Prevalence of adjunctive antipsychotic treatment for non-psychotic predominantly Latino depressed adults: a retrospective study.

Prevalencia del tratamiento adjunto con antipsicóticos en pacientes adultos predominantemente Latinos con depresión no psicótica: Un estudio retrospectivo.

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SUMMARY

The use of atypical antipsychotics as an adjunctive therapy to antidepressants for treating non-psychotic major depressive disorder (MDD) has been a common practice long before large-scale randomized double-blind placebo-controlled clinical trials demonstrated their efficacy. In this study, we aimed to study the frequency with which patients with non-psychotic major depression were prescribed antipsychotics (AP) and to examine the effect of age, race, and ethnicity on the type and dose of individual antipsychotics prescribed, in a cohort of patients before the recent Food and Drug Administration (FDA) approval of adjunctive aripiprazole. The charts of 1537 patients with unipolar depression were analyzed. 1376 had non-psychotic depression; among them 466 (33.9%) patients were prescribed antipsychotics with a significant predilection towards males (males vs. females: 41.7% vs. 27.8%. $z=2.4$, $p<.02$; odds ratio=1.97 with a standard error of 0.57) of Hispanic origin ($X^2 = 35.8$, $df = 1$, $p < 0.0001$). Quetiapine was the most commonly prescribed antipsychotic (n=209, 44.8%) with a mean (±SEM) 195.1±13.1 mg. Our results confirm previous reports of the common clinical practice of the use of atypical antipsychotics, specifically quetiapine, as adjunctive treatment for non-psychotic patients with unipolar depression. Further research is required to study the long term effect of this class of medications in patients without a primary psychotic disorder.

KEY WORDS: Major depressive disorder, atypical antipsychotics, pharmacotherapy.

RESUMEN

El uso de antipsicóticos atípicos como terapia adjunta a antidepresivos en el tratamiento del trastorno depresivo mayor (TDM) no psicótico fue práctica común por un largo periodo antes de que los ensayos clínicos a doble-ciego, controlados (con placebo) y al azar, llevados a cabo a gran escala, demostraran su eficacia. El presente estudio se propuso evaluar la frecuencia con la cual pacientes diagnosticados con TDM recibieron tratamiento con agentes antipsicóticos (AP) y examinar los efectos de edad, raza y etnicidad sobre el tipo y dosis de los anti-psicóticos prescritos a una cohorte de pacientes antes de la reciente aprobación de aripiprazole por la Administración de Alimentos y Drogas (FDA), como medicación adjunta para el manejo de esta entidad clínica. Se analizaron las historias clínicas de 1537 pacientes portadores del diagnóstico de depresión unipolar. 1376 presentaron depresión no psicótica y de ellos, 466 (33,9%) recibieron antipsicóticos con predominio de pacientes varones (hombres

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vs. mujeres: 41,7% vs. 27,8%. z=2,4, p<0,02; odds ratio (OR)=1,97, con error estándar (SE) de 0,57) de origen Hispánico (X^2 = 35,8, df = 1, p < 0,0001). Quetiapina fue el antipsicótico más comúnmente prescrito (n=209, 44,8%) con una dosis promedio (±SEM) de 195,1±13,1 mg. Nuestros resultados confirman reportes previos del uso de antipsicóticos (específicamente quetiapina) en la práctica clínica habitual, como tratamiento adjunto en pacientes no psicóticos con diagnóstico de depresión unipolar. Se requiere investigación adicional que indague los efectos a largo plazo de este tipo de medicación en pacientes sin un diagnóstico de trastorno psicótico primario.

PALABRAS CLAVE: Trastorno depresivo mayor, antipsicóticos atípicos, farmacoterapia.

INTRODUCTION

Until recently, the routine and prolonged use of neuroleptics among patients suffering from affective disorders was widely discouraged for fear of increasing their risk of tardive dyskinesia, as opposed to patients with psychosis (1). However, with the introduction of atypical antipsychotics, clinical trials examined their efficacy in improving mood symptoms and current clinical guidelines recommend atypical antipsychotics as augmenting agents in the management of treatment-refractory depression (2). Recently, aripiprazole received FDA approval as an adjunctive therapy in major depressive disorder following two successful trials (3,4).

