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ORIGINAL PAPER

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The prevalence of tardive dyskinesia after a nine month naturalistic randomized trial comparing olanzapine with conventional treatment for schizophrenia and related disorders

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Abstract *Aims of the study* To assess the impact of olanzapine versus conventional neuroleptic therapy among subjects with schizophrenia on ratings of tardive dyskinesia (TD). *Method* The naturalistic study was conducted in three psychiatric hospitals in Brazil. Patients had a diagnosis of schizophrenia and related disorders (DSMIV) and with a BPRS score > 24. Patients were evaluated by means of the PANSS scale for symptomatology (Kay et al. 1986), the Clinical Global Impression, The UKU side effect rating scale (Lingjaerde et al. 1987), and the Tardive Dyskinesia AIMS scale (Guy et al. 1976). Patients were seen by the treating physician routinely while hospitalized and then monthly on an out-patient basis. All scale assessments were repeated after 9 months of discharge. *Result* The sample was comprised of 190 patients (99 in the olanzapine and 91 in the standard treatment), with a completion rate of 88.2 % for olanzapine and 84.9 % for the conventional treatment ($p = 0.385$, n. s.). The mean change from baseline in the PANSS total score favored olanzapine regarding negative symptoms (2.3, 95 % C. I. 0.6–4.1, $p < 0.001$); and general psychopathology (4.0, 95 % C. I. 0.8–7.2, $p < 0.02$) factors. TD was defined by applying Morgenstern & Glazer (1993) and Schooler & Kane (1982) criteria, on the basis of the AIMS scale. Both results favored olanzapine at the end of the follow-up (Morgenstern & Glazer: 25.6 % versus 56.3 %; Schooler & Kane: 16.3 % versus 45.2 %). At the end of the follow-up, by using the overall rating of the AIMS scale, the presence of TD was 2.3 % for olanzapine (2/87), and 16.7 % (12/72) for the conventional treatment. *Conclusions* The results of this open label naturalistic trial showed that olanzapine had an impact on negative symptoms, decreased general psychopathology and reduced the risk of tardive dyskinesia.

Key words schizophrenia · tardive dyskinesia · randomized controlled trial · olanzapine · typical antipsychotic

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Introduction

Tardive dyskinesia (TD) is a distressing syndrome, involving late onset symptoms of involuntary, often rapid, and abnormal movements. The mouth and tongue are the parts of the body most commonly affected, leading patients to experience stigma, undermining adherence to treatment. The Abnormal Involuntary Movement Scale (AIMS) has been an important research tool for the classification of TD. The abnormal involuntary movements are scored for seven body areas (face, lips, jaw, tongue, upper extremities, lower extremities, trunk), in a 5-point rating scale. Schooler and Kane (1982) defined TD as the presence of at least moderate abnormal, involuntary movements in one or more body areas or at least mild movements in two or more body areas, and Morgenstern & Glazer (1993) used the criterion of a total AIMS score of 3 or more in the rating of

these seven areas or at least the presence of one anatomic score of 2 or more. The only difference between the two criteria is the count of mild and abnormal movements that would be 2 for Schooler and Kane and 3 for Morgenstern & Glazer. As there is no consensus about a valid diagnosis of TD, the use of these operational criteria is part of a common vocabulary strategy for defining cases. In addition, these symptoms should follow the administration of an antipsychotic over a period of at least 3 months in the absence of any other reason to explain these involuntary movements. These case definitions are important for obtaining homogenous populations, to test the hypothesis of etiology and clinical course of the syndrome.

