Psychiatry Research 188 (2011) 315–319

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Time to rehospitalization in patients with schizophrenia discharged on first generation antipsychotics, non-clozapine second generation antipsychotics, or clozapine

Ana Paula Werneck [a,*], Jaime Cecilio Hallak [b], Eduardo Nakano [c], Helio Elkis [a]

[a] Department and Institute of Psychiatry, University of Sao Paulo Medical School, Rua Dr. Ovidio Pires de Campos 785, Sao Paulo, 05403-010, Brazil
[b] Department and Institute of Psychiatry, University of Sao Paulo Medical School, Ribeirao Preto, Brazil
[c] Department of Statistics, University of Brasilia, Brasilia, Brazil

ARTICLE INFO

Article history:
Received 16 June 2010
Received in revised form 10 April 2011
Accepted 12 April 2011

Keywords:
Risperidone
Olanzapine
Amisulpride
Depot antipsychotics
Oral antipsychotics
Outcome
Clozapine

ABSTRACT

Rehospitalization is an important outcome of drug effectiveness in schizophrenia. In this study, the hypothesis that clozapine and some second generation antipsychotics (SGA) were superior to first generation antipsychotics (FGA) in preventing rehospitalization of patients with schizophrenia discharged from a university hospital in Brazil was tested. A retrospective observational study was conducted designed to evaluate time to rehospitalization of patients with schizophrenia discharged on a regimen of oral FGA, depot FGA, risperidone, olanzapine and amisulpride, other SGA, or clozapine, during a three-year follow-up period. Risk factors associated with rehospitalization were examined. Of the 464 patients with schizophrenia discharged from hospital, 242 met criteria for study entry. Higher rehospitalization rates were observed in patients treated with depot FGA (30%), risperidone (30%) and other SGA groups (28.5%), respectively. Clozapine was significantly associated with lower rehospitalization risk compared with risperidone. The risk of rehospitalization in patients on olanzapine and amisulpride, and oral FGA, was similar to that of patients in use of clozapine. These results however, are limited by the heterogeneity of illness severity across the groups.

1. Introduction

It is well established that antipsychotics represent the mainstay of schizophrenia treatment. Recent meta-analyses and systematic reviews of randomized controlled trials (RCT) provide evidence that Second Generation Antipsychotics (SGA) are not a homogeneous class of drugs, with amisulpride, clozapine, olanzapine and risperidone being more efficacious than First Generation Antipsychotics (FGA) (Leucht et al., 2009). Clozapine possesses a differential among the SGA since it has shown superior efficacy in patients with treatment-resistant schizophrenia in randomized controlled trials (Elkis, 2007) as well as in pragmatic trials (Lewis et al., 2006; McEvoy et al., 2006).

Effectiveness of antipsychotics can be evaluated by various outcome measures such as discontinuation of treatment (Lieberman et al., 2005), quality of life (Burns, 2007a), relapse and rehospitalization rates (Burns, 2007b). Hospitalization rate has been used in some observational studies as an outcome measure to evaluate antipsychotic effectiveness (Conley et al., 1999; Rabinowitz et al., 2001; Patel et al., 2002; Conley et al., 2003; Lin et al., 2006; Castro and Elkis, 2007; Herceg et al., 2008) as shown in Table 1.

The data in Table 1 reveal a dearth of long-term studies comparing various antipsychotics for the prevention of rehospitalization in schizophrenia. Therefore, the aim of the present study was to extend previous findings (Table 1) by comparing a broader range of antipsychotics for the prevention of rehospitalization in a 3-year retrospective follow-up study of patients with schizophrenia discharged from a university psychiatric hospital in Sao Paulo, Brazil.

2. Methods

A retrospective observational study was conducted (Grimes and Schulz, 2002) designed to evaluate the impact of antipsychotic treatment on the prevention of rehospitalization. All inpatient records of the Institute of Psychiatry (IPq) of the University of São Paulo General Hospital were reviewed and patients with the diagnosis of schizophrenia, discharged between December 1, 1997, and December 31, 2004, were selected. The IPq is one of the largest and most modern psychiatric university hospital in Brazil and provides inpatient and outpatient treatment. This period was chosen due to the fact that SGA were made available free of charge for the treatment of schizophrenia from 1997 under the High Cost Medication Program supported by the Brazilian Federal Government. In the initial years of the program, only risperidone and clozapine were available and, as mentioned earlier, the results for this period have previously been published (Castro and Elkis, 2007). Only after 2000 were olanzapine, quetiapine and ziprasidone included in the High Cost Medication Program, and the observations reported in the present study are related to this period.

After discharge, all patients included were followed up at the IPq outpatient clinic. Follow-up care consisted of psychiatric visits with psychiatric residents and supervisors, and no additional special care or other forms of therapy or programs were provided.

* Corresponding author. Tel.: +55 11 30696971; fax: +55 11 30697808.
E-mail address: apwerneck@gmail.com (A.P. Werneck).

0165-1781/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.psychres.2011.04.004

Table 1
Observational studies comparing patients with schizophrenia treated with antipsychotics for percentage time remaining discharged during follow-up period.

