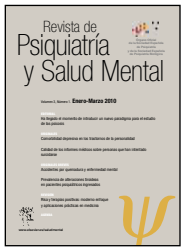
Rev Psiquiatr Salud Ment (Barc.) 2010;**3(3)**:106–110

Revista de Psiquiatría y Salud Mental

www.elsevier.es/saludmental



SHORT ORIGINAL ARTICLE

Quetiapine treatment in adolescents: a 6-month naturalistic study

David Fraguas[a,b,*], Mara Parellada[a], Dolores Moreno[b], and Celso Arango[b]

[a]*Servicio de Salud Mental, Complejo Hospitalario Universitario de Albacete, Albacete, Spain*
[b]*Unidad de Adolescentes, Departamento de Psiquiatría, Hospital General Universitario Gregorio Marañón, Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, Madrid, Spain*

Received March 17, 2010; accepted June 23, 2010

KEYWORDS
Adolescent;
Antipsychotics;
Compliance;
Discontinuation;
Parkinsonism

Abstract
Introduction: The aim of this study was to evaluate discontinuation of quetiapine treatment in adolescents (12-18 years) in a 6-month naturalistic follow-up study and to assess the influence of distinct demographic and clinical factors on quetiapine discontinuation.
Material and methods: We performed a naturalistic 6-month follow-up study in 61 antipsychotic-naïve patients [39 boys (64%)] who initiated quetiapine treatment. The dependent variable was treatment discontinuation for any cause (continuation/discontinuation was a dichotomic variable). The independent variables were age, gender, race, duration of mental illness, Global Assessment of Functioning (GAF) score at treatment initiation, adverse effects in the first 16 days of treatment, the presence of involuntary movements before starting treatment, and abusive consumption or toxic dependency.
Results: Of the 61 patients participating in the study, 42 (68.9%) complied with quetiapine treatment for 6 months, while 19 (31.1%) discontinued the treatment (for any cause). The presence of Parkinson-like symptoms before starting treatment was a risk factor for discontinuation (Hazard ratio=8.3, *P*=.007).
Conclusions: Continuation/discontinuation of quetiapine was influenced by the presence of motor symptoms before treatment initiation, which therefore affected the patient's overall prognosis. Consequently, we recommend that the presence of motor symptoms be evaluated before treatment with antipsychotic drugs is started.

*Corresponding author.
E-mail: david.fraguas@cibersam.es (D. Fraguas).

1888-9891/$ - see front matter

PALABRAS CLAVE
Adolescente;
Antipsicótico;
Cumplimiento;
Discontinuación;
Parkinsonismo

Tratamiento con quetiapina en adolescentes: estudio naturalístico de 6 meses de seguimiento

Resumen
Introducción: Este trabajo pretende evaluar la discontinuación del tratamiento con quetiapina en pacientes adolescentes (12-18 años) en un seguimiento naturalístico de 6 meses, así como valorar la influencia de distintos factores demográficos y clínicos sobre la suspensión de quetiapina.
Material y métodos: Seguimiento naturalístico a 6 meses de un total de 61 pacientes (39 varones (64,0%) naïve para antipsicóticos que iniciaron tratamiento con quetiapina. La variable dependiente fue la suspensión del tratamiento por cualquier causa (continuación/discontinuación en forma de variable dicotómica). Las variables independientes analizadas fueron: edad, género, raza, tiempo de evolución de enfermedad mental, puntuación GAF al inicio de tratamiento, síntomas adversos en los primeros 15 días de tratamiento, presencia de movimientos involuntarios antes del inicio del tratamiento, y consumo abusivo o dependencia de tóxicos.
Resultados: De los 61 pacientes que participaron en el estudio, 42 (68,9%) cumplieron el tratamiento con quetiapina durante los 6 meses de tratamiento, mientras que 19 (31,1%) discontinuaron el tratamiento (cualquier causa). La presencia de síntomas parkinsoniformes antes de comenzar el tratamiento constituyó un factor de riesgo para la discontinuación de la medicación (Hazard Ratio = 8,3, p = 0,007).
Conclusiones: La presencia de sintomatología motora antes de la primera prescripción de antipsicótico influye sobre la continuación/discontinuación de la medicación y, por tanto, sobre la evolución global del caso. Por ello, recomendamos evaluar la presencia de sintomatología motora antes del inicio del tratamiento farmacológico con antipsicóticos.

