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ORIGINAL PAPERS

COMPARATIVE DISCONTINUATION RATES IN PATIENTS TREATED WITH ANTIPSYCHOTICS

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Abstract. Continuity of antipsychotic treatment is a prerequisite for obtaining maximum benefit and favourable treatment outcome. However, there are considerable differences between studies in terms of the level of discontinuation rates and the estimated time to discontinuation for different antipsychotics. In order to clarify these aspects more information is needed on treatment discontinuation in routine clinical settings. The **aim** of this study was to compare the rate of treatment discontinuation among patients with schizophrenia or related disorders treated with antipsychotics. **Material and methods.** The study was a one-year follow-up, observational study of 131 patients with schizophrenia or related disorders treated with haloperidol, olanzapine, risperidone, quetiapine, or aripiprazole. The main outcome variable measured was time in months to treatment discontinuation. Reason of discontinuation was also registered. **Results.** Rate of discontinuation as resulted from Kaplan-Meier univariate analysis was significantly higher in patients treated with haloperidol compared to both atypical treated group and olanzapine treated group. In Cox proportional hazards regression analysis, the group of patients with at least one previous psychotic episode was associated with a 2.5-fold increased risk of treatment discontinuation, compared to first psychotic episode patients (HR=2.571 [CI 1.077-6.139], p 0.033). After adjustment for this covariate in the Cox model, resulted HR for discontinuation with haloperidol as the reference group confirmed the order of risk of discontinuation for any reason decreasing (highest for haloperidol, lowest for olanzapine), but differences between groups did not reach the level of statistical significance. When the same analysis was performed differentiated according to specific causes, the only difference between treatment groups confirmed as statistically significant was in case of non-adherence, for olanzapine compared to haloperidol: HR= 0.109 [CI 0.013-0.923], p 0.042. **Conclusion.** The results of this observational study suggest that the differences between typical and atypical antipsychotics and between atypicals cannot be excluded in what persistence to treatment is concerned and that the choice of antipsychotic may be an important factor in the long term evolution in patients with schizophrenia and related disorders.
Keywords: antipsychotics, atypicals, treatment discontinuation, haloperidol, olanzapine, risperidone, quetiapine, aripiprazol

Introduction

Adherence to antipsychotic treatment is essential in the long term course of schizophrenia and related disorders. Continuity of antipsychotic treatment is a prerequisite for obtaining maximum benefit and favourable treatment outcome. Discontinuation of antipsychotics may have multiple causes, such as insufficient efficacy or inefficacy, non-tolerability, or non-compliance. Non-adherence to antipsychotic treatment was estimated at 50% of patients [1] and can reach 70-80% [2], and represents a major problem, with undesirable clinical consequences and social and economic implications. It was associated with relapse, poor prognosis, increased rates of hospitalization and higher costs of health care [3]. Many factors determining the patient to discontinue antipsychotic treatment have been described, as well as management strategies of non-compliance [4].

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The rate of discontinuation is considered an important parameter that integrates physician as well as patient perception on treatment tolerability, safety profile and efficacy [5]. Most studies investigating this issue in latest years have shown that antipsychotic choice influence the time to and the rate of treatment discontinuation [5-13]. However, there are considerable differences between studies in terms of the level of discontinuation rates and the estimated time to discontinuation for different antipsychotics [9,12-14]. In CATIE trial (Clinical Antipsychotic Trials of Intervention Effectiveness Schizophrenia) [5], a large double blind randomized clinical trial, 74% of study subjects discontinued the initially prescribed antipsychotic before 18 months. Objections to the validity and interpretation of CATIE trial results have been raised, among them the suspicion that the high rate of discontinuation could have been resulted following the study protocol according to which switching medication was an "invited alternative" [15].

In order to clarify these aspects and to establish if there are any differences among antipsychotics, more information is needed on treatment discontinuation in routine clinical settings. Understanding the time course of treatment response is important in the search of improving individualized therapeutic strategies in patients with schizophrenia or related disorders. Randomized clinical trials (RCT) provide the most reliable data on the efficacy of antipsychotic treatment, but generalization of such data may be limited by multiple factors, related to the controlled conditions of an experimental approach (e.g. selection criteria, rigidity of drug schemes). The distance between the data derived from RCTs and those from routine psychiatric practice might be underestimated [16]. Assessment of treatment response course in everyday medical practice through the so-called naturalistic observational studies could fill this gap.

The aim of this study was to compare the rate of treatment discontinuation among patients with schizophrenia or related disorders treated with haloperidol, olanzapine, risperidone, quetiapine, or aripiprazole.

Material and method

The study was a one-year follow-up, observational study of patients with schizophrenia or related disorders treated with haloperidol, olanzapine, risperidone, quetiapine, or aripiprazole. The study sample consisted of 131 patients hospitalized in the Clinical Emergency Central Military Hospital "Dr. Carol Davila", Bucharest from February 2009 to May 2010 for schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder or brief psychotic disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria. Subjects were followed-up after discharge at 6 and 12 months, during scheduled visits. The main outcome variable measured was time in months to treatment discontinuation. Reason of discontinuation was also registered: inefficacy or insufficient efficacy, adverse reaction (both evaluated by treating physician who decided the change of antipsychotic medication) or non-adherence (when treatment discontinuation was the decision of the patient). If there was more than one reason for discontinuation, the first of these was registered, in the following order: lack of efficacy, adverse reaction, non-adherence. Assessments outside the scheduled visits were performed in case of readmission. Selected patients gave written informed consent for anonymous data processing and analysis.

