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Amoxapine as an Atypical Antipsychotic: A Comparative Study *Vs* Risperidone

Rogelio Apiquian*[,1,4], Ana Fresan[2], Rosa-Elena Ulloa[3,4], Camilo de la Fuente-Sandoval[4], Miguel Herrera-Estrella[5], Alejandra Vazquez[4,5], Humberto Nicolini[4,6] and Shitij Kapur[7]

[1]Department of Psychiatry, National Institute of Neurology and Neurosurgery Manuel Velasco Suarez, Mexico City, Mexico; [2]Clinical Research Division, National Institute of Psychiatry Ramón de la Fuente, Mexico City, Mexico; [3]Child Psychiatric Hospital JN Navarro, Mexico City, Mexico; [4]Carracci Medical Group, Mexico City, Mexico; [5]Psychiatric Hospital Fray Bernardino Alvarez, Mexico City, Mexico; [6]Department of Genomic Medicine, Mexico City University, Mexico City, Mexico; [7]Schizophrenia Program and the Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Amoxapine is marketed as an antidepressant. However, its *invitro* profile, receptor occupancy and preclinical effects are very similar to atypical antipsychotics. Amoxapine has also shown efficacy as an atypical antipsychotic in open trials. The objective of this study was to compare the antipsychotic and side effect profile of amoxapine and risperidone in a randomised assignment, standardized dosing, double-blind trial of acutely psychotic patients with schizophrenia. A total of 48 schizophrenic patients were enrolled and randomized in a double-blind 6-week trial to receive either risperidone (up to 5 mg/day) or amoxapine (up to 250 mg/day). Positive, negative, affective symptoms and motor side effects were measured using standardized weekly assessments. Prolactin levels were also determined at baseline and at the end of the study. A total of 39 patients (amoxapine, $n = 22$; risperidone, $n = 21$) completed the trial. Both pharmacological treatments, amoxapine 228.0 mg/day (SD = 34.6) and risperidone 4.5 mg/day (SD = 0.7), showed equivalent improvement in positive, negative, and depressive symptoms. Amoxapine was associated with less EPS and less prolactin elevation than risperidone. These data support previous reports about the efficacy of amoxapine as an atypical antipsychotic. Since amoxapine is off-patent, it may be a valuable low-cost alternative to new atypical antipsychotics, particularly in low-income countries where the majority of the patients are still treated with typical antipsychotics.
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INTRODUCTION

The introduction of atypical antipsychotics represents an advance in the treatment of schizophrenia because they are generally better tolerated than conventional antipsychotics and have been associated with improved efficacy in certain domains (Kinon and Lieberman, 1996). However, they are many times more expensive than older options, thus practically inaccessible for most patients with schizophrenia around the world. This has led to search for pharmacological alternatives like the minimum effective doses of conventional antipsychotic drugs (Emsley *et al*, 1999; McEvoy *et al*, 1991; Oosthuizen *et al*, 2001) or the study of older and off-patent drugs for possible atypical antipsychotic efficacy.

Given our interest in this question, we chose to examine amoxapine's therapeutic potential as an atypical antipsychotic, given that first, amoxapine is a close chemical relative of clozapine, a dibenzazepine (Greenblatt *et al*, 1978); second, as an antidepressant it was noted to be especially effective in psychotic depression (Anton and Burch, 1990; Anton and Sexauer, 1983; Lydiard and Gelenberg, 1981); third, it blocks serotonin 5HT2 and dopamine D2 receptors in normal healthy volunteers, and *in vitro* its 5HT2/D2 and D4/D2 ratios are similar to those of clozapine (Kapur *et al*, 1999; Stockmeier *et al*, 1993), and finally, at a preclinical level, amoxapine, like risperidone, olanzapine and clozapine, shows a wide therapeutic window between the efficacy/mesolimbic doses *vs* doses at which it causes catalepsy/striatal effects (Greenblatt *et al*, 1978; Wadenberg *et al*, 2000).

