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Effectiveness and tolerability of duloxetine in two different ethnic samples: a prospective observational cohort study.

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To the editors:

Researchers have begun to study the pharmacological properties of medications in different ethnic minority groups and national populations. In this context, delimitation of the ethnic or national category is essential to ensure sufficient cultural and genetic homogeneity to render the study meaningful. In Spain, the “Latino” population tends to have its origins in the Andean region of South America. There is some evidence that there is genetic variation in isoenzymes CYP2D6 and CYP1A2 (1) in Amerindians which impacts the gene that encodes the serotonin transporter (1, 2), which would appear to impact the metabolism of SSRI drugs but much less so dual acting drugs such as duloxetine.

The antidepressant efficacy of duloxetine in the treatment of major depressive disorder (MDD), as well as its faster onset of action, has been demonstrated (3-7). These results appear to hold in studies comparing different ethnic samples (8, 9). As duloxetine has a dual effect on both the serotonin and norepinephrine systems (10), it appears to be a viable therapeutic option for treating depressive disorders, effective in the management of somatic symptoms, especially pain, more frequently present in depressed non-Westernized populations (11). The objective of this study is to examine the effectiveness of, and tolerability to, duloxetine in Amerindian immigrants and Spaniards of Caucasoid origin diagnosed with major depressive disorder. The main study hypothesis is that duloxetine will be effective with both Amerindians and Spaniards.

Methods

Study setting and participants

This was a prospective observational cohort study with a sample of 71 patients divided into two cohorts: 30 Spaniards and 41 Amerindian immigrants. Amerindian was operationalized narrowly to ensure homogeneity, in accordance with FDA guidelines (12). Participants were recruited consecutively from the outpatient services of the psychiatry department of Vall d'Hebron University Hospital in Barcelona (Spain) during the time period from 2007 and 2010. Any adult between the ages of 18 and 64 who suffered from MDD as confirmed by the MDD module of the Structured Clinical Interview for Axis I DSM-IV (SCID I) (13) and a score of 15 or more on the Hamilton Depression Scale (HAMD, 14) and a baseline score of the somatic symptoms subscale of the Patient Health Questionnaire (PHQ-15 see below, 15) in treatment with Duloxetine (Eli Lilly and Co., Indianapolis, IN, USA) for a maximum of two weeks, with no remarkable exclusion characteristics, were included in the study. Patients undergoing any antidepressant treatment prior to the initiation of the study were excluded. Those patients who required concomitant treatment with anxiolytics were treated with low doses of lorazepam, diazepam or clonazepam. It is worth noting that at the time of the study, duloxetine was newly present in the Spanish market, and as such was not widely prescribed.

Procedures

Once recruited, patients participated in a 12 week protocol in which the treatment with duloxetine was continued with a dose of 30 or 60 mg that could be modified according to patients' response or with the appearance of adverse effects, in accordance with clinical indications. Over the course of the subsequent visits depending on tolerability and response, the dose could be reduced, maintained or increased up to a

maximum of 120 mg. Effectiveness was assessed for both depressive and somatic symptoms. The former were assessed by remission, defined as a final score in the Hamilton scale equal to or lower than 7, and response, defined as a final score in the Hamilton scale equal to or lower than 50% of the baseline score (5). Remission and response were analysed using both an intent-to-treat and a per-protocol approach due to the high drop-out rate in the Amerindian group. Tolerability was evaluated by the presence of at least one or absence of any adverse effects, regardless of severity. Informed consent was obtained from the participants as a requisite for inclusion in the study.

Measures.

Depressive symptomatology was evaluated using the first 17 items of the Hamilton Rating Scale for Depression (HAM-D, 14). For a more detailed assessment of somatic symptoms the somatic symptoms subscale of the PHQ, a continuous measure of somatic symptom severity, was used (15).

Statistical Analysis

Baseline characteristics, retention and per protocol results were compared among groups using bivariate statistics (T and Chi squared tests and Mann-Whitney U for non-normal distributions). A logistic regression was carried out with retention as dependent variable and study group as independent variable controlling for sociodemographic and clinical characteristics. Last observation carried forward (LOCF) was used in order to analyze the effectiveness of duloxetine using an Intent to treat (ITT) approach only within patients attending at least a second visit. In addition to analysis of response and remission, ITT analyses were also carried out using repeated measures analysis of variance with HAM-D and PHQ-15 as dependent variables.

Results

Seventy one patients (41 Amerindians and 30 Spaniards) were enrolled in this study. No statistically significant differences were found in gender composition between the two cohorts. Amerindians were younger (38.63 vs. 47.77; $t = 3.674$, $p < .0001$) and less educated (11.90 vs. 15.33 years $t = 3.932$, $p < .0001$). No significant differences were detected at baseline in HAMD, but Amerindians had higher scores in the somatization subscale of the PHQ ($t = 4.067$, $p < .0001$). Initial doses of Duloxetine were similar in both ethnic groups; with a mean of 36 mg. Significantly more Spaniards completed the protocol (80%) than did Amerindians (46.3%) (OR = 4.63, 95% CI = 1.57-13.71, $p < .005$). Study withdrawal due to adverse effects occurred in 20% of Spaniard patients and 19.5% of Amerindian patients. Surprisingly enough, no Spaniard dropped out of the study by failing to attend scheduled appointments or withdrawing consent, whereas this occurred with Amerindians patients in 26.8% and 7.3% of cases respectively, half of them attended only the first visit. The flow diagram of the study can be seen as online extra material.

