Utility of quetiapine in tardive dyskinesia

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Utilidad de la quetiapina en la discinesia tardía

Summary

Introduction. *Neuroleptic induced tardive dyskinesia is a late appearing extrapyramidal disorder of involuntary, choreoatetoid movements. It may appear during chronic treatment with classical neuroleptics or a short time after its prolonged administration is interrupted. At present, there is no agreement on what would be the best way to treat dyskinesias. Clozapine is an alternative treatment to take into account, although the risk of agranulocytosis may be excessive to use it when there is a mild or moderate form of dyskinesia. Cases of improvement of dyskinesias both with olanzapine as well as with risperidone, although in a lower number, have been reported. Due to its receptor profile, quetiapine is the atypical antipsychotic that is most similar to clozapine, which leads us to consider it for the treatment of dyskinesias.*

Methods. *The first patient is a 66 year old woman with schizoaffective disorder of 16 years of evolution who has received many classical neuroleptics and who presents a picture or orolingual dyskinesias with a score of 28 on the AIMS scale. Treatment was substituted with Quetiapine until reaching a dose of 400 mg/day over 4 months, obtaining a decrease in the AIMS score up to 9. The second patient is a 60 year old woman diagnosed of bipolar disorder under treatment since 26 years of age with delusional jealousy ideation. Different atypical antipsychotics were used, all of them causing dyskinetic symptoms in the orolingual region, that disappeared with low doses of quetiapine, with good stabilization of her psychopathology. The third patient is a 33 old male diagnosed of paranoid schizophrenia when he was 18 years old. He was under maintenance treatment with haloperidol, biperiden and lorazepam, until 27 years of age, when the treatment was changed to risperidone, after presenting an orofacial tardive dyskinesia with masticatory type movements and lingual protrusion, with a 19 score on the AIMS scale. The change to quetiapine 600 mg/day reduced the score on the AIMS scale to 3.*

Discussion. *Our experience, based on 3 cases, shows an early and lasting improvement of the tardive dyskinesia with quetiapine. This experience is reinforced by other investigators with similar cases. In all, we have 12 cases that support the efficacy of quetiapine in the treatment of tardive dyskinesias.*

Key words: *Tardive dyskinesia. Atypical neuroleptics. Quetiapine.*

Resumen

Introducción. *La discinesia tardía inducida por neurolépticos es un trastorno extrapiramidal de aparición tardía de movimientos involuntarios, coreoatetoides. Puede aparecer durante el tratamiento crónico con neurolépticos clásicos o poco tiempo después de interrumpir la administración prolongada del mismo. No existe en el momento actual acuerdo sobre cuál sería la forma más adecuada de tratamiento de las discinesias. La clozapina constituye un tratamiento alternativo a tener en cuenta, aunque el riesgo de agranulocitosis pueda ser excesivo para usarlo ante una forma leve o moderada de discinesia. Se han comunicado casos de mejoría de las discinesias tanto con olanzapina como, aunque en menor número, con risperidona. Por su perfil receptorial, la quetiapina es el antipsicótico atípico más parecido a la clozapina, lo que nos lleva a tenerla en cuenta en el manejo de las discinesias.*

Métodos. *La primera paciente es una mujer de 66 años con trastorno esquizoafectivo de 16 años de evolución que ha recibido numerosos neurolépticos clásicos y que presenta un cuadro de discinesias orolinguales con una puntuación en la escala AIMS de 28. Se sustituye el tratamiento por quetiapina hasta alcanzar una dosis de 400 mg/día a lo largo de 4 meses, consiguiendo una disminución de la puntuación AIMS hasta 9. La segunda paciente es una mujer de 60 años diagnosticada de trastorno bipolar en tratamiento desde los 26 años con ideación delirante celotípica. Se emplean diferentes antipsicóticos atípicos, provocando todos ellos síntomas discinéticos en la región orolingual, que con tratamiento de quetiapina a dosis bajas desaparecen, con buena estabilización de su psicopatología. El tercer paciente es un varón de 33 años diagnosticado de esquizofrenia paranoide a los 18 años en tratamiento de mantenimiento con haloperidol, biperideno y lorazepam hasta los 27 años de edad, momento en que se le cambió el tratamiento a risperidona tras presentar una discinesia tardía de tipo orofacial con movimientos de tipo masticatorio y protrusión lingual, con una puntuación en la escala AIMS de 19. El cambio a quetiapina 600 mg/día redujo la puntuación en la escala AIMS a 3.*