Llorca et al. (2002) have showed the existence of two studies reporting the occurrence of TDs in the course of treatment with olanzapine (Beasley et al. 1996, 1999; Bymaster et al. 1996). Tollefson et al. (1997b) combined data from three clinical trials (n = 904), comparing the incidence of treatment-emergent TD with olanzapine (up to 20 mg/day) and haloperidol (up to 20 mg/day). The incidence of newly emergent TD was significantly lower in olanzapine-treated patients compared with haloperidol-treated patients (1.0 versus 4.6 %). Beasley et al. (1999) compared 1192 patients under olanzapine with 522 under haloperidol (including some patients used by Tollefson et al. 1997a), after 2.6 years of treatment. Overall, the one year risk of developing TD was 2.59 % with olanzapine and 8.02 % with haloperidol. Patients with a previous diagnosis of TD were excluded from the analyses. It has been estimated by Glazer (2000) that the annual risk of TD associated with typical antipsychotics ranges approximately between 4 % and 8 %. Moreover, Glazer et al. (1993) have estimated the risk of TD by means of a cohort study of 362 chronic psychiatric patients exposed to conventional anti-psychotics. The risk in the first 5 years was 31.8 %, and increased to 68.4 %, between 20 and 25 years. The aim of this study was to compare the presence of TD for olanzapine and conventional anti-psychotics, by means of a naturalistic effectiveness trial for schizophrenia and related disorders, after a nine-month follow-up, in three psychiatric hospitals in Brazil.

Method

The study was conducted in three psychiatric hospitals: Hospital Anna Rech, located in Caxias do Sul, a city in the South, the Pax Clinica Psiquiatrica in Goiania, in the Western part of the country, and a hospital from Salvador, in Northeast Brazil. These three hospitals are contracted by the Unified System of Health (SUS) to provide care for acute psychiatric admissions. All these hospitals offer assistance for severely ill patients.

Study subjects

All consecutive admissions, who received a diagnosis of schizophrenia or related disorders according to the DSM IV and presented a rating higher than 24 in the BPRS (extracted from the PANSS interview), were eligible for the trial. The study was restricted to people aged between 18 and 55 years old, and who were living in a 60 km area within the hospital. Patients were excluded if presenting a severe physical disorder, history of epilepsy, or previous use of any atypical antipsychotic in the last four months. After informed consent, patients underwent physical examinations (height and weight) and electrocardiogram. Laboratory tests included urinalysis, serum chemistry, hematology, and hepatitis B serology. Patients with significantly elevated laboratory measures were excluded from the study if not physically well to undertake antipsychotics. The screening phase was planned to take less than 3 days and clinicians were allowed to use medicines to control agitation if necessary.

Randomization and blindness

After a description of the study, informed written consent was obtained from the patient and/or a key relative. Randomization was performed only after medical clearing and consent was received. A central office was responsible to inform the clinician about treatment allocation into olanzapine or conventional treatment. The study was designed by JJM and MSL, and the protocol was submitted and approved by the Ethical Committee of the Federal University of São Paulo. The interviewers who assessed patients were psychiatrists or psychologists, not belonging to the hospital staff and blinded to the aims of the study. They were trained for interviews by JJM and MSL.

Study design

Patients admitted with a diagnosis of schizophrenia or related disorders (schizoaffective or schizophreniform) by the DSMIV and with a BPRS > 24 (extracted from PANSS scale) were asked to consent to be randomized either to olanzapine or to conventional neuroleptic treatment. They were required to be living with a relative in an area within 60 kilometers of the hospital, in order to allow follow-up visits in the same in-patient facility and with the same doctor. Patients with serious suicidal risk, physical illness (such as cancer or severe hepatic disease), female patients who were pregnant or lactating, and those who had received treatment with clozapine or risperidone in the previous 4 weeks were excluded. Subsequently doctors were advised to adhere to their routine approach to clinical practice. The dose of the antipsychotic could be titrated upward or downward as clinically indicated. Prophylactic use of anti-cholinergics was discouraged, but not prohibited. After randomization patients were evaluated by means of the PANSS scale for symptomatology (Kay et al. 1986), the Clinical Global Impression (CGI), the UKU side effect rating scale (Lingjaerde et al. 1987), and the Abnormal Involuntary Movement Scale for Tardive Dyskinesia AIMS (Guy 1976). The trained interviewers carried out the research assessments blinded to the treatment allocations and the aims of the study. Adverse events were recorded irrespective of their potential relationship to treatment, using the COSTART dictionary. Patients were seen by the treating physician routinely while hospitalized and then monthly on an out-patient basis. The AIMS and PANSS assessments were therefore carried out at randomization and after 9 months of discharge. The research team was well calibrated for these evaluations at the beginning of the study, though an inter-rater reliability of the scales during follow-up was not performed.

