (*t*=4.94; *df*=25; *P*=0.017). The current presence of psychotic symptoms measured by the composite score of the PANSS was borderline significant in the LAA group (*t*=2.37; *df*=25; *P*=0.08). There were no differences in frequency of visits, MARS or LSP scores between the two groups.

Table 1. General characteristics of adult outpatients with schizophrenia receiving either clozapine or long acting antipsychotic therapy.

	Long acting antipsychotics	Clozapine	P
N	9	18	
Age	48.3 ± 12.9	42.2 ± 14.1	0.09
Gender (m) [a]	7	13	0.76
Race White African American Hispanic	 0 7 2	 7 1 10	
Single [a]	8	15	0.91
Employed [a]	1	3	0.70
Dose Chlorpromazine Equi	189 ± 89.3 mg/mo 630 ± 297.6 mg/mo	400 ± 148.8 mg/d 800 ± 297.6 mg/d	0.01
Treatment > 5 years	7	10	0.48
> 5 hospitalizations before treatment	6	5	0.04
Hospitalizations during treatment	0	4	0.021
Suicide attempts before treatment	4	3	0.034
Side effects	tremor, akathisia	Sedation, sialorrhea	

[a]: X^2
P<0.05 (significant)

Table 2. Psychotic symptoms and clinical characteristics of schizophrenic patients receiving clozapine or long acting antipsychotic therapy.

	Long acting antipsychotics	Clozapine	P
N	9	18	
PANSS			
positive	11.8 ± 5.2	12.6 ± 5.6	0.365
negative	-17.8 ± 9.0	-14.7 ± 5.9	0.145
general	24.1 ± 5.6	22.9 ± 6.3	0.322
composite	-6.0 ± 7.3	-2.1 ± 6.1	0.08
MARS	9.1 ± 0.8	8.4 ± 1.5	0.108
LSP-39	20.3 ± 11.6	21.9 ± 10.5	0.360
CGI-S	3.2 ± 1.0	2.3 ± 1.0	0.017

PANSS (Positive and Negative Symptom Scale), MARS (Medication Adherence Rating Scale), LSP-39 (Life Skills Profile-39), CGI-S (Clinical Global Impression-Severity Index)
P<0.05 (significant)

Discussion

To our knowledge this is the first study comparing baseline clinical characteristics and outcomes in schizophrenia patients receiving clozapine or LAA. To date, few studies comparing LAIs and oral antipsychotics have been conducted; however, the results are mixed, and careful interpretation of the data is required [12]. An article recently published [13] argues, that the results on long-acting injectable versus oral antipsychotics in the treatment of schizophrenia rely heavily on the study design and the population studied. The author adds that to put LAA-oral comparisons into clinical context is urgently necessary. Other authors had already suggested [14] that long-term pragmatic randomized clinical trials of an LAA against an oral antipsychotic, in patients with problematic adherence, would be of value.

We found that patients receiving LAA had a more severe disease course prior to initiation of LAA treatment, reflected in more hospitalizations and suicide attempts, possibly due to previous non-compliance with oral treatment, poor insight and subsequent regular recurrence of psychosis. This set of patients appears to be more severely ill and more difficult to treat with standard measures. Our findings were unexpected and contrary to

our main hypothesis given the classical picture of lack of symptom control in schizophrenic patients resistant to treatment.

On the other hand, patients taking clozapine showed a significant trend to be hospitalized more frequently than those on LAA during their treatment period, possibly due to suboptimal dosing or partial treatment adherence. Unfortunately, information regarding clozapine levels at the time of hospitalization is lacking. The side effect profile was comparable to the one previously described for these medications [4,8]. A study comparing patient outcomes with risperidone long-acting injection (RLAI) or oral aripiprazole showed no significant difference between both groups during a 5 year follow-up, with relatively low continuation rates (18% and 16%) [15]. Although our study did not follow-up patients longitudinally, the retrospective approach provided a glimpse of the disease severity prior to treatment and current clinical status. An interesting finding was the racial difference between treatment groups. Most patients receiving clozapine were white and Hispanic; conversely, patients receiving LAA were generally black. This may be at least explained by the unusual demographic composition of the great Miami area with 65% of Hispanic origin. It is possible that in our sample white Hispanics are more treatment resistant than blacks. Another possible explanation could be the clinician bias; Hispanics tend to have more family support and are more likely to adhere to the rigorous blood monitoring of clozapine in comparison with black population.

In our study group, the patients on LAA had more negative symptoms and had more global severity of illness than the patients on clozapine as evidenced by the composite scores of the PANSS and the CGI-S scores. While these findings may suggest that clozapine might improve negative symptoms and provide better symptom control than LAA, this could also represent a selection bias in treatment choice, with the LAA group already presenting a more severe clinical deterioration pre-treatment. However, no differences were found in treatment adherence and social life skills, confirming our secondary hypothesis. These findings suggest that regardless of the treatment approach, the adherence to clozapine and LAA was similar as long as a standard and regular monitoring is in place. It is common practice in our clinic to locate a patient when an injection or blood test results are missed. Along these lines, a British study found that switch at randomization from LAA to an oral antipsychotic was associated with poorer clinical and functional outcomes at 1-year follow-up compared with switching from one oral antipsychotic to another. This effect appears to be moderated by adherence, and may not extend to switching to clozapine [16]. Interestingly, there is little data on the application of the MARS on patients receiving LAA. One study showed a positive correlation between receiving long acting fluphenazine and the MARS score [17] which agrees with our findings.

Limitations of our study include the small sample size, and the comparison groups being unmatched in numbers. Some of the differences in patients' current clinical and functional status may be antecedent rather than consequence of the treatment. The rating scales used as outcome measures were completed only following treatment. Lastly, most of the patients on LAA were receiving first-generation drugs.

Conclusion

Patients receiving LAA had a more severe disease course than patients receiving clozapine before treatment initiation, as evidenced by more hospitalizations and suicide attempts. Symptom control was similar with both clozapine and LAA. Overall, clozapine and LAA, present comparable symptom control, side effect profile and functional outcome.

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