Discusión. *Nuestra experiencia a propósito de tres casos muestra una mejoría temprana y duradera de la disquinesia tardía con la quetiapina. Esta experiencia se ve reforzada por la de otros investigadores con casos similares. En total contamos con 12 casos que avalan la eficacia de la quetiapina en el tratamiento de las discinesias tardías.*

Palabras clave: *Discinesia tardía. Neurolépticos atípicos. Quetiapina.*

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INTRODUCTION

Neuroleptic induced tardive dyskinesia (TD) is a late appearing extrapyramidal disorder characterized by the presence of involuntary choreoatetoid movements. It

may appear during chronic treatment with classic neuroleptics or a short time after discontinuing its prolonged administration[1], although it may also appear during the natural course of untreated mental diseases. Jeste and Caliguri (1995) found that elderly women diagnosed of affective disorder and diffuse cerebral disease presented a greater probability of suffering TD[2], and some case series even report the appearance of tardive dyskinesia in schizophrenic patients not treated with neuroleptics[3].

This is a relevant disease, both due to its incidence as well as to the consequences it presents for the patients and its resistance to treatment. The importance of trying to treat tardive dyskinesia has increased in view of the medical-legal implications of article 3 of the 1998 Human Rights Act that establishes that «no one should be subject to inhuman or demeaning treatments or punishments». Precisely, the interpretation of this article was used successfully to win an extrajudicial resolution for a patient with TD in the region of Warwick, United Kingdom[4]. Probably, TD was first recognized by Sigwald et al. in 1959 and defined later with greater clarity by Uhrbrand and Faurybye in 1960[5]. The clinical picture of tardive dyskinesia includes repeated, involuntary and hyperkinetic movements such as eye winks, lingual protrusion, vermicular movements of the tongue, stereotypal movements of the fingers or choreoatetoid movements of the legs or trunk. The most common ones affect the orofacial region and the finger and toes. Atetoid movements of the head, neck and hips are also observed in serious patients, and it can even affect speech and respiration. It increases with anxiety and is reduced during periods of somnolence, and frequently disappears during sleep[6]. Patients who suffer tardive dyskinesia often do not realize it, but it is a well known cause of stress and shame for the caretakers and contributes to the stigmatization of mental illness.

The most commonly used research criteria[7] require at least continuous exposure to neuroleptics for three months and include, for the diagnosis of tardive dyskinesia, mild movements in two or more body areas or moderate symptoms in a single region. The symptoms should continue for at least three months and other causes that may give rise to dyskinesia, such as medical diseases or drug consumption, should be ruled out.

The DSM-IV-TR[8] proposes some diagnostic characteristics: involuntary movements lasting more than 4 weeks, choreic, athetosic or rhythmic ones, during exposure to treatment with neuroleptics or in the 4 weeks following their discontinuation (or 8 weeks in the depot regimes) in individuals who have undergone neuroleptic treatment for a minimum of three months (or 1 month in those over 60 years), that are not due to other medical diseases, poorly adjusted dentures or exposure to other treatments, as long as the symptoms are not better explained by the presence of a neuroleptic induced acute motor disorder. Acute dystonia induced by neuroleptics appears in the first 7 days after the initiation or increase of neuroleptic treatment or after having decreased the dose of a drug especially aimed at treating acute extrapyramidal symptoms.

However, dyskinetic pictures of orolingual predominance, having an insidious onset and progressive seriousness, have been observed in the clinical practice in the weeks after the introduction of the neuroleptic, that fulfills criteria A, B, C, E and F for the diagnosis of tardive dyskinesia, but not D, of at least 3 months exposure to the drug, nor the time criteria B of appearing in the first 7 days for acute dystonia. These exceptions should not remain outside of the diagnosis of TD although they are atypical cases.