Over the past few decades, there have been reports documenting a steady increase in the use of antipsychotics for non-psychotic depressed patients (5), reviewed data from 270 general practices in the UK (an average of 1.4-1.7 million patients/ year) between the years 1991 and 2000, and found that the annual use of antipsychotic drugs during this period increased from 10.5 per thousand in 1991 to 12.2 per thousand in 2000. Over half of the antipsychotic prescriptions were used to treat conditions other than schizophrenia or bipolar disorder - including depression, agitation, anxiety, and panic.

The prevalence of antipsychotics prescribed for non-psychotic depressed patients varied widely. In a community sample of 2817 patients (6), found that only 2.5% of the patients diagnosed with non-psychotic unipolar depression and treated with SSRI were prescribed a concomitant antipsychotic; whereas (7) reported a higher prevalence of 11%. Another recent study found that as many as 20.3% of a large *Veterans Affairs* (VA) sample (n=191,522) of depressed patients received antipsychotics in 1997 (8).

With these alarming reports, we sought to study the prevalence of the prescription of antipsychotics for patients with non-psychotic unipolar depression in a large metropolitan outpatient psychiatric clinic, and to look for clinical predictors that could correlate with prescription patterns in this population.

METHODS

The study protocol was approved by the Institutional Review Board of the University of Southern California and Los Angeles County Hospital (LAC+USC). The charts of all patients who received treatment at the outpatient adult psychiatric department during the interval from 01/01/2002-12-31/2007 were reviewed. Demographic data and diagnosis at the last clinical visit during the study interval were collected. Only patients with a primary diagnosis of unipolar major depressive disorder were included in the study; those who had a diagnosis of bipolar disorder, schizophrenia or schizoaffective disorders at any time during the study interval were excluded. Data on antipsychotic medications at the last clinical visit were obtained from the pharmacy records.

Three racial groups were identified: Hispanic Americans, African Americans and Caucasians. The remaining ethnic groups of Asians, and mixed race were grouped together under (others).

Age, sex, ethnicity, and race were entered in a logistic regression analysis to identify the most significant variables that could predict antipsychotic prescription, followed by chi-square tests to compare the frequency of antipsychotic prescription between males and females. A general linear regression model was used to examine the predictive value of these same variables on the dose of antipsychotic medication prescribed. All statistical analyses were done using Systat v.13.0

RESULTS

A total of 1537 subjects (males = 530, 34.5%) with a mean age of 49.2 (±12.8) years and a primary diagnosis of unipolar major depression were included

in the analysis. Females were significantly older than males [50.2 (±12.9) vs. 40.0 (±12.3), t=14.97, df=1535, p< 0.0001].

As detailed in table 1, two thirds (64%) of all patients were prescribed SSRI antidepressants (Table 1).

We separated ethnic groups into African-American (n=89, 5.8%), Caucasian (n=161, 10.5%), Hispanic (n=1212, 78.9%), and others including Asian and mixed race (n=75, 4.9%). All subjects were diagnosed with unipolar major depression. The vast majority (89.5% n=1376) had unipolar major depression without psychotic features. About a third (n= 466, 33.9%) of all patients diagnosed with MDD without psychotic features were prescribed AP medications.

Table 1. Number and percentage of patients with non-psychotic unipolar depression who were prescribed AP medications grouped by gender and race.

Subjects		Number (%) prescribed AP
All (n=1376)		466 (33.9%)
Males (n=465)		193 (41.7%)
Females (n=911)		253 (27.8%)
Hispanics	All (n=1091)	353 (32.5%)
	Males (n=343)	156 (45.7%)
	Females (n=748)	197 (26.4%)
Caucasians	All (n=148)	60 (42.3%)
	Males (n=58)	28 (49%)
	Females (n=90)	32 (35.5%)
African Americans	All (n=71)	23 (32.3%)
	Males (n=34)	14 (41.1%)
	Females (n=37)	9 (26.4%)

"Others" are not shown in this table.

As shown in table 2, selective serotonin reuptake inhibitors were the most commonly prescribed antidepressants, with sertraline and citalopram being the most frequently used medications. No significant differences were observed in the mean dose between males and females or between different races.

Forward stepping logistic regression was employed to determine if age, gender, race, ethnicity, or their interactions could predict antipsychotic drug prescription. The overall model fit was significantly better than a constant only model, chi square =51.8, p<.001. The only significant predictor variable was gender (z=2.4, p<.02; odds ratio=1.97 with a standard error of 0.57). This effect was confirmed by post hoc X^2 with 41.4% of males being prescribed antipsychotics, compared to only 27.8% of females ($X^2 = 25.88$, df = 1, $p < 0.0001$). The gender effect was especially characteristic of the Hispanic sample ($X^2 = 35.8$, df = 1, $p < 0.0001$), and to a lesser extent of the African Americans ($X^2 = 3.68$, df = 1, $p < 0.06$), but not the Caucasians ($X^2 = 1.01$, df = 1, $p < 0.3$) (Table 3 and figure1). Chi square test showed no significant differences between the frequency of antipsychotic prescription between Asian and mixed race within the "others" group.