Introduction

Follow-up studies after a first psychotic episode show that up to 30% to 50% of patients suffer a relapse of symptoms during the first year after the onset of treatment.[1,2] Although anti-psychotic drugs have proven to be effective at reducing relapse rates in patients suffering their first psychotic episode,[2] it is considered that, during the first year of follow-up, around 40%-70% of the patients with a first psychotic episode stop taking their medication, and another 20% fail to adhere to the treatment guidelines correctly.[1,3] Therefore, the most common risk factor for relapse is suspending treatment.[2] Therefore, the time lapsed until treatment is suspended is an important predictor of antipsychotic effectiveness, whatever the cause of the suspension.[4] Continuing treatment with antipsychotic drugs is an important predictive factor of clinical progress, in particular in the early stages of the disease.[5] Studies of adherence to pharmacological treatment in patients after a first psychotic episode have suggested that abandoning treatment is more common among adolescents than the adult population with a long-term illness.[1,6,7] However, although there are a few exceptions,[8,9] most studies into antipsychotic medication compliance have been performed in adults. Therefore, data about compliance or non-compliance with antipsychotic medication in adolescents are very useful, especially if they provide information about variables which can predict treatment discontinuation.

This paper aims to assess the continuation/discontinuation of quetiapine treatment in adolescent patients (12-18 years) in a 6-month naturalistic follow-up study, and assess the influence of different demographic and clinical factors on abandoning quetiapine.

Method

All the adolescents (12-18 years) who began quetiapine treatment (as the first and only antipsychotic in their life) in the *Unidad de Adolescentes del Hospital General Universitario Gregorio Marañán* (Adolescent Unit at the Gregorio Marañán University General Hospital [HGUGM]) between August 2005 and February 2008 were invited to participate in this 6-month naturalistic follow-up study. A total of 61 patients (39 male [64.0%], with a mean age of 16.3 [SD, 1.0] years) fulfilled these requirements. The study was approved by the Ethics and Clinical Research Committees at the HGUGM. All the legal representatives signed an informed consent form before inclusion in the study and the patients gave their consent to the study.

The indication to prescribe quetiapine and the dose given were determined by psychiatrists, based on clinical criteria. Adjuvant medication was permitted, except other antipsychotic drugs. The study's dependent variable was discontinuing quetiapine treatment for any reason (patient's or healthcare professional's decision) during the 6 months

of follow-up. The patients who informed the interviewer that they had stopped taking the medication for over 24h were classified in the treatment discontinuation group. For those patients whose information was not very reliable, the interviewer checked the answers with an extra informer (e.g. a parent).

The independent variables were the following: age, sex, race, mental illness evolution time, GAF score at onset of treatment, adverse symptoms in first 15 days of treatment (assessed with the UKU scale),[10] involuntary movements before onset of treatment (dyskinesia, akathisia or Parkinsonism; assessed with the AIMS scale),[11] drug abuse or dependency (tobacco, alcohol, cannabis, cocaine, opiates, designer drugs, assessed in accordance with DSM-IV criteria), and diagnosis.

To standardise the diagnosis, in the initial interview and the one at 6 months, the study used a Spanish translation of the K-SADS-PL semi-structured interview,[12] which is based on DSM-IV criteria. In view of the characteristics of the sample, a dichotomous classification was used for the diagnoses: psychotic disorders (schizophrenia, bipolar disorder, schizoaffective disorder, schizophreniform disorder, or brief psychotic disorder) or non-psychotic disorders (1 patient diagnosed with obsessive compulsive disorder, and 3 with eating disorders).

Statistical analysis: means and standard deviation (SD) were used to describe the continuous variables, and frequencies and percentages to describe the discrete variables. A bivariate analyses were performed of the dependent variable (continuation/discontinuation) and each of the independent variables. The Chi-square test (or Fisher's exact test when necessary) was used to study the correlation between discrete variables. The Mann-Whitney U test was used to compare quantitative measures. Then, a Cox regression analysis was performed (continuation/discontinuation as the dependent variable; treatment time until discontinuation as the time variable; independent variables as covariables) to calculate the influence of the independent variables on quetiapine treatment continuation/discontinuation in the 6 months of follow-up. All the statistical tests were bilateral. The significance level was set at $P<.05$. The statistical analysis was performed using the SPSS, version 16.0 for Windows.

Results

Of the 61 patients that participated in the study, 42 (68.9%) completed the 6 months of quetiapine treatment, while 19 (31.1%) discontinued treatment (for some reason). Table 1 shows the findings of the bivariate analysis.