Statistical analysis

Univariate analysis of variance (ANOVA) models with last significant difference post hoc tests for continuous variables and chi-square tests for dichotomous variables were used to compare baseline demographic and clinical characteristics between treatment groups. The probability of treatment discontinuation at 12 months was estimated using the Kaplan-Meier simple linear regression method. The time to discontinuation was calculated from the date of study enter to the first treatment interruption. We compared the survival curve for haloperidol to atypical antipsychotics, as a group and also for pairs of antipsychotics with Gehan's Wilcoxon and log-rank tests. The level of statistical significance was considered for p lower than 0.05. Subjects who continued with their initially prescribed antipsychotic to the end of the 12 months follow-up period were included in the analysis as censored observations. The analysis was truncated at 12 months so that all patients had exactly the same period of follow-up. Factors associated with treatment discontinuation were determined by multivariate analysis using a Cox proportional hazards model with stepwise reduction. Covariates analysed included: age, sex, body mass index (BMI), residency area (urban/rural), living alone, employment, years of study, age at first psychotic episode, years since first psychotic episode, first psychotic episode/multiple episodes. Only factors resulted as significantly associated with treatment discontinuation were included in the final Cox model. With haloperidol as the reference group we estimated hazard ratios (HR) for discontinuation for each of the other antipsychotic group with 95% confidence intervals (CI). Adjusted survival curves were generated using the Mean of Covariates Method. Subgroup comparisons were based on the Wilcoxon-Gehan test.

Results

Sample description

Socio-demographic and clinical characteristics of group patients at baseline are presented in Table I. There were no significant differences between treatment subgroups in most of the baseline socio-demographic and clinical characteristics, except for the diagnosis when all of the 5 diagnosis entities were analysed (p 0.04). Further analysis revealed that the distribution of schizophrenia-schizoaffective-schizophreniform diagnostics within treatment subgroups was different. There were more cases of schizophrenia in the haloperidol group (89%), and more cases of schizophreniform and schizoaffective disorder in olanzapine (32%) and quetiapine subgroup (27%), respectively. However, no significant differences between treatment subgroups were found for the first psychotic episode versus multiple episodes or for years since onset variables.

Treatment discontinuation

A total of 48 individuals (36.64%) discontinued their medication during the study period. As the proportion of patients who discontinued their antipsychotic agent did not reach 50% during the study, the median survival time for all cause treatment discontinuation could not be estimated from the Kaplan–Meier survival analysis. For subjects who discontinued, the median and average time to discontinuation with standard deviation (SD) were calculated for each antipsychotic, using descriptive statistics (Table II).

Mean and median time to treatment discontinuation were lowest in the haloperidol group (mean [SD] 5.85 [3.16] months, median 5.5 months), followed by risperidone (mean 7.77 [3.11] months, median 7.5 months), quetiapine and aripiprazole, while the mean time was highest in olanzapine treated group 8.9 [3.99] months (Figure 1). Differences between means were analyzed with ANOVA test and were not statistically significant; relatively close to the level of significance was the difference haloperidol - olanzapine (p=0.07).

Kaplan-Meier curves of time to any cause dis-

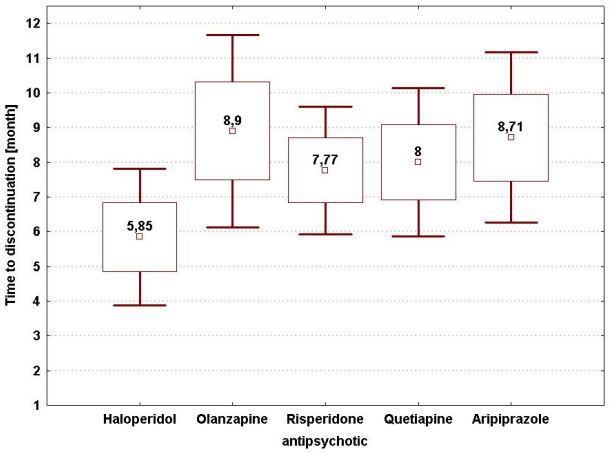

Figure 1 Time to discontinuation for patients who interrupted the treatment (mean+/-SD)