In keeping with this, a prospective open-label study with 17 schizophrenic patients showed that amoxapine was associated with a clinically significant improvement in

*Correspondence: Dr R Apiquian, Department of Psychiatry, National Institute of Neurology and Neurosurgery Manuel Velasco Suarez, Av. Insurgentes Sur 3877, Mexico City, 14296 Mexico, Tel: 5255 56115822, Fax: 5255 56150067,
E-mail: rogelioapiquian@yahoo.com.mx
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positive, negative, and general symptoms. Also, a trend towards improvement in independently measured affective symptoms and a low propensity for extrapyramidal side effects was observed (Apiquian *et al*, 2003).

Given the strong rationale and the encouraging results from the open-label study, the purpose of this study was to test the 'atypical antipsychotic' potential of amoxapine by comparing it to the leading atypical antipsychotic, risperidone, in a double-blind clinical evaluation. The main hypotheses of the present study were: (a) amoxapine would show an antipsychotic effect comparable to risperidone's; (b) amoxapine would not show treatment emergent extrapyramidal symptoms (EPS) and would be comparable to risperidone in this regard; and (c) amoxapine would show a lesser degree of prolactin elevation and weight gain than risperidone.

METHODS

Study Setting

The study was conducted in accordance with Good Clinical Practices and the World Medical Association Declaration of Helsinki, Edinburgh 2000. The study protocol was approved by the Institutional Review Boards of the Centre for Addiction and Mental Health at the University of Toronto and Carracci Medical Group, Mexico City. Written informed consent was obtained after the procedures had been fully and detailed explained to patients.

Subjects

The subjects were recruited from the inpatient, emergency, and outpatient services of two public hospitals at Mexico City. Patients were included in the study if they met the following criteria: (1) Men and nonpregnant, nonlactating women aged between 18 and 50 years; (2) DSM-IV criteria for schizophrenia; (3) free of concomitant medical or neurological illness (as per review of systems, general physical examination, and a baseline laboratory evaluation); (4) free of DSM-IV current substance abuse or a history of substance dependence in the last 6 months; and (5) baseline PANSS positive syndrome score at least 16, with two items scoring at least four. Patients were excluded if (1) they had a history of bipolar disorder; (2) a high risk for suicide or high risk for agitation/violence; (3) they were pregnant or child-bearing age women who were not practising reliable forms of contraception; (4) were refractory to antipsychotics (defined as those who have received more than two typical or atypical neuroleptics, at doses equivalent to 5 mg/day of haloperidol, for at least 6 weeks each with little significant clinical improvement; and (5) had a history of previous adverse response to risperidone.

Study Design and Procedures

This was a 6-week, randomized, double-blind, flexible, dose-controlled study. Patients on oral antipsychotics prior to entry into the study participated in a 3-day washout, while patients receiving depot antipsychotic therapy prior to study entry underwent in a washout period of one cycle plus 1 week. After the baseline evaluation, subjects were titrated to the starting dose of 150 mg/day of amoxapine or 3 mg/day of risperidone within 3 days. The dose ratio of 50 : 1 was chosen based on PET data which suggested that this ratio would give raise to similar effects on 5-HT2 and D2 receptors (Kapur *et al*, 1999). The dose was held at 150 or 3 mg till day 14. Patients who showed 'much improvement' (reflected by a score of >3 on a CGI-Improvement) by day 14 of treatment continued with this dose for the rest of the study. Those patients who showed 'no' or 'little' improvement (reflected by a score of <2 on a CGI-Improvement) have their dose increased to 200 mg/day of amoxapine or 4 mg/day of risperidone at day 14 and if necessary 250 mg/day of amoxapine or 5 mg/day of risperidone on day 21. Symptoms and safety assessments were obtained at screening, baseline, and throughout the double-blind treatment phase.

Psychotropic drug administration other than the prescribed study medication was prohibited throughout the study except for benzodiazepines prescribed for anxiety, insomnia, or emerging agitation as deemed necessary by the investigator. The maximum daily benzodiazepine dose was not to exceed the equivalent of 4 mg/day of lorazepam. Anticholinergic drugs for EPS were permissible if clinically indicated. All concomitant medication use was recorded.