Atypical AP were prescribed in the majority of cases (n= 443, 94.8%). Quetiapine was the most commonly prescribed AP (n=209, 44.8%), followed

Table 2. mean (±SEM) daily dose (n) of different antidepressants prescribed.

Antidepressants	All subjects	Males	Females	Hispanic Americans	African Americans	Caucasians	Others
Amitriptyline	45.83±4.8(48)	42.27±8.2(11)	46.89±5.8(37)	43.97±5.4(34)	45.71±8.8(7)	55.00±19.6(7)	
Bupropion	267.6±8.5(112)	266.3±12.3(49)	268.7±11.7(63)	258.2±10.2(73)	307.1±31.6(7)	276.1±18.5(22)	290.0±37.1(10)
Citalopram	35.19±1.2(239)	35.31±2.2(81)	35.13±1.4(158)	34.35±1.3(193)	39.17±6.5(12)	47.22±5.1(18)	28.75±3.9(16)
Escitalopram	17.39±0.6(119)	17.40±0.9(48)	17.39±0.8(71)	16.51±0.7(83)	17.69±1.6(13)	20.77±2.3(13)	16.51±0.7(83)
Fluoxetine	35.58±1.6(156)	35.80±3.3(50)	35.47±1.8(106)	35.47±1.8(106)	34.29±7.5(7)	37.62±5.2(21)	35.47±1.8(106)
Mirtazapine	25.50±1.2(105)	27.83±2.3(38)	24.18±1.4(67)	24.11±1.4(79)	24.00±3.6(5)	31.07±3.6(14)	31.07±6.6(7)
Paroxetine	33.69±3.4(88)	33.06±2.5(31)	34.04±5.1(57)	34.59±4.1(73)	34.29±5.2(7)	26.00±2.4(5)	23.33±3.3(3)
Sertraline	112.3±3.0(371)	118.4±5.2(125)	109.1±3.7(246)	110.8±3.2(318)	103.1±14.7(16)	139.3±10.3(28)	97.22±16.9(9)
Venlafaxine	149.3±8.4(104)	156.5±16.6(29)	146.5±9.8(75)	142.8±9.7(83)	140.6±38.6(4)	181.7±22.4(13)	187.5±15.3(4)

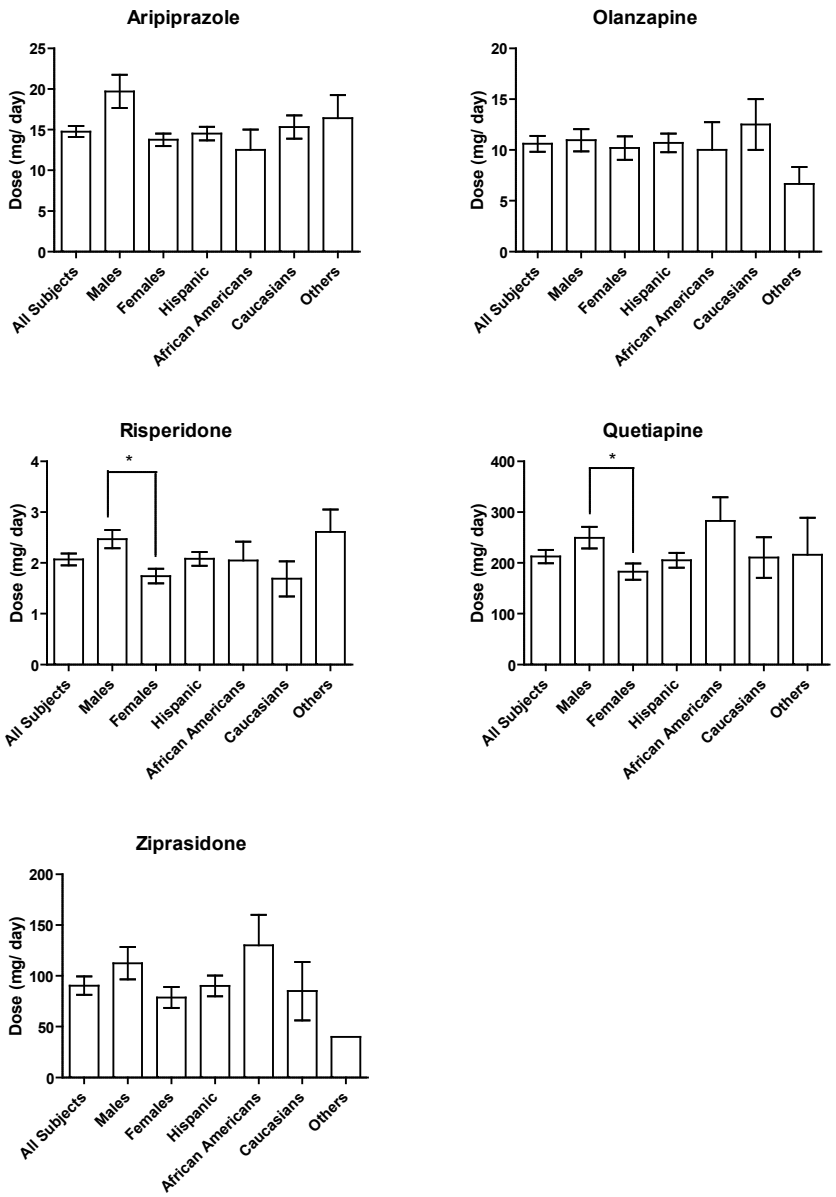
Other antidepressants were prescribed to a very small number of subjects [Nortriptyline (n=12), Clomipramine (n=7), Imipramine (n=4), Fluvoxamine (n=4), Desipramine (n=2), Doxepin (n=2), Phenelzine (n=1) and Tranylcypromine (n=1)