Tardive dyskinesia occurs in more than 25% of the patients treated with dopamine receptor antagonists for more than 4 years. The risk factors detected are: long term treatment with neuroleptics, elderly age, female gender, presence of mood disorder, treatment with electroconvulsive therapy (ECT), leukotomy, negative symptoms of schizophrenia, diabetes mellitus and presence of cognitive disorder. In addition, it presents a cumulative index of more than 5% per year[9-11]. There is a marked increase of the incidence after 45 years and the prevalence seems to increase to 60% in elderly subjects[12]. History of acute extrapyramidal symptoms is probably related with an increased risk of tardive dyskinesia. Prolonged intervals without medication are also a risk factor: more than two interruptions increase the risk of tardive dyskinesia by more than three times[13].

The physiopathology of tardive dyskinesia is not known since research with neuroimaging, positron emission tomography (PET) and magnetic resonance (MRI) have not been able to identify associated lesions. Although the post-mortem studies have not been able to demonstrate the hypothesis of dopaminergic receptor hypersensitivity, this theory has been commonly used to explain dyskinesia[14] since pharmacological clinical data indicate that dopamine metabolism could be involved in it[15]. Carlsson proposed that it could be due to an upward regulation and to dopamine hypersensitivity resulting from prolonged dopaminergic blockage in the nigostriatal dopaminergic pathway. Other hypotheses point towards the neurotoxicity of the free radicals, gabaergic insufficiency or towards the noradrenergic dysfunction models[16].

There is no consensus in regards to the treatment of tardive dyskinesias. The use of GABA agonists[17], calcium channel antagonists[18], vitamin E[19], ceruletide, essential fatty acids, estrogens, and lithium[20] have been proposed, without observing their clinical benefit in the Cochrane revisions. It also has not been possible to establish reliable interpretations on the efficacy of benzodiazepines[21], anticholinergic drugs[22] and the old cholinergic drugs. There are no clinical trials that make it possible to evaluate the efficacy of the modern cholinergic molecules[23]. Significant improvement of dyskinetic symptoms have been observed with insulin, although the reduced number of patients included in the trials requires the replication of the results in future trials[20].

A proposal has also been made to stop or reduce the neuroleptics to decrease the dyskinesia symptoms,

although there is no evidence that the former of these measures is effective. On the other hand, the risk of relapse in the psychotic picture is increased. There seems to be better proof of benefit with the dose reduction[24].

On the other hand, the literature indicates that all typical antipsychotics may give rise to tardive dyskinesia. Clozapine has a very low risk of presenting it and very scarce risk of extrapyramidal side effects[25,26]. Serotonin-dopamine antagonists present a very low risk of developing tardive dyskinesia and may be an effective therapeutic group[27-31].

The new antipsychotic, quetiapine (ICI-204636; [2-(2-[4-(dibenzol[b,f][1,4]thiazepin-11-yl-1-piperazinyl] ethoxy)ethanol], presents similarities with clozapine in a pharmacodynamic profile[32]. The predictive preclinical tests of risk of EPS show similarities to clozapine[33-35]. Quetiapine shows, as clozapine, low occupation of the striatal D_2 receptors[36]. On the other hand, it has been confirmed and semiquantitatively measured during PET studies that the D_2 receptors are intensely blocked during treatment with typical neuroleptics D_2[37-40]. Up to the present, only two cases have been reported of patients treated with quetiapine[41,42] who have presented TD and in both, there is the possibility that the presence of dyskinesia is really due to a delayed effect of the conventional neuroleptics that the patient was taking previously, a fact that has also been reported with clozapine. In any case, this is an extremely low rate.

Thus, quetiapine, in principle, seems to be a promising drug in the prevention and treatment of the important clinical problem posed by TD, either as a therapeutic strategy in the psychotic disorders capable of limiting the risk of this fearsome complication or as an alternative for the patients who have already developed the TD picture and need to maintain therapy with antipsychotic drugs. The clinical cases shown in the following reinforce this last hypothesis.