The site of the study was entered into each of the models to determine whether controlling for this altered findings on the main outcomes. All analyses were carried out on an intent-to-treat basis, in which all patients were randomly assigned. Patients were included in the analysis of change if they had both a baseline and at least one post-baseline observation. Total scores on rating scales were derived from the item scores, and if any single item score was missing the total sore was treated as missing. All end point analyses used a Last-Observation-Carried-Forward (LOCF) algorithm. For all analyses, main effects were tested at a two-sided alpha level of 0.05.

Results

Social and demographic characteristics

The sample comprised 190 patients (99 in the olanzapine and 91 in the standard treatment). Twelve subjects under olanzapine (12%) and 14 under conventional treatment (15%) did not complete follow-up, a difference not statistically significant (p = 0.385, n. s.), with an overall completion rate of 86%. There was one withdrawal in the olanzapine because of an adverse event. For lack of efficacy the treatment was interrupted for 7 olanzapine and 5 conventional cases. There were no significant differences between the olanzapine and conventional treatment groups on any demographic variable (Table 1). The sample was mainly comprised of males, Caucasians, with approximately a ten year history of the disease. At the end of the study, 88 patients were under olanzapine (mean = 10.47, s. d. = 2.45, median = 10.00), and most of the patients in the conventional treatment were under haloperidol (73/91, mean = 15.82, s. d. = 23.73, median = 10.00). The second antipsychotic most used was chlorpromazine (13/91, mean = 346.15, s. d. = 150.64, median = 300.00). The median of antipsychotic usage shows the standard doses usually applied in routine clinical practice.

Psychopathology

There were no significant differences between the two groups for clinical characteristics (Table 2). These patients were severely symptomatic as shown by all PANSS assessments at baseline. A total of 46% in the olanzapine group and 31% in the conventional treatment had a global severity clinical rating lower than 2 at the end of the follow-up (two-sided chi square = 4.09, 1d. f., p = 0.05). The mean endpoint scores of the PANSS, scored on a 1 to 7 scale, can be seen in Table 3. The two treatments did not differ significantly for positive symptoms. For negative symptoms there was a superiority of olanzapine for all symptomatology, with significant differences for blunted affect, emotional withdrawal and social withdrawal. In the general psychopathology assessments, three symptoms were statistically significant for olanzapine: somatic concern, motor retardation and poor attention. All the subscales' mean differences at the PANSS were in favor of olanzapine: 1.2 for the positive symptoms (95% C. I. –1.0–3.4, p = 0.30); 2.3 for the negative symptoms (95% C. I. 0.6–4.1, p < 0.001); and 4.0 for general psychopathology (95% C. I. 0.8–7.2, p < 0.02).

The two groups were compared, based on the proportion of patients who had a reduction of 40% or more on the PANSS scale: 46% for olanzapine and 35% for conventional treatment were found, a difference not sta-

Table 1 Social and demographic characteristics of patients assigned to olanzapine or conventional treatment

Characteristic	Olanzapine (N = 99)		Conventional (N = 91)		Analysis		
	n	%	n	%	χ^2	Df	P
Site					0.042	2	0.979
Caxias	60	57.7	54	58.1			
Goiânia	25	24.0	23	24.7			
Salvador	19	18.3	16	17.2			
Males	78	77.2	76	82.6	0.865	1	0.352
Race					0.797	2	0.671
Caucasian	65	53.3	57	46.7			
African descent	22	55.0	18	45.0			
Other	14	45.2	17	54.8			
Not married	89	88.1	73	79.3	2.135	1	0.144
	mean	SD	mean	SD	t-test	df	p
Age (years)	34.05	8.84	33.52	8.66	0.171	1	0.679