	Haloperidol (N=19)	Olanzapine (N=31)	Risperidone (N=28)	Quetiapine (N=33)	Aripiprazole (N=20)	TOTAL
Age, mean (SD)	42,32(11,47)	39,13(12,88)	41,43(10,98)	43,88(15,16)	38,95(14,92)	41,25(13,21)
Male	10/19(53%)	19/31(61%)	8/28(29%)	11/33(33%)	8/20(40%)	56/131(43%)
Years of study, mean (SD)	12,89(3,02)	13,26(2,24)	12,86(2,09)	12,73(2,82)	13,75(2,75)	13,06(2,55)
Urban residency (N,%)	14/19(74%)	25/31(81%)	24/28(86%)	23/33(70%)	14/20(70%)	100/131(76%)
Living alone (N,%)	4/19(21%)	3/31(10%)	8/28(29%)	6/33(18%)	3/20(15%)	24/131(18%)
Student or employed	10/19(53%)	20/31(65%)	19/28(68%)	14/33(42%)	11/20(55%)	74/131(56%)
Diagnostic*						
Schizophrenia	17/19(89%)	16/31(52%)	18/28(64%)	14/33(42%)	15/20(75%)	80/131(61%)
Schizophreniform	2/19(11%)	10/31(32%)	4/28(14%)	8/33(24%)	2/20(10%)	26/131(20%)
Schizoaffective	0/19(0%)	2/31(6%)	2/28(7%)	9/33(27%)	2/20(10%)	15/131(11%)
Acute psychoses	0/19(0%)	2/31(6%)	2/28(7%)	0/33(0%)	0/20(0%)	4/131(3%)
Delusional disord.	0/19(0%)	1/31(3%)	2/28(7%)	2/33(6%)	1/20(5%)	6/131(5%)
First psychotic episode	2/19(11%)	11/31(35%)	8/28(29%)	9/33(27%)	3/20(15%)	33/131(25%)
Age at onset	34,32(10,89)	34,52(12,94)	35,79(9,01)	35,88(15,49)	30,65(12,31)	34,51(12,5)
Years since onset	8,05(7,76)	4,48(5,3)	5,54(5,85)	7,29(8,38)	8,15(8,96)	6,49(7,29)
Number of prior hospitalisations	4(3,67)	2,42(2,31)	3,11(4,32)	3,64(4,28)	4,45(4,19)	3,41(3,92)
Antipsychotic naive	2/19(11%)	11/31(35%)	7/28(25%)	8/33(24%)	3/20(15%)	31/131(24%)

Table I Baseline characteristics of patients

** significant difference among treatment subgroups at p<0.05*

	Haloperidol (N=19)	Olanzapine (N=31)	Risperidone (N=28)	Quetiapine (N=33)	Aripiprazole (N=20)	Total/p
Mean dose (mg/day [SD])	7.89 [5.44]	14.52 [4.35]	4.93 [1.15]	366.67 [145.1]	11.38 [3.76]	
Discontinuation for any cause (n,%)	10/19 (52,63%)	8/31 (25,81%)	11/28 (39,29%)	12/33 (36,36%)	7/20 (35,00%)	48/131 (36.64%)
Month to discontinuation* (mean, [SE, 95% CI])	8.76 [0.86, 7.07-10.45]	11.2 [0.42, 10.38 -12.02]	10.34 [0.52, 9.31-11.37]	10. 55 [0.53, 9.51-11.58]	10.85 [0.54, 9.80-11.9]	10.44 [0.26, 9.94-10.95]
Cumulative proportion of maintaining therapy*	43.06%	64.62%	52.80%	54.86%	54.74%	
Median time to discontinuation** (months)	5.5 (n=10)	5.5 (n=8)	7.5 (n=11)	10 (n=12)	10 (n=7)	10 (n=48)
Mean time to discontinuation** (months [SD])	5.85 [3.16] (n=10)	8.9 [3.99] (n=8)	7.77 [3.11] (n=11)	8.00 [3.77] (n=12)	8.71 [3.3] (n=7)	7.75 [3.5] (n=48)
Cox-model treatment comparisons (HR [95% CI]) reference - haloperidol		0.45 [0.18-1.16] p 0.097	0.71 [0.3-1.67] p 0.427	0.61 [0.26-1.41] p 0.244	0.53 [0.20-1.39] p 0.2	p 0.51
Discontinuation because of insuffi ent effi cacy (n,%)***	0/19	1/31 (4.17%)	3/28 (15%)	9/33 (30%)	6/20 (31.58%)	19/131
Discontinuation because of side-eff ects (n,%)***	4/19 (15%)	6/31 (30%)	1/28 (31.58%)	0/33	0/20	11/131
Cox-model treatment comparisons (HR [95% CI]) reference - haloperidol	--	0.75 [0.20-2.78] p 0.666	0.19 [0.02-1,71] p 0.138	--	--	p 0.33
Discontinuation because of non-adherence (n,%)***	6/19 (40%)	1/31 (4.17%)	7/28 (29.17%)	3/33 (12.50%)	1/20 (7.14%)	18/131
Cox-model treatment comparisons (HR [95% CI]) reference - haloperidol	--	0.11 [0.01 0.92] p 0.042	0.78 [0.26-2.34] p 0.656	0.29 [0.07-1.18] p 0.084	0.15 [0.02-1.24] p 0.078	p 0.080

Table II Treatment discontinuation by antipsychotic

* *Kaplan Meier estimates at 12 months*
** *calculated for subjects who discontinued treatment*
*** *The percentages are Kaplan-Meier estimates of treatment discontinuation within 12 months*

continuation for each antipsychotic are presented in Figure 2. Differences between the curves for the 5 types of antipsychotics did not reach the level of statistical significance (p=0.21), but the rate of discontinuation for any reason was significantly higher in patients treated with haloperidol compared with patients treated with atypical antipsychotics (p = 0,039, Gehan's Wilcoxon Test) and in haloperidol compared to olanzapine group (p = 0,023, Gehan's Wilcoxon Test; p = 0,027, logrank test) (Figure 3).