After controlling for baseline sociodemographic variables, HAMD, PHQ-15 and duloxetine dose and using a multivariate logistic regression analysis, ethnic group was the only variable found to be statistically significant accounting for study retention. Twenty two patients (6 Spaniards (20%) and 16 Amerindians (39%) (OR = 2.560, 95% CI = .858-7.635, $p = .087$) reported at least one adverse effect, of which fourteen discontinued treatment (6, 20% Spaniards and 8, 19.5% Amerindians OR = 1.301, 95% CI = .316-3.362, $p = .959$). At the end of the study, no statistically significant differences in depression level were found between completers of both groups. Although both showed a reduction in somatization, Amerindians still had higher but not statistically significant levels than did Spaniards. No statistically significant differences were found

in remission or response. Spaniards received higher maximum dosage means than Amerindians (Spaniards 68.28 ± 23.91 vs. Amerindians 56 ± 20.44 , $Z=2.117$, $p=.034$). All of the Spaniards correctly complied with the scheduled prescription, whereas three Amerindians did not correctly adhere to the treatment, and thus discontinued participation in the study. No statistically significant differences were found in remission (Spaniards 55.2% vs. Amerindians 37.5%, $OR=2.051$ 95% $CI=.737-5.709$, $p=.167$) nor in response (Spaniards 62.1% vs. Amerindians 56.3%, $OR=2.051$ 95% $CI=.457-3.547$, $p=.644$). Figure 1 shows the evolution of HAMD and PHQ-15 among groups both with an ITT and PP approach. As can be seen, the reduction of depression symptoms followed an identical pattern. In the ITT calculation, reduction of depressive symptoms was found to be statistically significant for the whole sample (Greenhouse-Geisser $F=97.508$, $p<.0001$) but no difference between groups were significant (Greenhouse-Geisser $F=.565$, $p=.536$). Reduction of PHQ15 was also significant (Greenhouse-Geisser $F=47.710$, $p<.0001$). Amerindians showed a larger reduction in somatic symptoms as could be seen in the interaction of symptom reduction and group effect (Greenhouse-Geisser $F=8.888$, $p<.001$).

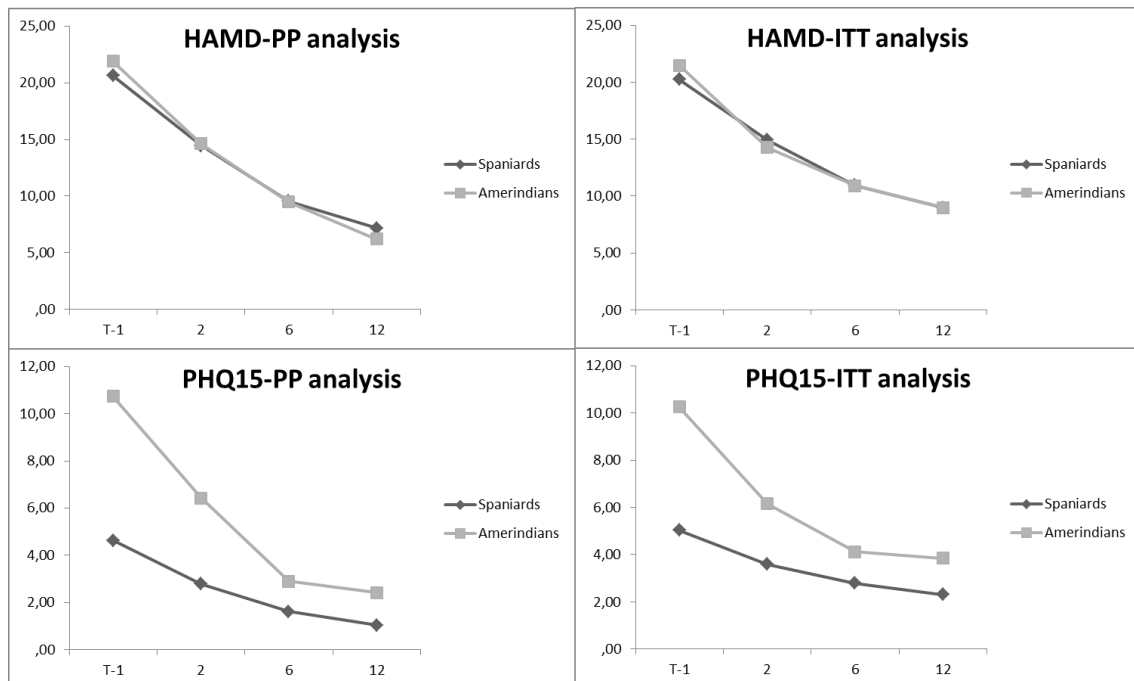
Discussion

The results of this study suggest that Duloxetine is effective in Amerindians and in Spaniards with properly adjusted doses. More adverse effects were observed in Amerindians, although this was not significant, nor were they found to be related to differences in drop-outs.

Statistically significant differences were found in remission when using LOCF. Differences in the dosage adjustment between groups may be due to Amerindian's faster response and lower tolerability to high doses of Duloxetine. Study limitations include slow patient recruitment due to the volume of Amerindian patients seen at the

study site combined with the recency of the introduction of duloxetine into the Spanish market, and elevated rate of Amerindian drop-outs which, due to lack of reachability, prevented exploration of the relevant causes. In addition, the study used a narrowly defined ethnic category of “Amerindians”; even so, it must be recognized that a certain level of within group variability remains, even between those belonging to the same narrowly defined ethnic group.

FIGURE 1. Evolution of HAMD and PHQ-15 among groups both with an ITT and PP approach.



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