DESCRIPTION OF CLINICAL CASES

Case 1

A 66 year old woman with schizoaffective disorder of 13 years' evolution. During this time, she has received treatment with biperiden (4 mg/day), pimozide (4 mg/day), thioridazine (50 mg/day), levomepromazine (100 mg/day) and haloperidol (2 mg/day). She has also undergone a subtotal nephrectomy due to renal lithiasis with moderate renal insufficiency.

Seven months after discontinuing thioridazine and levomepromazine, discreet tremors appeared in her hands and arms without clear extrapyramidal signs with discreet movements in mouth and tongue and the treatment with haloperidol and pimozide was substituted by zuclopenthixol (35 mg/day), biperiden (4 mg/day) and fluvoxamine (50 mg/day).

For three years, she was stabilized in this situation without any increase in the extrapyramidal symptoms and without deterioration of the schizoaffective picture. After that time, the extrapyramidal picture began to increase. The at rest tremor became clear in both hands, walking was akinetic, without swinging, there was cogwheel rigidity and orolingual movements. The patient manifested urinary incontinence with minimum efforts. Progressive decrease of zuclopenthixol and its change to thioridazine (50-100 mg/day) was proposed, and the orolingual dyskinesias increased even more with this. There was a score of 28 at this time on the AIMS scale.

Quetiapine was introduced slowly until reaching a dose of 400 mg/day over 4 months, and the urinary incontinence of cogwheel rigidity disappeared completely and the abnormal orolingual movements disappeared almost completely. The tremor persisted but was hardly perceptible in the upper left limb and she walked without swing. The AIMS scale score had decreased to 9.

After 10 months of treatment with quetiapine, there was a delusional relapse that was treated by adding olanzapine at a dose of 10 mg/day, and she improved clinically and maintained the improvement of the movement pathology, the orolingual dyskinesias disappearing.

Case 2

A 60 year old woman diagnosed of bipolar disorder under treatment since 26 years of age. The first time she came to our out-patient clinic, she was taking lithium carbonate (1-1/2-1) and amitriptyline 25 (0-0-1).

She was psychopathologically stable for 5 years with good controls of lithemia. Due to an episode of dysphoric EDA, agitation and delusional jealousy ideation, amitriptyline was substituted by olanzapine 5 mg (0-0-1), and she initiated dyskinetic type orolingual movements that improved when this treatment was withdrawn while producing a shift to the depressive phase, with predominance of inhibition and staying in bed.

When the previous treatment (amitriptyline) was reestablished, the patient became stabilized, until one year later when she had a new phase of agitation, irritability, aggressiveness, verbosity and delusional jealousy ideation, and an attempt was made to stabilize it with risperidone, the orolingual dyskinetic movements and distal tremor appearing again.

We observed that this patient had an exaggerated sensitivity to antipsychotics, with significant sedation, ataxia, extrapyramidalism and important increase of the dyskinesia.

Faced with a new episode of manic decompensation, she had to be admitted to the Acute Psychiatry Unit, using risperidone 4 ml/day, clonazepam drops (10-10-20) and lithium (1/2-1/2-1) for her stabilization. In our clinic, on discharge, she presented a serious dyskinetic syndrome (orolingual dyskinesia), ataxia, sialorrhea, cogwheel rigidity, distal tremor, etc.), and was prescribed treatment with thioridazine 100 (0-0-1/2), biperiden extended release (1-0-0), lithium carbonate (1/2-1/2-1) and clonazepam drops (10-5-10). The orolingual movements

decreased but did not disappear, cogwheel rigidity, of right predominance and parkinsonian gait persisting, with favorable psychopathological evolution. The AIMS scale score was 25.

One year later, treatment was introduced with quetiapine at a dose of 25 mg/day with progressive increase until 200 mg/day for 2 months, maintaining lithium and clonazepam and discontinuing thioridazine. A clear improvement of the psychotic symptoms that disappeared totally and of her affective signs and symptoms, being euthymic, was observed. In this time, the bucolingual dyskinesia has completely disappeared. At present, the patient has a 12 score on the AIMS scale. Given that the patient has suffered frequent falls due to dizziness, the dose was decreased to 150 mg/day.