The reason for discontinuation was inefficacy in 19/48 cases, non-adherence in 18/48 cases and adverse reactions in 11/48 cases. Of the 19 cases of discontinuation due to inefficacy 9 cases were in the quetiapine treated group, 6 cases in the group treated with aripiprazole, 3 cases in the group treated with risperidone and one case in the group treated with olanzapine. Kaplan-Meier surviving curves for discontinuation due to inefficacy are shown in Figure 4.

Even though the level of statistical significance was not reached when comparing all groups (p 0.071), rate of discontinuation due to ineffectiveness was significantly lower in patients treated

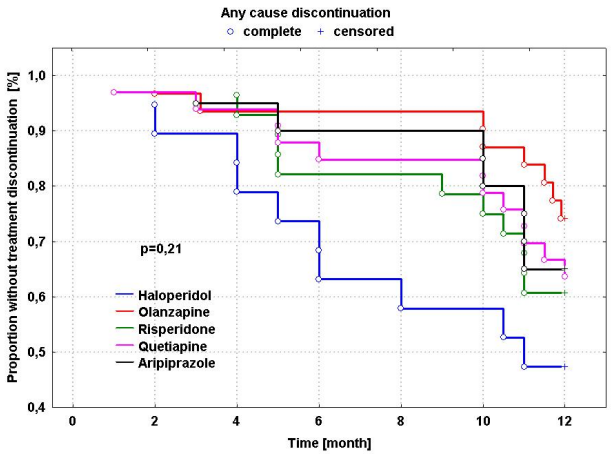

Figure 2 Rate of any cause treatment discontinuation (Kaplan-Meier survival curve n=131; (discontinued (completed) n=48, censored n=83) according to the treatment

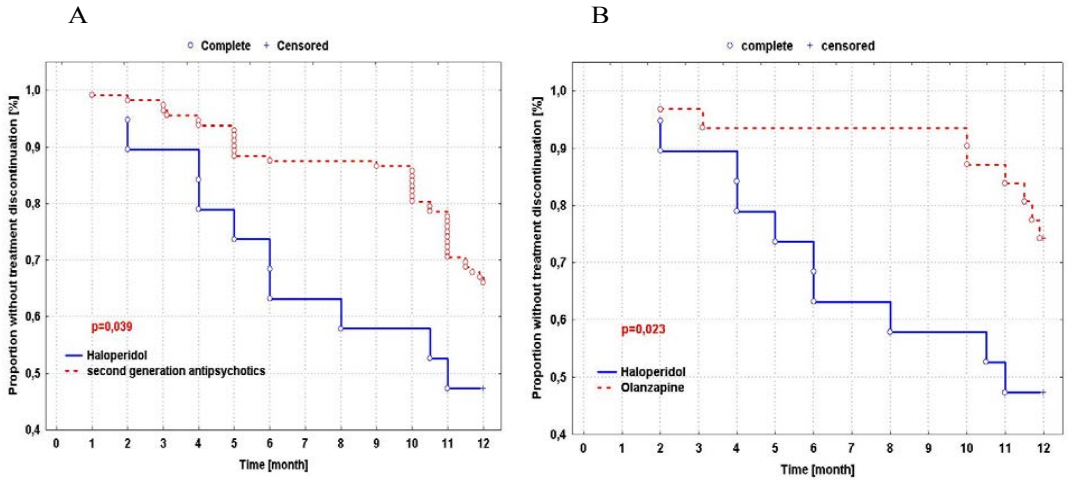

Figure 3 Rate of any cause treatment discontinuation (Kaplan-Meier survival curve n=131; discontinued (complete) n=48, censored n=83) according to the treatment: A. haloperidol – second generation antipsychotics; B. haloperidol – olanzapine

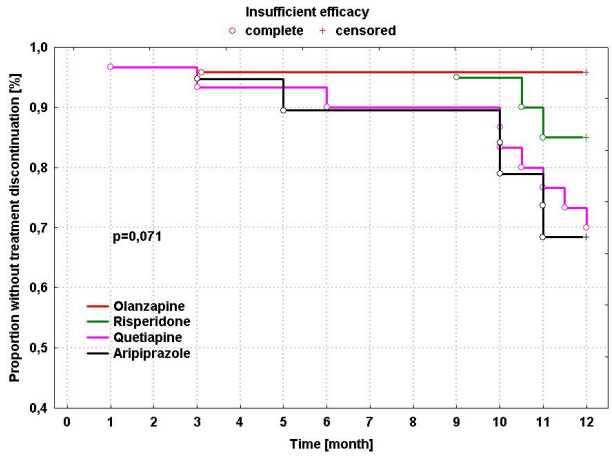

Figure 4 Rate of treatment discontinuation due to insufficient efficacy (Kaplan-Meier survival curve)