Assessments

Efficacy. Psychopathology was assessed by using the Positive and Negative Syndrome Scale (30 items, 1–7 severity scale) (Kay *et al*, 1990), the Calgary Depression Scale for Schizophrenia (CDSS) (Addington *et al*, 1996), and the Clinical Global Impression—Severity of Illness (CGI-S) and Improvement of Illness (CGI-I) scales (Guy, 1976). The reliability of these scales, as measured using intraclass correlation coefficients, were between 0.80 and 0.91, as established in previous studies of similar populations in our Centre (Apiquian *et al*, 1997). The CGI-S was administered at baseline and weekly, the CGI-I was rated weekly, while the PANSS and the CDSS were administered at baseline, weeks 2, 4, and 6. The response criteria *a priori* specified in the study required a $\geqslant$30% decrease from baseline in PANSS total score to study end point.

Safety. Extrapyramidal side effects were evaluated at baseline, weeks 2, 4, and 6 using the Simpson-Angus Scale (SAS) (Simpson and Angus, 1970) and the Barnes Akathisia Rating Scale (BAS) (Barnes, 1989). The Abnormal Involuntary Movement Scale (AIMS) (National Institute of Mental Health, 1975) was used at baseline and at the end point of the study.

Further safety investigations included electrocardiogram (EKG), vital signs, and body weight measurement. Laboratory testing of blood included determination of fasting total glucose and prolactin assays. Prolactin levels were determined using an automated two-site chemiluminometric immunoassay with a minimum detectable limit of 0.3 ng/ml and a coefficient of variance of 3.6–4.5% (ACS, Ciba-Corning Diagnostics). These measurements were determined at baseline, week 3 and at the end of the study.

Statistical Procedures

Demographic and clinical characteristics description was done with frequencies and percentages for categorical variables and with means and standard deviations (SD) for continuous variables. Chi square test (χ^2) was used for categorical contrasts. Patients were included in the analysis of mean change from baseline to last-observation-carried-forward (LOCF) end point if the patient had received at least one dose of double-blind medication and had at least one efficacy measurement during the study. In addition, patients who completed the study were included in an observed-cases (OC) using analysis of covariance (ANCOVA) model, which contained baseline status as covariate, and the treatment as the effect of interest. The primary efficacy parameter was the change in PANSS total score from baseline to end point. Secondary efficacy parameters included change from baseline to end point in the CGI-S score, end point values of the CGI-I score, and change from baseline to end point in the CDSS score. The analysis of safety measures included changes in vital signs, body weight, EKG, clinical laboratory tests, BAS, SAS, and AIMS scores. Statistical tests were two-sided and performed at 0.05 significance level.

RESULTS

Patients

A total of 48 schizophrenic patients were recruited and randomized; five patients were lost at the first week of the follow-up (amoxapine $n=3$, risperidone $n=2$) and were excluded from analysis as there was no postbaseline measurement in these subjects. The remaining 43 patients were assigned to amoxapine ($n=22$) or risperidone ($n=21$) treatment. Completion rates between the risperidone-treated ($n=20$, 95.2%) and the amoxapine-treated ($n=19$, 86.4%) patients were not significantly different ($\chi^2=1.00$, df 1, $p=0.31$). Two patients from the amoxapine group and one from the risperidone group failed to complete the study because of lack of efficacy while one patient from the amoxapine group did not consent after week 4.

A total of 51.2% ($n=22$) of the sample were men and 48.8% ($n=21$) were women. The mean age of the patients was 30.8 years (SD = 9.0, range 18–50 years). The educational level was 10.2 years (SD = 3.5, range 0–18 years), 93.0% ($n=40$) were single and 53.5% ($n=23$) were unemployed at their recruitment. Diagnoses of the sample were paranoid schizophrenia (69.8%, $n=30$), undifferentiated schizophrenia (16.3%, $n=7$), and disorganized schizophrenia (14.0%, $n=6$). The mean length of illness was 330.0 weeks (SD = 367.4, range 24–1872 weeks).

Prior to the trial, four (18.2%) patients from the amoxapine group and four (19.1%) from the risperidone group were naive to antipsychotic treatment, while nine (40.9%) patients from the amoxapine group were under atypical antipsychotic treatment (amisulpride = two, sulpiride = two, risperidone = five) in comparison to nine (42.8%) from the risperidone group (amisulpride = two, sulpiride = three, risperidone = three, olanzapine = one). Nine patients (40.9%) from the amoxapine group and eight (38.1%) from the risperidone group were under haloperidol treatment. The patients with previous antipsychotic treatment were included if they had a lack of improvement or worsening of their symptoms on their previous medication. Patients who had previously been treated with risperidone were only included if they had not failed the treatment (ie their current exacerbation was due to noncompliance).