All the patients who completed the follow-up had a diagnosis of psychosis, while 4 of the 19 patients (21.1%) who dropped out had a diagnosis different to psychosis ($P=.007$).

Parkinson's-like symptoms, assessed before starting treatment, appeared in 15.8% of the patients who dropped out, but in only 2.4% of those who completed the study ($P=.021$).

The Cox regression analysis showed that the presence of Parkinson's-like symptoms before beginning treatment was a risk factor for treatment discontinuation (Hazard Ratio [HR]=8.3, $P=.007$).

Tabla 1 Independent variables in accordance with quetiapine treatment discontinuation

Variable	Total N=61	Complete 6 months N=42	Drop out before 6 months N=19	
Age, years (SD) range	16.3 (1.0), 14-18	16.3 (0.9), 14-17	16.2 (1.1), 15-18	
Sex				
	M: N (%)	39 (63.9%)	27 (64.3%)	12 (63.2%)
	F: N (%)	22 (36.1%)	15 (35.7%)	7 (36.8%)
Race (Caucasian) N (%)	53 (86.9%)	35 (83.3%)	18 (94.7%)	
Diagnosis (psychotic disorder) N (%)	57 (93.4%)	42 (100%)**	15 (78.9%)**	
Evolution time of condition (weeks)	14.7 (11.7)	12.1 (11.4)	19.3 (12.3)	
Baseline GAF score	63.5 (11.7)	61.8 (10.8)‡	77.5 (10.6)‡	
Tobacco habit, N (%)	26 (42.6%)	18 (42.9%)	8 (42.1%)	
Cannabis, N (%)	24 (39.3%)	16 (38.1%)	8 (42.1%)	
Cocaine N (%)	2 (3.2%)	2 (4.8%)	0	
Alcohol, N (%)	19 (31.1%)	15 (35.7%)	4 (21.0%)	
Designer drugs, N (%)	4 (6.6%)	4 (9.5%)	0	
Opiates N (%)	0	0	0	
Drugs (any) N (%)	28 (45.9%)	20 (47.6%)	8 (42.1%)	
Positive UKU	10 (16.4%)	9 (21.4%)	1 (5.3%)	
Dystonia N (%)	9 (14.8%)	7 (16.7%)	2 (10.5%)	
Parkinsonism, N (%)	4 (6.6%)	1 (2.4%)*	3 (15.8%)*	
Akathisia, N (%)	0	0	0	

Significance level (comparison between the group that completed treatment and the group that did not): *($P<.05$), **($P<.01$), ***($P<.001$), ‡($P<.1$ and $\geq.05$).

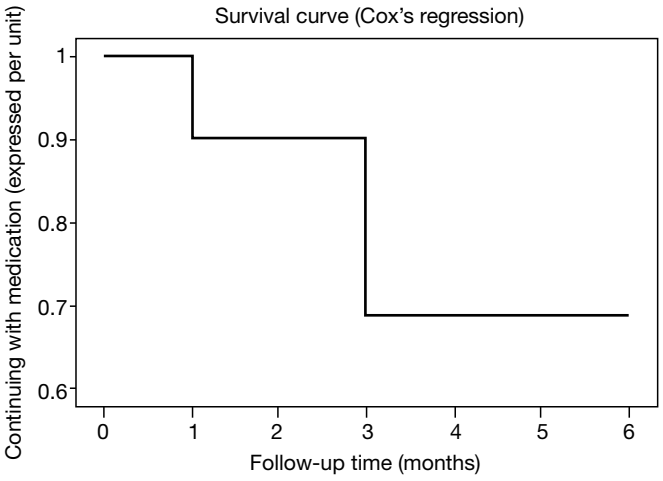


Figure 1 Overall continuation/discontinuation rates during follow-up.

Age (HR=0.9, *P*=.711), sex (HR=1.1, *P*=.778), race (HR=0.4, *P*=.275), GAF score (HR=1.1, *P*=.112), evolution time of condition (HR=1.0, *P*=.327), presence of adverse symptoms (assessed with UKU scale) (HR=0.3, *P*=.256), presence of dyskinesia or akathisia (HR=1.1, *P*=.881), drug abuse or dependence (HR=0.8, *P*=.790), diagnosis (HR=1.2, *P*=.105) had no significant influence on treatment discontinuation. Figure 1 shows the overall continuation/discontinuation rates during follow-up.