Table 3. Mean (±SEM) daily dose (n) of different atypical antipsychotics prescribed for patients with non-psychotic depression.

Antipsychotic	All subjects	Males	Females	Hispanic Americans	African Americans	Caucasians	Others
Aripiprazole	14.2±0.6	19.7±2.0	13.7±0.7	14.5±0.8	12.5±2.5	15.3±1.4	16.4±1.8
Olanzapine	9.7±0.7	10.9±0.1.0	10.1±1.1	10.7±0.9	10.0±2.7	12.5±2.5	6.6±1.6
Risperidone	2.0±0.11	2.4±0.17	1.7±0.14	2.0±0.13	2.0±0.36	1.6±0.34	2.6±0.4
Quetiapine	195.1±13.1	249.5±21.1	182.9±16.1	205.2±14.6	282.4±46.7	210.7±39.8	216.1±72.6
Ziprasidone	84.6±9.0	112.4±15.8	78.8±10.2	90.1±10.2	130.0±30	85.0±28.7	40±0

Different conventional antipsychotics were prescribed to a very small number of subjects (n=23)

Figure 1. Significantly lower dose of risperidone and quetiapine are prescribed to females compared to males.



by risperidone (n=108, 23.1%), aripiprazole (n=62, 13.9%), olanzapine (n=44, 9.4%), and finally ziprasidone (n=20, 4.3%). The mean (±SEM) for quetiapine dose was 195.1±13.1 mg, risperidone: 2.0±0.11 mg, aripiprazole: 14.2 ±0.6 mg, olanzapine: 9.7 ±0.7 mg, and for ziprasidone was 84.6 ±9.0 mg (Table 3).

Multiple regression analysis was employed to determine if the variables of gender, race, age, or their interactions could predict quetiapine or risperidone dose. No predictor variables were significant for quetiapine dose. However, the overall model for risperidone was highly significant ($F=3.7$, $p<.001$). In this model six scores were outliers (3.4 to 4 SD) and were dropped from the analysis. Interactions of gender and race, but not age, were apparent. Post hoc Tukey tests showed a significant effect of gender on dose (males>females, $p<.005$, Figure 1). Black males were prescribed higher doses of Risperidone than white males ($p=.04$). Male Hispanics were prescribed higher doses of Risperidone than female Hispanics ($p=.007$) (Figure 1). Student t-tests comparing the mean quetiapine and risperidone doses between Asians and mixed race within the "other" group showed no significant differences.