There were no significant differences between the two treatment groups on baseline demographic characteristics. Both groups were also comparable in terms of some illness features at baseline (Table 1). For patients included in the OC analysis, the mean amoxapine dose at the end of week 3 was 178.9 mg/day (SD = 25.3), at week 4 of 223.6 mg/day (SD = 34.8), and at the end of the study was 228.0 mg/day (SD = 34.6), while for risperidone the mean doses were 3.7 mg/day (SD = 0.5), 4.4 mg/day (SD = 0.7), and 4.5 mg/day (SD = 0.7) at weeks 3,4, and 6, respectively.

Efficacy Data

Mean baseline and change from baseline to LOCF end point efficacy rating scale scores in both treatment groups are shown in Table 2A, and mean baseline and change from baseline to week 6 efficacy rating scale scores for completers in both treatment groups are shown in Table 2B. In both LOCF and OC analyses, amoxapine and risperidone were associated with similar improvement in psychotic symptoms as measured by changes from baseline on the total PANSS, PANSS subscales, CGI-S, CGI-I, and depressive symptoms assessed by the CDSS. Although patients on the amoxapine group showed a higher score on the CDSS at baseline when compared to the risperidone group in the OC analysis ($t=2.23$, df 37, $p=0.03$), no statistically reliable differences emerged between groups in week 6 (amoxapine = 2.26, SD = 2.21 *vs* risperidone = 1.25, SD = 2.12) ($t=1.46$, df 37, $p=0.15$).

Response Rate Analysis

Using the $\geqslant$30% in PANSS total score response criteria, the LOCF response rate was 72.7% in the amoxapine group and 76.2% in the risperidone group ($\chi^2=0.06$, df 1, $p=0.79$). For completers, similar response rates were found in both treatment groups (amoxapine 78.9% *vs* risperidone 75.0%) ($\chi^2=0.08$, df 1, $p=0.77$).

Safety

There were no clinically relevant differences in vital signs between treatment groups. Mean baseline and change from baseline to LOCF end point safety measures are shown in Table 3A, and mean baseline and change from baseline to week 6 safety measures for completers (OC) are shown in Table 3B. In the LOCF analysis, the risperidone-treated patients had significantly greater mean SAS scores than the amoxapine-treated patients at baseline ($t=2.54$, df 41, $p=0.01$) and at the end of the study (amoxapine = 0.18, SD = 0.39; risperidone = 1.48, SD = 2.36) ($t=2.53$, 41, $p=0.01$). There were no significant baseline differences between the treatment groups in the OC analysis. Amoxapine was superior to risperidone for SAS mean change from baseline scores in the LOCF ($F=6.62$, df 1, $p=0.01$),

Table 1 Demographic and Clinical Characteristics between Treatment Groups

	Amoxapine ($n=22$)		Risperidone ($n=21$)		
	n	**%**	***n***	**%**	**Statistic**
Gender					
Male	10	45.5	12	57.1	$\chi^2=0.5$, df 1, $p=0.44$
Female	12	54.5	9	42.9	
Marital status					
Married	1	4.5	2	9.5	$\chi^2=0.4$, df 1, $p=0.52$
Single	21	95.5	19	90.5	
Employment status					
Housewife	6	27.3	3	14.3	
Student	2	9.1	1	4.8	$\chi^2=1.7$, df 1, $p=0.63$
Employed	4	18.2	4	19.0	
Unemployed	10	45.5	13	61.9	
Schizophrenia type					
Disorganized	2	9.1	4	19.0	
Paranoid	18	81.8	12	57.1	$\chi^2=3.1$, df 1, $p=0.20$
Undifferentiated	2	9.1	5	23.9	
	Mean	**SD**	**Mean**	**SD**	
Age	31.0	9.7	30.7	8.4	$t=0.1$, df 41, $p=0.91$
Years of education	10.2	4.4	10.3	2.4	$t=-0.09$, df 41, $p=0.92$
Length of illness (weeks)	364.0	349.8	294.5	390.3	$t=0.6$, df 41, $p=0.54$