She remained stable for 1 year, and then re-presented manic decompensation with psychotic symptoms having a delusional jealousy content that was superimposed on the previous, and psychomotor agitation. After stabilization in the Acute Psychiatric Unit, using 100 mg/day amisulpride at that time, dyskinetic bucolingual movements, appetite increase, at rest tremor, cogwheel rigidity and daytime somnolence re-appeared.

Quetiapine was introduced again at a dose of 50 mg/day in dose increases until 100 mg/day after 8 days of treatment associated to amisulpiride (100 mg/day), the clonazepam drops (15-15-20) and biperiden (1-0-0) were maintained, and lithium was withdrawn progressively. At present, she is psychopathologically stable and the AIMS scale has a 10 score.

Case 3

A 33 year old male, single patient. He was diagnosed of paranoid schizophrenia at 18 years of age. After the first episode, lasting six months, that required psychiatric admission, he presented a deficit picture and was treated with haloperidol (15 mg/day), biperiden (4 mg/day) and lorazepam (2 mg/day), until 27 years of age. Treatment was changed to risperidone, after he presented orofacial tardive dyskinesia with masticatory type movements and lingual protrusion.

Previously, at the onset of the treatment with neuroleptics, he had presented cervical type acute dystonia symptoms that had abated with administration of biperiden. When treatment was introduced with risperidone, at a dose of 6 mg/day, an attempt was made to withdraw biperiden, however parkinsonian type extrapyramidal symptoms, such as rigidity and akathisia, appeared then, so that the biperiden regime was reintroduced.

When the patient was seen in our out-patient clinic, he was receiving treatment with risperidone (6 mg/day), biperiden (4 mg/day) and clonazepam (3 mg/day). The change to risperidone did not change the clinical picture. This was characterized by the previously mentioned defectual symptoms, among which apathy, affective blunting, social withdrawal, and cognitive deficits such as memory loss and attention/concentration capacity stand out. He also presented poorly structured paranoid type ideation with limited experiential repercussion of being pursued by a terrorist organization. In the examination of the abnormal movements, facial and oral movements (facial expression, perioral area, mandibula and tongue) appeared, with a 19 AIMS scale score. The patient was aware of his movements and of the reactions that these caused in others, contributing to his withdrawal tendency.

The change to quetiapine was produced over two weeks, in hospital admission regime. Gradual withdrawal of risperidone (1 mg every three days) was performed and quetiapine was introduced simultaneous, beginning with a 25 mg/day dose, while withdrawing biperiden, also gradually. The clonazepam doses were not changed. When the drug change was completed, the patient was taking 600 mg/day of quetiapine, in three doses of 200 mg and 3 mg of clonazepam. The abnormal movements began to improve at two weeks of having completed the change in medication, beginning with facial expression musculature movements. At three months of treatment, the AIMS scale score decreased to 10 points, at three months later to three points, only the lingual protrusion remaining.

DISCUSSION

There are not many demonstrative cases of the efficacy of atypical antipsychotics in the treatment of TD. Our short experience, based on 3 cases, shows an early and lasting improvement of tardive dyskinesia with quetiapine. This experience is reinforced by other investigators[43-45],4 with series of similar cases. In all, there are 12 published cases that support the efficacy of quetiapine in the treatment of TD (table 1). It is unlikely that most in these cases were not due to quetiapine, given the chronicity of the symptoms prior to the onset of the treatment.

Quetiapine, as clozapine, is bond to a variety of receptors, including D1, D2, α1 and α2-adrenergics, 5HT-2A and 5HT-1A, and both have a much greater affinity for the 5HT-2 receptors than the D2 ones[46]. Improvement of both negative as well as positive symptoms for schizophrenia with quetiapine has been shown in many clinical trials with a profile of extrapyramidal side effects that does not differ from the placebo[44], and similar to that of clozapine. The mechanism by which quetiapine decreases tardive dyskinesias should be similar, therefore, to that of clozapine[47]. In the case of Vesely[43], 10 weeks after the onset of treatment with quetiapine, the dyskinesia disappeared completely, and in this same period, the occupation of the D2 receptors substantially decreased in measurements with SPECT, using I-iodobenzamide as tracer substance in weeks 17 and 77 of the treatment.