Study	Follow-up period	Antipsychotics studied (Number of patients)	Rehospitalization rate	Statistical results
Conley et al. (1999)	1 year	Clozapine (49)	13%	Not significant
		Risperidone (75)	17%	
	2 years	Clozapine (49)	13%	Not significant
		Risperidone (75)	34%	
Rabinowitz et al. (2001)	1 year	FGA (458)	35%	Not significant
		Olanzapine (313)	28%	
		Risperidone (268)	31%	
	2 years	FGA (458)	45%	Significant difference [a]
		Olanzapine (313)	31%	
		Risperidone (268)	33%	
Patel et al. (2002)	1 year	FGA (137)	20%	Not significant
		Olanzapine (95)	34%	
		Risperidone (73)	35%	
Conley et al. (2003)	1 year	Fluphenazine decanoate (59)	21%	Significant difference [b]
		Haloperidol decanoate (59)	35%	
		Clozapine (41)	10%	
		Olanzapine (103)	13%	
		Risperidone (149)	12%	
Lin et al. (2006)	2 years	FGA (272)	27%	Not significant
		Risperidone (49)	22%	
		Clozapine (61)	21%	
Castro and Elkis (2007)	3 years	Haloperidol (43)	26%	Not significant
		Risperidone (22)	41%	
		Clozapine (31)	16%	
Herceg et al. (2008)[c]	2 years (acute patients)	Haloperidol (30)	47%	Not significant
		Fluphenazine (42)	31%	
		Clozapine (13)	46%	
		Olanzapine (25)	40%	
		Risperidone (25)	36%	
	2 years (chronic patients)	Haloperidol (130)	47%	Not significant
		Fluphenazine (101)	58%	
		Clozapine (60)	45%	
		Olanzapine (40)	60%	
		Risperidone (67)	39%	

FGA = first generation antipsychotics.
[a] Mantel–Cox Log-Rank test = 8.07, d.f. = 2, $p = 0.02$.
[b] Log-Rank test with Holm's procedure to adjust for multiple comparisons between haloperidol decanoate versus risperidone ($\chi^2 = 14.8$, $p = 0.0001$, adjusted $p = 0.001$), olanzapine ($\chi^2 = 11.1$, $p = 0.0009$, adjusted $p = 0.008$) and clozapine ($\chi^2 = 7.5$, $p = 0.006$, adjusted $p = 0.049$).
[c] Herceg et al. (2008) compared acute vs. chronic patients with schizophrenia.

Outpatient follow-up information was carefully assessed to identify whether patients were to be kept on the same antipsychotic prescribed at discharge. Although patient records are not completed in a structured manner by clinicians, significant information such as drug switches or rehospitalization is reported, as cases are often subsequently discussed with supervisors.

Rehospitalization was defined as readmission to any hospital due to a psychiatric condition. Upon discharge from other public hospitals, patients tended to return to the Institute of Psychiatry for maintenance treatment. All patients were followed up to verify for rehospitalization over a three-year period up to December 31, 2007. Data were collected from charts held on IPq databases. Chart reviews were conducted to verify the most recent diagnosis based on the 10th edition of the International Classification of Diseases (ICD 10). The diagnosis of schizophrenia reached by the clinicians was confirmed using the OPCRIT system (version 4.0). This comprises an operational criteria checklist for psychotic illness that offers good diagnostic reliability (McGuffin et al., 1991).

Of the 464 patients initially selected, those who had another comorbid psychiatric axis I disorder or a neurological disorder, had their diagnosis changed during the follow-up period ($n = 72$), abandoned treatment during or immediately after discharge ($n = 64$) or whose data or chart was not found, were excluded ($n = 51$). Patients discharged on polytherapy with two or more antipsychotics ($n = 17$) or on electroconvulsive therapy ($n = 1$), and those involved in other clinical trials ($n = 17$), were also excluded.

This study was approved by the Internal Review Board of the University of São Paulo General Hospital.

2.1. Statistical analyses

Survival analysis was used to assess time to readmission, and takes into account differences in length of follow-up time as patients entered and left the study at different times. Observation in the study ceased when the patient was rehospitalized, abandoned the medication prescribed at discharge, had their medication switched during the outpatient clinic follow-up, or had reached the 3-year point in the study on the same

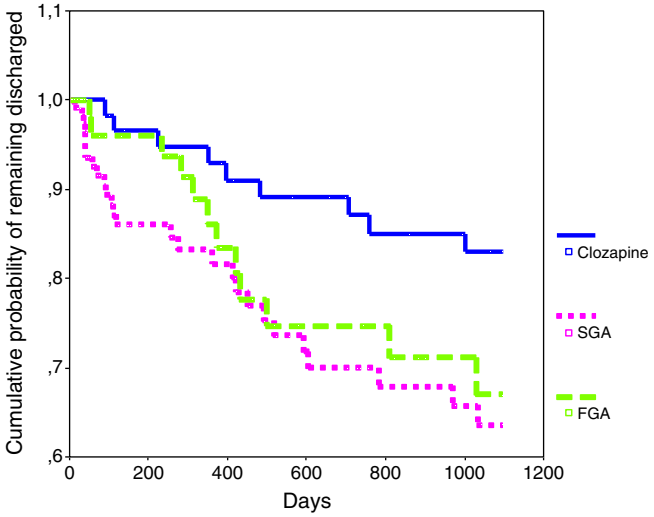

Fig. 1. Time to hospitalization of patients with schizophrenia discharged on FGA, SGA, or clozapine (cumulative probability of remaining discharged).[a,b] SGA = second generation antipsychotics and FGA = first generation antipsychotics. [a]Significant difference between groups (Mantel–Cox $\chi^2 = 6.59$, d.f. = 2, $p = 0.037$). [b]Significant difference between clozapine and SGA groups (Mantel–Cox $\chi^2 = 6.24$, d.f. = 1, $p = 0.0125$).