Table 2 Mean Change from Baseline to LOCF End Point (A) and to Week 6 in Completers (B) in Efficacy Rating Scales

(A) LOCF analysis

	Amoxapine ($n=22$)		Risperidone ($n=21$)		
Test	**Mean**	**SD**	**Mean**	**SD**	**Statistic[a]**
Positive PANSS					
Baseline	22.8	6.3	22.9	5.5	
Mean change	**−9.8**	**7.0**	**−9.5**	**7.8**	$F=0.03$, df 1, $p=0.86$
Negative PANSS					
Baseline	21.7	9.2	24.7	7.3	
Mean change	**−6.4**	**9.1**	**−8.4**	**7.2**	$F=0.001$, df 1, $p=0.98$
General PANSS					
Baseline	43.6	9.5	43.0	9.0	
Mean change	**−14.8**	**14.2**	**−12.9**	**13.6**	$F=0.15$, df 1, $p=0.69$
Total PANSS					
Baseline	88.7	23.0	90.7	16.6	
Mean change	**−31.5**	**28.4**	**−30.8**	**25.0**	$F=0.11$, df 1, $p=0.74$

Table 2 Continued

(A) LOCF analysis

	Amoxapine ($n=22$)		Risperidone ($n=21$)		
Test	**Mean**	**SD**	**Mean**	**SD**	**Statistic[a]**
Calgary Depression Scale					
Baseline	5.3	1.0	2.9	4.1	
Mean change	**−2.0**	**5.7**	**−1.7**	**4.1**	$F=0.93$, df 1, $p=0.33$
Clinical Global Impression—Severity					
Baseline	5.3	1.0	5.3	0.8	
Mean change	**−2.3**	**1.8**	**−2.1**	**1.4**	$F=0.26$, df 1, $p=0.61$
Clinical Global Impression—Improvement					
Week 1	3.3	0.9	3.6	0.6	
Mean change	**−1.2**	**1.8**	**−1.4**	**1.4**	$F=0.01$, df 1, $p=0.89$

(B) OC analysis

	Amoxapine ($n=19$)		Risperidone ($n=20$)		
Test	**Mean**	**SD**	**Mean**	**SD**	**Statistic[a]**
Positive PANSS					
Baseline	23.4	5.8	23.1	5.5	
Mean change	**−11.8**	**3.7**	**−9.6**	**8.0**	$F=1.35$, df 1, $p=0.25$
Negative PANSS					
Baseline	23.3	8.9	24.8	7.5	
Mean change	**−8.2**	**8.0**	**−8.4**	**7.4**	$F=0.11$, df 1, $p=0.74$
General PANSS					
Baseline	45.7	8.4	42.5	8.9	
Mean change	**−18.7**	**8.8**	**−12.5**	**13.9**	$F=1.39$, df 1, $p=0.24$
Total PANSS					
Baseline	93.2	21.0	90.5	17.0	
Mean change	**−39.4**	**18.0**	**−30.5**	**25.6**	$F=1.36$, df 1, $p=0.25$
Calgary Depression Scale (CDSS)					
Baseline	5.3	4.2	2.5	3.6	
Mean change	**−3.0**	**4.3**	**−1.2**	**3.6**	$F=0.74$, df 1, $p=0.39$
Clinical Global Impression—Severity (CGI-S)					
Baseline	5.5	0.8	5.3	0.8	
Mean change	**−2.7**	**1.1**	**−2.1**	**1.4**	$F=1.32$, df 1, $p=0.25$
Clinical Global Impression—Improvement (CGI-I)					
Week 1	3.4	1.0	3.6	0.6	
Mean change	**−1.6**	**1.1**	**−1.5**	**1.4**	$F=0.82$, df 1, $p=0.36$

Bold values represent the mean score change from baseline to end point.
[a]Based on analysis of covariance adjusted for baseline score.

while a trend was observed in the OC analysis ($F=3.68$, df 1, $p=0.06$). No significant differences between groups were observed for mean change in BAS or AIMS scores in the LOCF and OC analyses. Similar rates of body weight gain and increased glucose levels were observed in both treatment groups in the LOCF and OC analyses.