Two of the cases reported herein presented relapses of psychotic symptoms after the introduction of quetiapine. It is likely that the use of low doses (200-400 mg) has a relationship with the onset of their symptoms, al-

TABLE 1. Bibliographic review quetiapine and tardive dyskinesia

Author	*N*	*Diagnosis*	*Years of evolution*	*Previous treatments*	*AIMS*	*Dyskinesia treatment*	*AIMS*
Navarro B, Montejo AL, Martín M (2003)[48]	3	1. Schizoaffective D.	16	Pimocide halop., thiorid., levomeprom., zuclopenthixol	28	Subst. quetiapine 400 mg/4 months	9
		2. Bipolar D.	34	Amitriptyline, lithium, olanzapine, risperidone, thioridacine, amisulpride	25	Subst. quetiapine 200 mg/2 months	12
		3. Paranoide E.	15	Haloperidol, risperidone	19	Subst. quetiapine 600 mg/2 weeks	10
Alptekin K,	3	1. Late onset E.	9	Thioridacine	19	Subst. quetiapine 300 mg/3 weeks	7
Kvrck BB (2002)[41]		2. Residual E.	20	Thiorid halop. clorprom.	15	Subst. quetiapine 800 mg/6 months	4
		3. Undifferentiated E.	10	Clorprom. and risperidone	19	Subst. quetiapine 700 mg	8
Farah A (2001)[42]	2	1. Schizoaffective D.	30	Thiorid. halop. fluphen. lithium	21	Add. quetiapine 100 mg/2 weeks	12
		2. Schizoaffective D.	25	Halop. risper. clorprom. Valproic fluphen.	22	Add. quetiapine 75 mg/2 weeks	11
Chari S, et al. (2001)[4]	3	1. Schizophrenia	25	Conventional, depot and atypical	22	Subst. quetiapine 600 mg	—
		2. Schzoaffective D.	30	ECT, depot and oral	19	Subst. quetiapine	3
		3. Psychotic D.	5	Flupenthixol depot oral	17	Quetiapine in 24 weeks	10
Vesely C, et al. (2000)[43]	1	1. Paranoid E.	12	Haloperidol, risperidone, fluphenazine, clozapine, tioridazine	21	Sust. quetiapine 600 mg/1 week	11

though their increase was limited by the hypotension that appeared in an elderly patient with great sensitivity to adverse effects of neuroleptics in the first case and by the presence of bipolar disorder in the second.

The limited therapeutic response of TD to other treatment strategies makes it necessary to assess acceptable clinical methods which do not affect antipsychotic efficacy. Treatment with atypical antipsychotics is probably the most reasonable strategy to improve the TD symptoms, permitting the continued use of medication without resorting to dose decreases or treatment withdrawal.

In any event, performance of controlled clinical trials to study quetiapine as a treatment of tardive dyskinesias in depth is necessary.

REFERENCES

1. Kane JM, Lieberman JA. Tardive dyskinesia. En: Kane JM, Lieberman JA, editores. Adverse effects of psychotropic drugs. New York: The Guilford Press, 1992, p. 235-45.
2. Jeste DV, Caliguri MP, Paulsen JS, et al. Tardive dyskinesia. Schizophr Bull 1993;19:305-15.
3. García Rivera C. La discinesia tardía, hoy. Primera mesa redonda. Simposium: esquizofrenia, más que un misterio, un rompecabezas. Córdoba, 2003.
4. Chari S, Jainer A, Ashley-Smith A, Cleaver M. Quetiapine in tardive dyskinesia. Int J Psych Clin Practice 2001;6:175-7.
5. Uhrbrand L, Faurybye A. Reversible and irreversible dyskinesia after treatment with perphenazine, chlorpromazine, reserpine and ECT. Psychopharmacology 1960;I:408-18.
6. Bazire S. Psychotropic drug directory 2000: a profesionals' pocket hendbook and aide memoire. Dinton: Mark Allen Puclishing, 2000; p. 82.
7. Schooler NR, Kane JM. Research diagnosis for tardive dyskinesia. Arch Gen Psychiatry 1982;39:486-7.
8. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Barcelona: Ed. Masson, 2002.
9. Yassa R, Jeste DV. Gender differences in tardive dyskinesia: a critical review of the literature. Schizophr Bull 1992;18(4): 701-5.
10. Woerner MG, Kane JM, Lieberman JA, et al. The prevalence of tardive dyskinesia. J Clin Psychopharmacol 1991;11:34-42.
11. American Psychiatric Association. Tardive dyskinesia: a task force report of the American Psychiatric Association. Washington: APA.