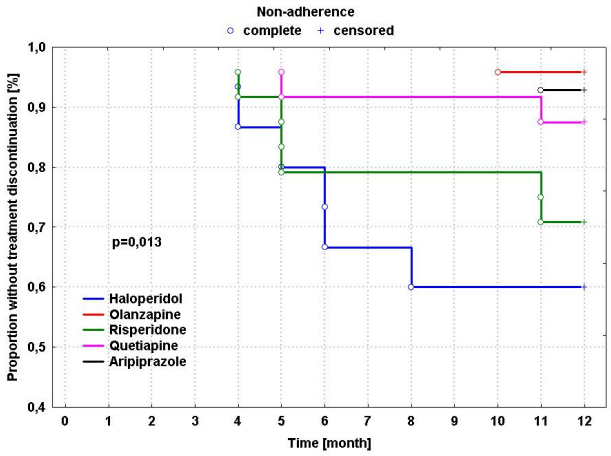

Figure 5 Rate of treatment discontinuation due to non-adherence (Kaplan-Meier survival curve)

with olanzapine compared to those treated with quetiapine (p 0.02) or aripiprazole (p 0.021) (Gehan's Wilcoxon Test). In case of discontinuation due to non-adherence, significant differences between Kaplan-Meier curves were found (Figure 5, Table III). The rate of discontinuation was, in descending order: haloperidol, risperidone, quetiapine, aripiprazole and olanzapine. The difference between olanzapine and haloperidol reached a high level of statistical significance (p <0.01). There were no cases of discontinuation due to adverse reactions in the groups treated with quetiapine or aripiprazole. From the total of 11 cases, 6 cases were in the olanzapine treated group, 4 in the haloperidol treated group, and 1 case in the group treated with risperidone; the only difference approaching statistical significance level was the haloperidol-risperidone (p = 0.06). Specific causes that led to discontinuation were extrapyramidal effects (4 cases in the group treated with haloperidol), weight gain (4 cases in the group treated with olanzapine), akathisia (1 case treated with olanzapine), erectile dysfunction (2 cases treated with olanzapine), and amenorrhea (one case treated with risperidone).

The only covariate detected as significantly associated with the rate discontinuation of the analyzed covariates (sex, age, years since onset, age at onset, duration of current episode, social activity, and first psychotic episode) was the first psychotic episode/ multiple episodes. In Cox analysis, the group of patients with at least one previous psychotic episode was associated with a 2.5-fold increased risk of treatment discontinuation, compared to first psychotic episode patients (HR=2.571 [CI 1.077-6.139], p 0.033). After adjustment for this covariate in the Cox model, resulted HR for discontinuation

	Haloperidol	Olanzapine	Risperidone	Quetiapine	Aripiprazole
Haloperidol		**	NS	*	*
Olanzapine			*/**	NS	NS
Risperidone				NS	NS
Quetiapine					NS

Table III Differences between pairs of antipsychotics in treatment discontinuation due to non-compliance - Gehan's Wilcoxon test

** statistically significant at p<0.05 level*
*** statistically significant at p<0.01 level*
NS not significant

with haloperidol as the reference group (Table II) confirmed the order of risk of discontinuation for any reason decreasing, but differences between groups did not reach the level of statistical significance. When the same analysis was performed differentiated according to specific causes, the only difference between treatment groups confirmed as statistically significant was in case of non-adherence, for olanzapine compared to haloperidol HR= 0.109 [CI 0.013-0.923], p 0.042. As there were no cases of discontinuation due to inefficacy in haloperidol treated group, we could not calculate HR with haloperidol as the reference group in this instance. For the same reason HR for aripiprazole and quetiapine could not be calculated in case of discontinuation due to side effects (no cases of discontinuation due to adverse reactions in those two antipsychotic groups) (Table II).