Discussion

A third of the patients in this study discontinued quetiapine treatment in the first 6 months, the decision being made by either the patient or the healthcare professional. This figure is higher than those in 3-month follow-up studies of first-episode psychosis patients (19%[8] and 15.4% [unpublished data, Álvarez-Segura et al., sent for publication]). However, our figures for quetiapine treatment discontinuation are significantly lower than those in 12-month follow-up studies with patients with early onset psychosis (70%),[3] a first psychotic episode (50%)[13] or long-term psychosis (80%).[4] The difference between our discontinuation rates (31.1% in 6 months of follow-up) and those of the 12-month studies could be attributed to the duration of the follow-up. But it is also worth highlighting that the follow-up carried out by the team at the *Unidad de Adolescentes* (Adolescent Unit) at HGUGM has a specific clinical programme with psychosocial support (group therapy, psycho-education, frequent visits), which may have contributed to these lower discontinuation rates.

Our study found that the presence of extrapyramidal symptoms before beginning treatment led to an 8.3-fold increase in the risk of discontinuing medication during the 6 months of follow-up. For many years, the onset of Parkinsonism as an adverse effect of the treatment has been known to increase the risk of abandoning medication.[14] However, our findings suggest that the presence of this type of involuntary movement before beginning the treatment is already a risk factor for discontinuation. This finding seems to be in conflict with quetiapine's favourable extrapyramidal side effects profile.[15] In this respect, the lack of comparative data with other drugs is an important limitation of this study. Another notable limitation is the lack of data about the specific causes for abandoning treatment.

Forty-two patients who completed follow-up were diagnosed with psychosis, while 4 of the 19 patients (21.1%) who dropped out were diagnosed with a different disorder, i.e. none of the 4 patients who had a diagnosis different to psychosis completed the study. However, the regression analysis did not reveal diagnosis to be a risk factor for discontinuation. Naturally, the reduced sample size may have led to a false negative, with significant differences not being detected.

As a general conclusion, our results suggest that the presence of extrapyramidal symptoms before being prescribed an antipsychotic drug affects treatment continuation/discontinuation and, thus, the patients' overall clinical progress. Therefore, we recommend assessing the presence of motor symptoms before beginning treatment with quetiapine, or probably any other antipsychotic drug.

Funding

This study was funded by Astra-Zeneca.

References

1. Coldham EL, Addington J, Addington D. Medication adherence of individuals with a first episode of psychosis. Acta Psychiatr Scand. 2002;106:286-90.
2. Ucok A, Polat A, Cakir S, Genc A. One year outcome in first episode schizophrenia. Predictors of relapse. Eur Arch Psychiatry Clin Neurosci. 2006;256:37-43.
3. McEvoy JP, Lieberman JA, Perkins DO, Hamer RM, Gu H, Lazarus A, 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.
4. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353:1209-23.
5. Wunderink L, Nienhuis FJ, Sytema S, Slooff CJ, Knegtering R, Wiersma D. Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. J Clin Psychiatry. 2007;68:654-61.
6. Kampman O, Laippala P, Vaananen J, Koivisto E, Kiviniemi P, Kilkku N, et al. Indicators of medication compliance in first-episode psychosis. Psychiatry Res. 2004;110:39-48.
7. Agarwal MR, Sharma VK, Kishore Kumar KV, Lowe D. Non-compliance with treatment in patients suffering from schizophrenia: a study to evaluate possible contributing factors. Int J Soc Psychiatry. 1998;44:92-106.
8. Gearing RE, Charach A. Medication adherence for children and adolescents with first-episode psychosis following hospitalization. Eur Child Adolesc Psychiatry. 2009;18:587-95.
9. Fraguas D, Llorente C, Rapado-Castro M, Parellada M, Moreno D, Ruiz-Sancho A, et al. Attitude toward antipsychotic medication as a predictor of antipsychotic treatment discontinuation in first episode early-onset psychosis. Revista de Psiquiatría y Salud Mental. 2008;1:10-7.

10. Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl. 1987;334:1-100.
11. Guy W. ECDEU Assessment Manual for Psychopharmacology, revised ed. Washington, DC: US Department of Health, Education, and Welfare; 1976.
12. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. JAACAP. 1997;36:980-8.
13. Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, et al, EUFEST study group. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet. 2008;371:1085-97.
14. Robinson DG, Woerner MG, Alvir JM, Bilder RM, Hinrichsen GA, Lieberman JA. Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. Schizophr Res. 2002;57:209-19.
15. Correll CU. Antipsychotic use in children and adolescents: minimizing adverse effects to maximize outcomes. J Am Acad Child Adolesc Psychiatry Jan. 2008;47:9-20.