12. Jeste DV, Caliguri MP, Paulsen JS, et al. Risk of tardive dyskinesia in older patients. A prospective longitudinal study of 266 outpatients. Arch Gen Psychiatry 1995;52:756-65.
13. van Harten PN, Hoek HW, Matroos GE, et al. Intermittent neuroleptic treatment and risk for tardive dyskinesia: the Curaçao extrapyramidal syndrome study III. Am J Psychiatry 1998;155:565-7.
14. Tarsy D, Baldessarini RJ. Pharmacologically induced behavioural supersensivity to apomorphine. Nature 1973;245:262-3.
15. Casey DE. Tardive dyskinesia. En: Hirsch SR, Weinberger DR, editores. Schizophrenia. New York: Blackwell Science, 1995; p. 553-65.
16. Carlsson A. Biochemical implications of dopa-induced actions on the central nervous system with particular reference to abnormal movements. En: Barbeau A, McDowell FH, editores. L-dopa and parkinsonism. Philadelphia: Davis, 1990.
17. Soares KVS, Mc Grath JJ, Deeks JJ. Gamma-aminobutyric acid agonists for neuroleptic-induced tardive dyskinesia Cochrane review. En: The Cochrane Library, Issue 1 Oxford: Update Software, 2003.
18. Soares KVS, McGrathJJ. Calcium channel blockers for neuroleptic-induced tardive dyskinesia. (Cochrane review). En: The Cochrane Library, Issue 1. Oxford: Update Software, 2003.
19. Soares KVS, Mc Grath JJ. Vitamin E for neuroleptic-induced tardive dyskinesia (Cochrane review). En: The cochrane Library, Issue 1. Oxford: Update Software, 2003.
20. McGrath JJ, Soares-Weiser KVS. Miscellaneous treatments for neuroleptic-induced tardive dyskinesia. (Cochrane review). En: The cochrane Library, Issue 1. Oxford: Update Software, 2003.
21. McGrath JJ, Soares KVS. Benzodiazepines for neuroleptic-induced tardive dyskinesia (Cochrane review). En: The cochrane Library, Issue 1. Oxford: Update Software, 2003.
22. Soares KVS, Mc Grath JJ. Anticholinergic medication for neuroleptic-induced tardive dyskinesia (Cochrane review). En: The cochrane Library, Issue 1. Oxford: Update Software, 2003.
23. Tammenmaa IA, McGrath JJ, Sailas E, Soares-Weiser KVS. Cholinergic medication for neuroleptic-induced tardive dyskinesia (Cochrane review). En: The cochrane Library, Issue 1. Oxford: Update Software, 2003.
24. McGrath JJ, Soares-Weiser KVS. Neuroleptic reduction and/or cessation and neuroleptics as specific treatments for tardive dyskinesia (Cochrane review). En: The cochrane Library, Issue 1. Oxford: Update Software, 2003.
25. Casey DE. Tardive dyskinesia. En: Meltzer H, editor. Psychopharmacology: the third generation of progress. New York: Raven Press, 1987; p. 1411-9.
26. Lieberman JA, Saltz BL, Johns CA, Pollack S, Kane JM. Clozapine effects on tardive dyskinesia. Psychopharmacol Bull 1989;25:57-62.
27. Agarwal V, Kumaz P. Olanzapine in treatment of tardive dyskinesia: a report of two cases. J Clin Psychiatry 2001;62:298-9.
28. Chong SA, Remington G, Tan CH. Olanzapine in treatment of tardive dyskinesias: a report of two cases. J Clin Psychiatry 1999;62:298-9.
29. Esel E, Turan MT, Gönül AS. Improvement of tardive dyskinesia in a bipolar patient with olanzapine. Eur Psychiatry 2000;15:438-9.