Discussion

Rate of discontinuation in this observational 12 months follow-up study in routine clinical practice settings of 131 patients with schizophrenia and related disorders was significantly higher in univariate analysis in patients treated with haloperidol compared to both atypical treated group and olanzapine treated group. Estimated probability of maintaining therapy at 12 months was maxim in olanzapine treated group (64.62%). These results are consistent with the majority of controlled clinical studies. A report published in July 2010 [17] from a meta-analysis of controlled clinical trials (RCT) showed that olanzapine had a lower rate of discontinuation compared to aripiprazole, quetiapine and risperidone, with sensitivity analysis confirming these results for subgroups of first episode of schizophrenia or in patients with symptoms resistant to treatment. Another systematic analysis of RCT found that olanzapine may be superior to other second generation antipsychotics in chronic schizophrenia [18]. The superiority of olanzapine in what treatment persistence is concerned was reported in controlled trials in patients with chronic disease [5,19,20], as well as in patients with first psychotic episode or schizophreniform disorder [21-23]. The differences observed between the antipsychotics were however lower in patients with first psychotic episode, compared with those seen in schizophrenia or related chronic disorders [24]. The differentiation of first episode disease/multiple episodes condition has also been detected in our study as an independent factor influencing the likelihood of interruption of antipsychotic treatment, which is why it was introduced as the covariate in the final Cox proportional hazard regression model. In the adjusted Cox analysis of differences between olanzapine and haloperidol in the rate of discontinuation for any reason did not reach statistical significance (HR 0.45 CI 0175-1156, p 0097). Although a possible explanation could be insufficient statistical power due to the relatively small number of patients in treated groups, the hypothesis that the differences detected in Kaplan-Meier analysis were not caused by the treatment cannot be rejected. Compared to clinical trials, in observational studies possible differences between antipsychotics in terms of discontinuation rates seem to be more difficult to prove, and if detected, they are many times different from one study to another [4,7,11,12,25]. The decreasing order of discontinuation risk for any reason in our group according to Kaplan Meier curves, with a minimum for olanzapine, comparable intermediate values for quetiapine and risperidone, and a maximum for haloperidol, is similar to that found by Ascher-Svanum et al. in 2008 [12] in a prospective non-interventional, follow-up 3 years study, which included 878 patients with schizophrenia. Different in our study was that we had no clozapine treated group, but we had instead a group treated with aripiprazole, the latest introduced among the studied atypical agents, characterized by particular pharmacological properties [26,27,28]. Nevertheless, there were studies in which the superiority of olanzapine could not be demonstrated [4]. With regard to haloperidol, it is worth mentioning that it was associated with the maximum discontinuation rate despite its usage in moderate doses (average dose 7.89 mg/day). This could be of interest because

most clinical trials with atypical antipsychotics have used relatively high doses of haloperidol as a comparator, which, according to some authors [29,30], could have influenced the results in favour of newer antipsychotics, an idea that is not, however, widely accepted [31].The results of observational studies are even more heterogeneous regarding the comparison between the antipsychotics placed in our study intermediary between olanzapine and haloperidol: risperidone, quetiapine and aripiprazole. For quetiapine, several studies have reported a relatively high risk of discontinuation, similar to that of first generation antipsychotics [7], or higher, when compared with olanzapine [11,25], and the results are contradictory for risperidone [32]. While observational studies that compared risperidone with olanzapine in patients with schizophrenia found significantly lower rates of discontinuation in the groups treated with olanzapine [33-35], Moisan and Grégoire [25] found a significantly longer time to interruption in individuals treated with risperidone or polytherapy (defined as more than one first-generation antipsychotic drug or combination of a first generation with a second generation drug) than those treated with olanzapine. In our study there were no significant differences between risperidone, quetiapine and aripiprazole.

In addition to most of observational studies to date comparing antipsychotic discontinuation rate from any cause [4,7,11,12,25,33-37], we recorded in our study the reason for discontinuation. The most common reason for discontinuation was inefficacy or insufficient efficacy, as in the large trials CATIE [5] and EUFEST [23], as well as in some observational studies, such as SOHO study [6,36]. In all these studies, the antipsychotics who held the extreme positions in a hierarchy of rates of discontinuation due to inefficacy were olanzapine, with the fewest treatment interruptions and quetiapine, with the highest rates of discontinuation due to inefficacy. A similar tendency of positioning for the two antipsychotics was also observed in our study, which additionally provides data on aripiprazole.

Contrary to the results of EUFEST trial, the only one from aforementioned studies that had a group treated with haloperidol, for which the discontinuation rate due to inefficacy was highest, we did not record any case of haloperidol discontinuation due to inefficacy. There are various possible explanation for this discrepancy, such as the different doses, which were lower in EUFEST study (1-4 mg), but even more important, the low number of patients in our study, especially in the haloperidol treated subgroup (n = 19), which was further reduced when analysis was performed on specific causes. Moreover, at this small number of subjects, the recording of one cause of another, when more than one cause explained the treatment interruption might have significantly altered the results. Although the patient's subjective perception must be a central concern, we cannot neglect the fact that patient decision of discontinuing treatment may have multiple explanations and may mask situations between which there are important clinical differences: insufficient relief of symptoms, lack of insight, or intolerable side effects. Capturing the patient before or after he/she has stopped the treatment by his/her own decision might lead to a different recorded reason of discontinuation, for the same patient. Scheduled visits every month at the beginning of EUFEST study, unlike in our study, in which the first scheduled visit after discharge was at 6 months could underlie the occurrence of such differences.

We noticed in our study a reversal of the extreme positions when the reason for discontinuation was related to side effects. Olanzapine had in this case the highest rate of discontinuation among atypicals, after that of haloperidol, while there were no cases of interruption from side effects in the quetiapine and aripiprazole treated groups. This change in the hierarchy, noted also in other studies, with the loss of superiority for olanzapine [5] and repositioning of quetiapine [23], might mask the differences between atypicals when the reason for the discontinuation is not taken into account. Curves obtained after analyzing discontinuation due to non-adherence paralleled those from any cause discontinuation, with more pronounced the difference between extreme groups haloperidol-olanzapine, the only difference that retained statistical significance after multivariate analysis. The parallelism between the results for all-cause discontinuation and those for the discontinuation due to patient decision has also been observed in CATIE trial [5], as well as in Ascher-Svanum's observational study [12], aimed to compare adherence and persistence to typical versus atypical antipsychotics and between specific atypicals in the usual care of schizophrenia The authors reported a strong correlation between adherence, assessed with specific tools (Medication Possession Ratio (MPR)), and persistence to treatment and suggested the possibility of interchanging the two measures, with applicability to both medical practice and research, provided the idea was confirmed [12].