DISCUSSION

In this study we reviewed medical records from a large public sector outpatient clinic with a predominantly Hispanic population and found that over a third of all patients with non-psychotic unipolar depression are prescribed atypical antipsychotic medications. We specifically chose to study a cohort of patients receiving treatment prior to 2007, the year aripiprazole received FDA approval as an adjunctive in the treatment of unipolar depression. Our findings are consistent with previous reports of a rising trend in the use of atypical antipsychotics in the treatment of patients with non-psychotic unipolar depression (7,8). This observation may reflect the sub-optimal efficacy of antidepressants in achieving remission in a significant number of patients and the increased necessity for augmenting agents. Lithium (9) and thyroid hormone (10) augmentation strategies have been widely accepted. However, the need to monitor blood levels, kidney and thyroid functions with these medications limit their use. Atypical antipsychotics provide a simple and effective alternative that does not demand such tedious monitoring requirements. This class of medication is known to uniquely target the monoaminergic system which is highly implicated in the pathophysiology of depression (11). However, the neurobiological basis for its efficacy remains under intense investigation.

Moreover, we found that quetiapine is the most frequently prescribed (44.8%) antipsychotic in this group of patients, followed not so closely by risperidone at 23.1%. This pattern is also similar to previous reports from a VA sample (8), but differs from practice in the United Kingdom where conventional antipsychotics are much more frequently used (5). Interestingly, quetiapine XR received FDA approval about two years after aripiprazole; however clinicians have used it more frequently in the treatment of patients with unipolar depression. Quetiapine's wider dose range and aripiprazole's higher cost, among other factors could be the main reasons behind this pattern of practice. To the best of our knowledge, there are no randomized controlled clinical trials comparing their efficacy as augmenting agents.

Another intriguing finding related to the use of quetiapine was the mean daily dose – which reached about 200 mg, a dose that is much higher than the one usually prescribed for sleep (25 mg). This stands in contrast to the mean daily dose of risperidone at 2.0 mg, which is also the ordinary dose used in an augmentation strategy. Quetiapine was shown to have an antidepressant efficacy as monotherapy and an augmenting agent at doses of 150-300 mg (12).

Since we were focused on MDD treatment with antipsychotics, we analyzed the data by forward stepping logistic regression to determine if age, gender, race, ethnicity, or their interactions could predict antipsychotic drug prescription. The overall model fit was significantly better than a constant only model; the only significant predictor variable was gender. The gender effect was especially characteristic of the Hispanic sample and to a lesser extent of the African American sample. Following that analysis we used multiple regressions to determine if the variables of gender, race, age, or their interactions could predict the doses of quetiapine or risperidone. No predictor variables were significant for the quetiapine dose. However, the overall model for risperidone was highly significant, and interactions of gender with race, but not age were apparent. Post hoc Tukey tests showed a main effect of gender on risperidone dose. Black males were prescribed higher risperidone doses than white males. Male Hispanics were prescribed higher risperidone doses than female Hispanics. African Americans received higher doses of antipsychotics. However this

effect did not reach statistical significance because of the small sample size and the large standard deviation.

The gender and racial differences are also difficult to explain. It could be related to differences in metabolism through the CYP P450 isoenzymes (13,14). For example, Hispanic women showed 3.6- and 5.0-fold higher CYP2B6 hepatic microsomal activity compared with Caucasian women and African-American women respectively (13). Another factor could be the higher prevalence of comorbid substance use disorder among males (15). Language barrier and the subtle differences in symptom expression by Hispanic male patients may be one explanation (16). Possibly unconscious ethnic and gender discrimination is another possible explanation for the higher prescribed antipsychotic dose among Black and Hispanic males. Previous reports of similar disparities found that African Americans were less likely than whites to receive atypical antipsychotic medications (17), and more likely to be exposed to discrimination (18). However, our results go in the opposite direction where males in the African American and Latino groups were prescribed higher doses of the same antipsychotic medications. More research is needed to understand this intriguing finding and to build clearer criteria outlining the prescription of antipsychotics to patients with non-psychotic unipolar depression in order to achieve optimal results.

The results of this study should be seen in light of several limitations such as the reliance on invalidated clinical diagnosis, the use of atypical antipsychotics for the treatment of other symptoms such as insomnia, anxiety, or agitation, the absence of a detailed look at comorbid conditions such as substance use disorders or PTSD, and the lack of data on therapeutic response rates and side effect profiles. Nevertheless, this work suggests that both gender and race/ethnicity may be factors affecting the prescription of atypical antipsychotic drugs in the treatment of major depressive disorder. Prospective clinical trials are needed to build on this observation in order to individualize our treatment strategies for better outcomes.

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Recibido: 05/11/2013
Aceptado: 15/12/2013