Table 3 Mean Change from Baseline to LOCF End Point (A) and to Week 6 in Completers (B) in Safety Measures

(A) LOCF analysis

	Amoxapine ($n=22$)		Risperidone ($n=21$)		
Test	**Mean**	**SD**	**Mean**	**SD**	**Statistic[a]**
Simpson-Angus Scale score					
Baseline	0.23	0.87	0.38	1.07	
Mean change	**−0.04**	**0.99**	**1.09**	**1.84**	F = 6.62, df 1, $p=0.01$
Barnes Akathisia Rating Scale score					
Baseline	1.0	2.39	0.57	2.18	
Mean change	**−0.22**	**2.70**	**0.95**	**2.76**	F = 1.75, df 1, $p=0.19$
Abnormal Involuntary Movement Scale score (AIMS)					
Baseline	0.68	1.46	1.05	2.52	
Mean change	**−0.22**	**1.60**	**0.28**	**4.7**	F = 0.94, df 1, $p=0.33$
Body weight (kg)					
Baseline	68.47	11.63	67.00	11.36	
Mean change	**1.05**	**2.42**	**1.30**	**2.06**	F = 1.36, df 1, $p=0.25$
Glucose level (mg/dl)					
Baseline	81.00	8.43	84.57	16.86	
Mean change	**2.68**	**8.54**	**0.10**	**12.98**	F = 0.74, df 1, $p=0.39$
Prolactin levels (ng/ml)					
Baseline	15.63	12.12	34.48	25.16	
Mean change	**5.59**	**25.49**	**6.07**	**36.31**	F = 0.82, df 1, $p=0.36$
QTc prolongation (mc)					
Baseline	401.36	32.70	400.00	36.46	
Mean change	**−11.81**	**27.19**	**0.95**	**19.72**	F = 0.82, df 1, $p=0.36$

(B) OC analysis

	Amoxapine ($n=19$)		Risperidone ($n=20$)		
Test	**Mean**	**SD**	**Mean**	**SD**	**Statistic[a]**
Simpson-Angus Scale score					
Baseline	0.05	0.23	0.40	1.10	
Mean change	**0.15**	**0.50**	**1.15**	**1.87**	F = 3.68, df 1, $p=0.06$
Barnes Akathisia Rating Scale score					
Baseline	0.63	1.38	0.60	2.23	
Mean change	**0.26**	**1.72**	**0.55**	**2.11**	F = 0.26, df 1, $p=0.61$
Abnormal Involuntary Movement Scale score (AIMS)					
Baseline	0.74	1.56	1.10	2.57	
Mean change	**−0.26**	**1.72**	**0.30**	**4.82**	F = 0.87, df 1, $p=0.35$
Body weight (kg)					
Baseline	68.02	11.52	67.45	11.46	
Mean change	**1.04**	**2.59**	**1.37**	**2.09**	F = 1.36, df 1, $p=0.25$

Table 3 Continued

(B) OC analysis

Test	Amoxapine ($n=19$) Mean	Amoxapine ($n=19$) SD	Risperidone ($n=20$) Mean	Risperidone ($n=20$) SD	Statistic[a]
Glucose level (mg/dl)					
Baseline	81.26	8.97	84.50	17.30	
Mean change	**3.10**	**9.15**	**0.10**	**13.32**	F = 0.74, df 1, $p=0.39$
Prolactin levels (ng/ml)					
Baseline	15.27	12.61	33.29	25.19	
Mean change	**6.26**	**27.25**	**8.67**	**35.18**	F = 0.82, df 1, $p=0.36$
QTc prolongation (ms)					
Baseline	396.31	32.00	398.00	36.21	
Mean change	**−15.26**	**23.18**	**1.00**	**20.23**	F = 0.82, df 1, $p=0.36$

Bold values represent the mean score change from baseline to end point.
[a]Based on analysis of covariance adjusted for baseline score.