The limits of our study are mainly related to its observational design. Potential selection bias could occur as a result of naturalistic design, non-randomized study, in which groups were different in terms of some variables at baseline. Despite detailed analysis of socio-demographic and clinical data of patients and statistical adjustments performed when possible for observed differences, other differences, that would have been missed, could have theoreti-

cally influenced the results. Although we cannot totally exclude the possibility of selection bias, it is important to note that our results are consistent with a number of studies previously mentioned, with different design and locations, both observational and randomized controlled trials, in which the possibility the bias is minimized. In studies with non-blinded design there is the theoretical risk of introducing observer bias, when the observer evaluation criteria differ from one group to another. However, is very unlikely that the results in our study could have been influenced this way, as the variable under investigation, discontinuation (yes/no), is not based on a subjective evaluation.

Although it has a limited potential for generalization of results, our study helps complete the picture data on maintenance antipsychotic treatment in usual clinical practice, including data on aspects less studied in observational studies to date, such as reason for discontinuation or comparison with groups treated with aripiprazole.

Conclusion

The results of this observational, one year follow-up study of patients treated with antipsychotics show that the differences between typical and atypical antipsychotics and between atypicals, not a homogeneous group, cannot be excluded in what persistence to treatment is concerned and suggests that the choice of antipsychotic may be an important factor in the long term evolution in patients with schizophrenia and related disorders. Interpretation of results must however be done with caution, given the limitations of the study, related mainly to its observational design.

References

1. Byerly MJ, Nakonezny PA, Lescouflair E. Antipsychotic medication adherence in schizophrenia. Psychiatr. Clin. North Am. 2007;30:437–452.

2. Awad AG. Antipsychotic medications: compliance and attitudes towards treatment. Curr Opin Psychiatry 2004;17(2):75-80.

3. Kreyenbuhl J, Slade EP, Medoff DR, et al. Time to discontinuation of first- and second-generation antipsychotic medications in the treatment of schizophrenia. Schizophr Res. 2011 May 14. doi:10.1016/j.schres.2011.04.028, accessed 2.06.2011

4. Weiden PJ. Understanding and addressing adherence issues in schizophrenia: from theory to practice. J Clin Psychiatry 2007;68(Supl 14):14-9.

5. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N. Engl. J. 2005;353 (12):1209–1223.

6. Haro JM, Novick D, Suarez D, Roca M. Antipsychotic treatment discontinuation in previously untreated patients with schizophrenia: 36-month results from the SOHO study. J Psychiatr Res. 2009;43:265–273.

7. Ascher-Svanum H, Zhu B, Faries D, Landbloom R, Swartz M, Swanson J. Time to discontinuation of atypical versus typical antipsychotics in the naturalistic treatment of schizophrenia. BMC Psychiatry. 2006;6:8.

8. Chen L, McCombs JS, Park J. Duration of antipsychotic drug therapy in real-world practice: a comparison with CATIE trial results. Value Health. 2008;11:487–496.

9. Haro JM, Novick D, Belger M, Jones PB. Antipsychotic type and correlates of antipsychotic treatment discontinuation in the outpatient treatment of schizophrenia. Eur Psychiatry. 2006;21:41–47.

10. Kilzieh N, Todd-Stenberg JA, Kennedy A, Wood AE, Tapp AM. Time to discontinuation and self-discontinuation of olanzapine and risperidone in patients with schizophrenia in a naturalistic outpatient setting. J Clin Psychopharmacol. 2008;28:74–77.

11. Mullins CD, Obeidat NA, Cuffel BJ, Naradzay J, Loebel AD. Risk of discontinuation of atypical antipsychotic agents in the treatment of schizophrenia. Schizophr Res. 2008;98:8–15.

12. Ascher-Svanum H, Zhu B, Faries DE, Lacro JP, Dolder CR, Peng X. Adherence and persistence to typical and atypical antipsychotics in the naturalistic treatment of patients with schizophrenia. Patient Prefer Adherence. 2008;2:67–77.

13. Dossenbach M, Arango-Dávila C, Silva Ibarra H, et al. Response and relapse in patients with schizophrenia treated with olanzapine, risperidone, quetiapine, or haloperidol: 12-month follow-up of the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study.J Clin Psychiatry. 2005;66:1021–1030.

14. Karagianis J, Williams R, Davis L, et al. Antipsychotic switching: results from a one-year prospective, observational study of patients with schizophrenia. Curr Med Res Opin. 2009;25:2121–2132.