Table 2 The baseline characteristics for severity of illness

	Olanzapine		Conventional treatment				
	mean	SD	mean	SD	t-test	df	P
Age (years)	34.05	8.84	33.52	8.66	0.171	1	0.679
Length of illness	11.60	8.82	10.92	7.11	0.321	1	0.572
Age of onset (years)	22.03	6.82	22.78	7.92	0.473	1	0.492
Positive symptoms	28.01	7.27	26.14	7.56	1.807	188	0.803
Negative symptoms	26.06	7.28	26.03	7.64	0.025	188	0.756
Total PANSS	103.69	22.78	98.76	23.45	0.165	188	0.685
CGI severity	1.99	0.09	2.00	0.01	0.954	188	0.341

Table 3 End-point scores of the two groups and mean differences, corrected by analysis of covariance for baseline values (LOCF 95% C. I.)

	Olanzapine N = 84 Mean (s. d.)	Conventional N = 72 Mean (s. d.)	LOCF (95% C. I.) Mean (Differences)	Significance
Positive Symptoms	14.7 (6.82)	14.9 (7.98)	1.2 (–1–3.4)	P = 0.30
Negative Symptoms	19.6 (6.10)	22.1 (7.51)	2.3 (0.6–4.1)	P < 0.01
General Psychopathology	31.6 (11.3)	34.0 (12.5)	4.0 (0.8–7.2)	P < 0.02
Total Scores	65.9 (21.7)	71.1 (25.8)	4.9 (–1.7–11.6)	P < 0.01
CGI Severity	1.5 (0.5)	1.7 (0.5)	0.2 (0.003–0.3)	P < 0.05

tistically significant (chi square = 2.01, 1 d. f., p = 0.156). However, when this comparison was carried out for 20% or more, 68% was found for olanzapine and 38% for conventional treatment, a significant difference (chi square = 11.11, 1 d. f., p < 0.001). The intention to treat analysis, i. e., giving the worst prognosis to all missed olanzapine cases resulted in 60% for olanzapine and 38% for conventional treatment, a significant difference (chi square = 9.77, 1 d. f., p < 0.01). The effect of the site on treatment response was tested, and no interaction between treatment site and the PANSS measures was found.

Abnormal movements

The AIMS scale is comprised of seven items related to assess specific abnormal movements (face, lips, jaws, tongue, upper extremities, lower extremities and trunk), scored on a five point scale (1 for none, normal to 5 severe). Moreover, five global judgments scores were performed for the following items: Tardive Dyskinesia, Incapacitation due to the Abnormal Movements, Patient Awareness, Choreoathetosis and Dystonia. As can be seen in Table 4, none of the seven body items were significantly different in the two groups at baseline. At the end of follow-up, all assessments were statistically significant in favor of olanzapine. Table 5 summarizes the prevalence of TD by applying Morgenstern & Glazer (1993) (sum of the seven anatomical item scores above or equal to three, and at least one of the seven items above or equal to 2) and Schooler & Kane (1982) criteria (at least one of the seven anatomical item scores equal toor above 3, or at least two anatomical item scores above or equal to 2). In both criteria olanzapine showed a lower prevalence of TD at the end of the study. At baseline the proportion of TD was not statistically different between the two groups for both criteria. However, at the end of the follow-up, there was a reduction for olanzapine of 21.8% (Morgenstern & Glazer) and 26% (Schooler & Kane). In the conventional treatment the proportion of TD remained similar in the follow-up period. Further analysis was carried out by grouping rates in global assessment, 1 and 2 (minimal) as not present-

Table 5 Tardive dyskinesia according to Morgenstern & Glazer and Schooler & Kane, at baseline and after the 9-month follow-up