Mean serum prolactin levels were elevated above normal range at baseline in the risperidone group (LOCF = 34.48 ng/ml, SD = 25.16; OC = 33.29 ng/ml, SD = 25.19) and significantly different from the prolactin level observed in the amoxapine group (LOCF = 15.63 ng/ml, SD = 12.12; OC = 15.27 ng/ml, SD = 12.61) (LOCF $t=3.15$, df 41, $p=0.01$; OC $t=2.80$, df 37, $p=0.008$). On evaluation of individual subjects it was observed that this high serum prolactin level resulted from six patients in the risperidone group who had more than double the normal values even at baseline. The baseline mean prolactin level of these six patients (LOCF = 68.9 ng/ml; OC = 71.0 ng/ml). All of them were on oral haloperidol treatment before the study (mean dose = 16.2 mg/day). When these patients were excluded from the prolactin level analysis, no baseline differences were found between groups (LOCF = amoxapine 15.6, SD = 12.1; risperidone 20.7, SD = 10.3; $t=1.32$, df 35, $p=0.19$; OC = amoxapine 15.2, SD = 12.6; risperidone 20.7, SD = 10.3; $t=1.35$, df 32, $p=0.18$). After the exclusion of these six subjects, the risperidone group showed a higher mean prolactin level in the LOCF analysis than the amoxapine group (39.1 ng/ml, SD = 24.0 *vs* 21.2 ng/ml, SD = 22.3 respectively; $t=2.3$, df 35, $p=0.02$) at the end point. Similar findings were observed in the OC analysis (Risperidone 39.1 ng/ml, SD = 24.0 *vs* Amoxapine 21.5 ng/ml, SD = 23.8; $t=2.12$, df 32, $p=0.04$).

While amoxapine led to a decrease in the QTc interval, risperidone showed a very slight increase, this difference was significant only in the completer's analysis ($t=2.33$, 37 df, $p=0.02$). Nevertheless, no patient in any group had a potentially clinically significant increase in QTc interval (>450 ms and a $>10\%$ increase from baseline) during the double-blind treatment.

Concomitant use of biperiden for the potential treatment of extrapyramidal symptoms was similar in the two treatment groups (amoxapine $n=2$; risperidone $n=1$). Also, the use of benzodiazepines was comparable between the amoxapine and the risperidone groups ($n=6$ *vs* $n=6$, respectively).

The incidence of adverse events was similar in both treatment groups with all being mild to moderate intensity. A total of 19 patients (10 patients in the amoxapine group and nine in the risperidone group) experienced at least one adverse event. The more frequently reported adverse events with amoxapine were constipation, diarrhea, stomachache, anxiety, and akathisia. While dry mouth, somnolence, and motor disturbances were more frequently reported in the risperidone group. Extrapyramidal side effects were reported in two patients from each treatment group. There were no suicide attempts in either group during the study.

DISCUSSION

In this study, amoxapine showed similar efficacy to risperidone for the treatment of positive, negative, and depressive symptoms of patients with schizophrenia. The response rate based on a $\geqslant 30\%$ decrease on PANSS total score was superior to 70% in both treatment groups. The improvement on this broad set of dimensions supports the efficacy of amoxapine as an atypical antipsychotic.

Our findings are consistent with previous reports, both in preclinical data in animal models and PET studies, showing the blocking action of amoxapine of serotonin 5HT2 and dopamine D2 receptors (Greenblatt *et al*, 1978; Kapur *et al*, 1999; Wadenberg *et al*, 2000). They also support the previous open-label trial where we observed that 75% of patients met the criteria of response, and they also showed improvement in depressive symptoms and no significant EPS (Apiquian *et al*, 2003). These data suggesting an antipsychotic effect are also consistent with the observations on open clinical trials which established the efficacy of this drug in the treatment of depression with psychotic features (Anton and Burch, 1990; Anton and Sexauer, 1983).

However, our results differ from a brief report by Fitzgerald *et al* (2004) of five patients treated with amoxapine in a double-blind, 8-week trial comparing the efficacy of amoxapine and olanzapine in the treatment of schizophrenic patients. In that study, no clinical improvement was observed in patients treated with amoxapine. There were important differences between the two studies that must be taken in account: First, the study was closed after including five patients per group, reporting a lack of efficacy of amoxapine. Indeed, the authors proposed that their results should be taken with caution given the small simple size. Second, the patients in that study were more chronically ill (9 years) than patients in this study (6 years). Third, the doses differed between the two studies, the Fitzgerald *et al* study used doses of amoxapine less than 200 mg/day, meanwhile in the current study the mean dose was 228 mg/day. This may be a critical difference given that the recommended dose for the treatment of psychotic depression is more than 200 mg/day and the dose range recommended based on D2 receptors occupancy is also suggested to be superior to 200 mg/day (Anton and Burch, 1990; Kapur *et al*, 1999).