15. Tamminga, C.A., 2006. Practical treatment information for schizophrenia. Am. J.Psychiatry 163 (4), 563–565.

16. E. R. Heerdink. Need for medicine-based evidence in pharmacotherapy. The British Journal of Psychiatry (2004) 184: 452.

17. McDonagh M, Peterson K, Carson S, Fu R, Thakurta S, Drug Effectiveness Review Project. Drug class review: atypical antipsychotic drugs. Final update 3 [Internet]. Portland (OR): Oregon Health and Science University; 2010. [cited 2011 Mar 16]. Available from: http://derp.ohsu.edu/final/AAP_final_report_update%203_version%203_JUL_10.pdf, accessed 31.05.2011

18. Johnsen E, Jørgensen HA: Effectiveness of second generation antipsychotics: a systematic review of randomized trials. BMC Psychiatry 2008, 8:3.

19. Stroup TS, Lieberman JA, McEvoy JP, et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. Am J Psychiatry 2006, 163:611-22.

20. Stroup TS, Lieberman JA, McEvoy JP, et al: Effectiveness of Olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia after discontinuing perphenazine: A CATIE study. Am J Psychiatry 2007,164:415-27.

21. Green AI, Lieberman JA, Hamer RM, et al. Olanzapine

and haloperidol in fi rst episode psychosis: two-year data. Schizophr Res 2006;86:234–43.

22. McEvoy JP, Lieberman JA, Perkins DO, et al. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. Am J Psychiatry 2007;164:1050–60.

23. Kahn R, Fleischhacker WW, Boter H, et al. Effectiveness of antipsychotic drugs in firstepisode schizophrenia and schizophreniform disorder: an open randomized clinical trial. Lancet 2008, 371:1085-97.

24. Johnsen E, Kroken RA, Wentzel-Larsen T, Jørgensen HA. Effectiveness of second-generation antipsychotics: a naturalistic, randomized comparison of olanzapine, quetiapine, risperidone, and ziprasidone. BMC Psychiatry. 2010;10:26.

25. Moisan, J., Grégoire, J.P. Patterns of discontinuation of atypical antipsychotics in the province of Québec: a retrospective prescription claims database analysis. Clin. Ther. 2010;32 (Suppl 1), S21–S31.

26. Voicu VA. Aripiprazolul – antipsihotic atipic cu un nou mecanism de actiune. Terapeutica, farmacologie si toxicologie clinica 2005;9 (1):7-16.

27. Gheorghe MD; Voicu V.A.; Vasile D; Vasiliu O; Grigorescu G. Negative and cognitive symptomatology improvement during aripiprazole treatment in chronic schizophrenia, European Neuropsychopharmacology 2006;16 Suppl. 4: S409-S410.

28. Voicu VA, de Leon J, Medvedovici AV, Rădulescu FS, Miron DS. New insights on the consequences of biotransformation processes on the distribution and pharmacodynamic profiles of some neuropsychotropic drugs. Eur Neuropsychopharmacol. 2011, doi:10.1016/j.euroneuro.2011.08.004.

29. Geddes J, Freemantle N, Harrison P, et al.. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and metaregression analysis. BMJ 2000, 321:1371–6.

30. Rosenheck RA.. Open forum: effectiveness versus efficacy of second generation antipsychotics: haloperidol without anticholinergics as a comparator. Psychiatr Serv 2005, 56:85–92.

31. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009; 373(9657):31–41.

32. Voicu V, Medvedovici A, Miron D, Radulescu F. A novel approach on pharmacokinetic/pharmacodynamic correlations of risperidone: understanding its safety and efficacy profiles. Acta Endocrinologica 2010;6(2):265-285.

33. Cooper, D., Moisan, J., Gaudet, M., Abdous, B., Grégoire, J.P. Ambulatory use of olanzapine and risperidone: a population-based study on persistence and the use of concomitant therapy in the treatment of schizophrenia. Can. J. Psychiatry 2005;50 (14),901–908.

34. Ren, X.S., Qian, S., Lee, A.F., Herz, L., Miller, D.R., Kazis, L.E. Treatment persistence: a comparison among patients with schizophrenia who were initiated on atypical antipsychotic agents. J. Clin. Pharm. Ther. 2006;31 (1), 57–65.

35. Kilzieh, N., Todd-Stenberg, J.A., Kennedy, A., Wood, A.E., Tapp, A.M. Time to discontinuation and self-discontinuation of olanzapine and risperidone in patients with schizophrenia in a naturalistic outpatient setting. J. Clin. Psychopharmacol. 2008;28 (1), 74–77.

36. Kelin K, Lambert T Jr, Brnabic AJ, et al. Treatment discontinuation and clinical outcomes in the 1-year naturalistic treatment of patients with schizophrenia at risk of treatment nonadherence. Patient Prefer Adherence 2011;5:213-22.

37. Ciudad A, Haro JM, Alonso J, et al. The Schizophrenia Outpatient Health Outcomes (SOHO) study: 3-year results of antipsychotic treatment discontinuation and related clinical factors in Spain. Eur Psychiatry. 2008;23(1):1-7.