Morgenstern & Glazer	TD	RR (C. I. 95%)	p-value
Baseline			
Olanzapine	47.4%	0.78 (0.60–1.02)	0.070
Conventional	60.7%		
9-month follow-up			
Olanzapine	25.6%	0.45 (0.30–0.69)	0.000
Conventional	56.3%		
Schooler & Kane	**TD**	**RR (C. I. 95%)**	**p-value**
Baseline			
Olanzapine	42.3%	0.90 (0.65–1.23)	0.500
Conventional	47.2%		
9-month follow-up			
Olanzapine	16.3%	0.36 (0.21–0.62)	0.000
Conventional	45.2%		

Table 4 The mean comparisons of the AIMS scores between olanzapine and conventional antipsychotics at baseline and after the 9-month follow-up

	Baseline			9-month follow-up		
	Olanzapine Mean (s. d.)	Conventional Mean (s. d.)	p-value	Olanzapine Mean (s. d.)	Conventional Mean (s. d.)	p-value
Face	0.65 (1.47)	1.06 (2.04)	0.118	0.21 (0.77)	1.00 (2.15)	0.002
Lips	0.42 (1.28)	0.82 (1.84)	0.087	0.03 (0.44)	1.52 (4.82)	0.006
Jaw	0.34 (1.18)	0.60 (1.84)	0.257	0.02 (0.48)	1.30 (4.64)	0.015
Tongue	0.21 (0.87)	0.19 (0.67)	0.895	0.08 (0.32)	0.27 (1.04)	0.046
Upper extremities	2.12 (3.99)	2.56 (4.24)	0.469	0.44 (1.16)	3.70 (7.71)	0.000
Lower extremities	1.16 (2.39)	2.11 (4.46)	0.069	0.52 (1.67)	2.38 (4.15)	0.000
Neck & trunk	0.87 (2.55)	1.42 (3.74)	0.240	0.19 (1.05)	1.67 (3.92)	0.001

ing an abnormal movement and 2,3,4 as presenting the condition. The presence of TD was 2.3 % for olanzapine (2/87), and 16.7 % (12/72), for the conventional treatment. The prevalence of Tardive Dyskinesia in the conventional treatment was 4.1 times higher than those under olanzapine treatment, a difference statistically significant (RR = 4.1, 95 % C. I. 1.1–14.9, $p < 0.002$). Incapacitation due to the abnormal involuntary movements was also higher for the conventional treatment (R. R. = 2.6, 95 % C. I. 1.2–5.8, $p < 0.002$). These results are presented in Table 6.

Tolerability and adverse events

The global assessment of the interference with the patient's daily performance by adverse events captured with the UKU scale showed that patient and doctors rated less disruption with olanzapine (5.6 %) than for conventional treatment (patients 22 % and doctors 29 %). This difference was statistically significant favoring olanzapine ($p < 0.001$). In relation to weight gain, the mean baseline BMI was 25.5 for olanzapine and 23.4 for the conventional group. After 9 months the BMI mean for olanzapine was 28.7 and 25.3 for the conventional group, a difference statistically significant ($F = 224.30$, df 2, 139, $p < 0.001$). There was therefore a significant BMI increase for those receiving olanzapine. At the end of treatment 28 (32.2 %) patients under standard treatment were receiving anticholinergics and 7 (8.2 %) in the olanzapine group, a statistically significant difference (chi square = 15.2, 1 df, $p < 0.001$).