30. Taminga CA, Thaker GK, Moran M, Kakigu T, Gao XM. Clozapine in tardive dyskinesia: observations from human and animal model studies. J Clin Psychiatry 1994;55(Suppl B):102-6.
31. Kaplan HI, Sadock BJ. Sinopsis de Psiquiatría. 8.ª ed. Ed. Panamericana, 1999.
32. Saller CF, Salama AI. Seroquel: biochemical profile of a potential atypical antipsychotic. Psychopharmacology 1993; 112:285-92.
33. Migler BM, Warawa EJ, Malick JB. Seroquel: behavioral effects in conventional and novel tests for atypical antipsychotic drugs. Psychopharmacology 1993;112:299-307.
34. Borison RL, Arvanitis LA, Miller BG, Link CGG, Hong WW. Seroquel (ICI 204 636): a novel atypical antipsychotic. Biol Psychiatry 1995;37:661.
35. Wetzel H, Szegedi A, Hain C, Wiesner J, Schegel S, Benkert O. Seroquel (ICI 204 636), a putative «atypical» antypsichotic, in schizophrenia with positive symptomatology: results of an open clinical trial and changer of neuroendocrinological and EEG parameters. Psychopharmacology 1995;119:231-8.
36. Küfferle B, Tauscher K, Asenbaum S, Vesely C, Podrecka I, Brücke T, Kasper S. IBZM SPECT imaging of striatal dopamine-2 receptors in psichotic patients treated with the novel antispychotic substance quetiapine in comparision to clozapine and haloperidol. Psychopharmacology 1997;133:323-8.
37. Brücke T, Roth J, Podreka I, Strobl R, Wenger S, Asenbaum S. Striatal dopamine D2-receptor blockade by typical and atypical neuroleptics. Lancet 1992;339:497.
38. Farde L, Nordstrom AL, Wiesel FA, Pauli S, Halldin C, Sedvall G. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. Arch Gen Psychiatry 1992;49(7):538-44.
39. Nyberg S, Farde L, Erikson L, Halldin C, Eriksson B. 5-HT2 and D2 dopamine receptor occupancy in the living human brain. Psychopharmacology 1993;112:285-92.
40. Klemm E, Grünwald F, Kasper S, Menzel C, Boich K, Danos P, et al. (123I)IBZM-SPECT for imaging of striatal D2 dopaminereceptors in 56 schizophrenic patients taking various neuroleptics. Am J Psychiatry 1996;153:183-90.
41. Ghelber D, Belmaker RH. Tardive dyskinesia with quetiapine. Am J Psychiatry 1999;156:796A-7.
42. Ghaemi SN, Ko JY. Quetiapine-related tardive dyskinesia. Am J Psychiatry 2001;158:173.
43. Alptekin K, Kvrck BB. Quetiapine induced improvement of tardive dyskinesia in three patients with schizophrenia (case report). Int Clin Psychopharmacol 2002;17(5):263-4.
44. Farah A. Reduction of tardive dyskinesia with quetiapine [Letter] Schizophr Res 2001;47(2-3):309-10.
45. Vesely C, Küfferle B, Brücke T, Kasper S. Remission of severe tardive dyskinesia in a schizophrenic patient treated with the atypical antipsychotic substance quetiapine. Int Clin Psychopharmacol 2000;15(1):57-60.
46. Meats P. Quetiapine (seroquel): an effective and well tolerated atypical, 1997.
47. Lieberman JA, Salz BL, John CA, et al. The effects of clozapine on tardive dyskinesia. Br J Psychiatry 1991;158:503-10.
48. Navarro B, Montejo AL, Martín M. Quetiapina en el manejo de las discinesias tardías. Simposium: esquizofrenia, más que un misterio un rompecabezas. Córdoba, 2003.