Regarding safety data, no differences were observed on side effects (weight gain and glucose and levels) between the treatment groups. However, the risperidone group showed a higher frequency of EPS. Given the small sample size we would not want to over interpret these results, but they point to one possible area of superiority for amoxapine. The difference between the two drugs on prolactin elevation corresponds with previous reports that risperidone causes very notable levels of prolactin elevation more than other atypicals (Volavka *et al*, 2004), and some typical antipsychotics (David *et al*, 2000; Zhang *et al*, 2004). Amoxapine has also been associated with modest elevations in prolactin (Anton *et al*, 1983) as observed in this study; however, the magnitude seems to be lower. In addition, it is important to mention that none of the patients in any group reported side effects related to prolactin elevation. Concerning other side effects, its important to mention that in this study the patients treated with amoxapine presented constipation, which is related to the anticholinergic activity and has been reported in other clinical trials as equipotent to imipramine (Dugas and Weber, 1982). There were no reports of overdosing in the present study. The ingestion of doses superior to 1500 mg of amoxapine has been associated to multiple seizures, severe metabolic acidosis, acute renal failure, and coma (Coccaro and Siever, 1985). However, reports of death with amoxapine overdosage are only about 4% (Bishop and Kiltie, 1983). The administration of this drug should be monitored in patients with suicide risk.

The results of this study should be interpreted taking in account the small sample size and the short duration of the trial. The population in this study was early in the course of their illness, and given the Fitzgerald report, one should study a more chronic population to ensure that these results are generalizeable. Further, of the total dropouts after the first visit, three were in the amoxapine group (two for lack of efficacy, one for consent withdrawal) and one in risperidone (for nonefficacy). These numbers are too small to draw any conclusions—except that this is a trend that needs to be monitored in future studies. This was a trial designed as a proof-of-principle trial to be done in a single academic setting, and as such was not designed as a formal 'noninferiority' study. Nonetheless, the results do provide the data to plan for a definitive noninferiority study. Taking total PANSS to be the variable of greatest interest, both drugs showed an improvement (using LOCF figures, as they are more conservative) of 30.8–31.5 PANSS score, with an SD of 25–28. If one set a noninferiority acceptance margin as being an improvement of no less than six PANSS points inferior to risperidone—it would require anything from 80 to 100 subjects in each cell to reach a more definitive conclusion of noninferiority with the usual acceptance parameters.

In conclusion, current study demonstrates that amoxapine may be comparable to risperidone in its efficacy as an atypical antipsychotic. While our study is not definitive—it makes a strong case for further study. This is not just an academic point, but could be an issue of significant public health importance. In Mexico, where this study was conducted, access to atypical antipsychotics is restricted because of cost. The usual effective doses of olanzapine, risperidone, and aripiprazole cost anywhere from 100 to 300 USD. In contrasts, the treatment cost with generic, off-patent typical antipsychotics is in the range of $10 USD. Therefore, atypical antipsychotics are not frequently prescribed in Mexico, and approximately 80% of the patients are treated with typical antipsychotics (Apiquian *et al*, 2004), while in the USA, more than 80% of the patients are treated with atypicals (Hermann *et al*, 2002). This lack of accessibility of atypical antipsychotics, largely attributable to price, is not only an issue in Mexico but is likely to be the reality for the majority of the worlds' patients with schizophrenia who live in low-income countries. Amoxapine is now off-patent. It can be produced at generic prices that could rival those of the typical antipsychotics. Thus, the potential exists that amoxapine may turn out to be an atypical antipsychotic for the masses. Given this potential, we urge further multicentre, large-scale testing of amoxapine, as a low-cost equal-efficacy alternative to atypical antipsychotics, especially in jurisdictions which cannot afford the more established atypicals.

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STATEMENT OF INTEREST

None.

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