Discussion

There have been two studies comparing the occurrence of new TD cases between olanzapine and conventional anti-psychotics (Beasley et al. 1996a, Loza et al. 1999); both were controlled trials. The importance of naturalistic trials in psychiatry has been underscored by Hotopf et al. (1999). A strength of the present trial was that the three necessary criteria suggested by Hotopf for such a trial were fulfilled: a) the study was conducted in a realistic practice; b) the three psychiatric hospitals are representative of the overall interventions for acute admissions in Brazil; and c) usual clinical practice was not materially altered by the investigators. The results of this study demonstrated that olanzapine was clinically superior to conventional antipsychotic agents on the total PANSS score. Within the PANSS, olanzapine was either equivalent to conventional neuroleptics (positive symptoms) or significantly better on negative/general symptomatology. Moreover a significant proportion of patients in the olanzapine group achieved a response defined by the conventional criterion of at least a 20 % reduction in the PANSS scale. These findings are similar to the meta-analysis reported by Duggan et al. (2003). It is noteworthy that the treatment with olanzapine reduced the prevalence of TD for both criteria applied at the end of the follow-up (Morgenstern & Glazer, 21.8 % and Schooler & Kane 26 %). The prevalence of Tardive Dyskinesia, as assessed by the overall rating of the AIMS scale, was 4.1 times that of those under conventional treatment than of those randomized to olanzapine. This difference was statistically significant. It has been hypothesized that TD is a clinical manifestation of a supersensitivity response to a chronic dopamine blockade (Glazer 2000), and experiments with rats have shown that chronic administration of haloperidol could induce neuronal loss in the substantia nigra (Mitchell et al. 2002). These explanations could explain the better performance of olanzapine compared to the standard treatment group, where the majority of patients were using haloperidol. Therefore, the study observes both the emergence of new cases and the change in severity rates among patients who had it at baseline. Not surprisingly the perceived incapacitation due to the abnormal involuntary movements was also higher among the conventional treatment group.

All antipsychotic drugs occupy approximately 70–80 % of dopamine D2 receptors in the human striatum, and possibly higher in the limbic regions (Seeman & Tallerico 1998). However, drugs that exert parkinsonism such as haloperidol and chlorpromazine, largely applied as conventional treatment, bind more tightly than dopamine to D2 receptors when compared to olanzapine. It is very likely that atypicality is related to the transient occupation of D2 receptors, thus allowing for rapid normal dopamine neurotransmission (Seeman 2002). This "Fast-off D2" theory raised by Seeman would explain the lower prevalence of TD among olanzapine patients found in this study. According to Kapur & Seeman (2001) the most powerful predictor of atypicality is the fast dissociation from the D2 receptor, and not the high affinity for 5HT2, D4 or another receptor. In addition,

Table 6 The prevalence of abnormal involuntary movement after 9-month treatment with olanzapine or conventional anti-psychotics

	Olanzapine N (%)	Conventional N (%)	RR (95 % C. I.)	Significance
Tardive Dyskinesia	2 (2.3)	12 (16.7)	4.1 (1.1–14.9)	$P < 0.002$
Incapacitation	5 (5.7)	17 (26.3)	2.6 (1.2–5.8)	$P = 0.002$
Patient Awareness	9 (10.3)	12 (16.7)	1.7 (0.7–4.4)	n. s.
Choreoathetosis	0 (0.0)	2 (2.8)	0.4 (0.3–0.5)	n. s.
Dystonia	4 (4.5)	6 (8.3)	1.9 (0.5–7)	n. s.

Kapur & Remington (2001) have suggested that the lower propensity of atypicals for EPS was related to the low affinity and fast dissociation from the D2 dopamine receptor, once the dose applied induced appropriate blockade of the D2 receptors. The median dosage of 10 mg of olanzapine is an appropriated dosage for D2 blockade and decreased the risk of TD in the nine months follow-up.

It is noteworthy that many patients with schizophrenia go untreated in developing countries. Of those receiving treatment, most are with the conventional neuroleptic agents. Thus, despite their benefit:risk advantage the use of the new generation of antipsychotics is still modest, in part due to the acquisition cost of this new generation of antipsychotic agents (Leitão et al. 2002). This should be a matter of concern for the psychiatric community in developing countries, where access to mental health services for those with severe psychiatric illness can be particularly difficult. Ultimately, with the risk of less complete symptomatic control and adverse events such as TD, patients with schizophrenia should have access to these newer treatments just as their counterparts do for other medical disorders.

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References

1. Beasley CM, Hamilton S, Crawford AM, et al. (1997) Olanzapine versus Haloperidol: acute phase results of the international double-blind olanzapine trial. Eur Neuropsychopharmacol 7: 125–137
2. Beasley CM, Dellva MA, Tamura RN, et al. (1999) Randomized double blind comparison of the incidence of tardive dyskinesia in patients with schizophrenia during long term treatment with olanzapine or haloperidol. Br J Psychiatry 174:23–30
3. Bymaster FP, Calligaro DO, Falcone JF, et al. (1996) Radioreceptor binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology 14(2):87–96
4. Duggan L, Fenton M, Dardennes RM, et al. (2003) Olanzapine for schizophrenia. Cochrane Database Syst Rev (1):CD001359
5. Glazer WM, Morgenstern H, Doucette JT (1993) Predicting the long term risk of tardive dyskinesia in outpatients maintained on neuroleptic medications. J Clin Psychiatry 54:133–139
6. Glazer WM (2000) Review of incidence studies of tardive dyskinesia associated with typical antipsychotics. J Clin Psychiatry 61(Suppl 4):15–20
7. Guy W (1976) Psychopharmacology Research Branch, NIMH. Abnormal Involuntary Scale (AIMS). In: ECDEU Assessment Manual for Psychopharmacology, revised. DHEW Pub. No (ADM) 76–338. Rockville, MD: National Institute of Mental Health, pp 534–537
8. Hotopf M, Churchill R, Lewis G (1999) Pragmatic randomized controlled trials in psychiatry. Br J Psychiatry 175:217–223
9. Kapur S, Seeman P (2001) Does fast dissociation from the dopamine D-2 receptor explain the action of atypical antipsychotics? A new hypothesis. Am J Psychiatry 158:360–369
10. Kapur S, Remington G (2001) Dopamine D-2 receptors and their role in atypical antipsychotic action: Still necessary and may even be sufficient. Biol Psychiatry 50(11):873–883
11. Kay SR, Opler LA, Fizbein A (1986) Positive and Negative Syndrome Scale (PANSS) Manual. North Tonawanda, New York, Multi Health Systems, Inc
12. Leitão R, Ferraz MB, Mari JJ (2002) A prevalence based cost of illness study of schizophrenia in São Paulo State, Brazil. Schizophr Res 53(Suppl 3):259
13. Lingjaerde O, Ahlfors UG, Bech P, et al. (1987) The UKU side effect rating scale. Acta Psychiatr Scand 76(Suppl 334):1–100
14. Llorca PM, Chereeau I, Bayle F, et al. (2002) Tardive dyskinesias and antipsychotics: a review. Eur Psychiatry 17:129–138
15. Loza N, El-Dosoky AM, Okasha TA, et al. (1999) Olanzapine compared to chlorpromazine in acute schizophrenia. Eur Neuropsychopharmacol 9(Suppl 5):291
16. Mitchell IJ, Cooper AC, Griffiths MR, et al. (2002) Acute administration of haloperidol induces apoptosis of neuron in the striatum and substantia nigra in the rat. Neuroscience 109(1):89–99
17. Morgenstern H, Glazer WM (1993) Identifying risk factors for tardive dyskinesia among chronic outpatients maintained on neuroleptic medications: results of the Yale tardive dyskinesia study. Arch Gen Psychiatry 50:723–733
18. Schooler NR, Kane JM (1982) Research diagnoses for tardive dyskinesia (letter). Arch Gen Psychiatry 39:486–487
19. Seeman P, Tallerico T (1998) Antipsychotic drugs which elicit little or no Parkinsonism bind more loosely than dopamine to brain D2 receptors, yet occupy high levels of these receptors. Mol Psychiatry 3(2):123–134
20. Seeman P (2002) Atypical antipsychotics: Mechanism of action. Can J Psychiatry 47(1):27–38
21. Tollefson GD, Beasley CM, Tran PV, et al. (1997a) Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 154(4):457–465
22. Tollefson GD, Beasley CM, Tamura RN et al. (1997b) Blind, controlled, long-term study of the comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol. Am J Psychiatry 154(9):1248–1254