

DULOXETINE IN MAJOR DEPRESSED PATIENTS RESISTANT TO SSRIS AND/OR VENLAFAXINE

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SUMMARY

Several acute depression trials suggest that only 35% of the patients achieve remission state with antidepressant monotherapy. An increasing body of evidence is emerging suggesting that multi-action antidepressants might be more effective in treatment-resistant depressed patients than single-action agents. In this context, the purpose of the study was to assess the effectiveness of duloxetine in treatment-resistant major depressed outpatients.

We performed a retrospective study assessing the efficacy of duloxetine in major depressed outpatients who did not achieve full symptom remission (CGI-S (severity) ≥ 3) after treatment of adequate dose and duration (more than 8 weeks) with at least either one SSRI or the SNRI venlafaxine. We excluded patients with a severe medical illness and a personality disorder. CGI-S was used as a measure of symptom severity and administered before the prescription of duloxetine and 6 weeks later. The sample included 29 patients (9 M, 20 F). We observed a very significant decrease in CGI-S scores ($4,86 \pm 0,51$ to $2,17 \pm 1,44$, $p < 0,0001$) after treatment with duloxetine (dose between 60 and 120 mg). Remission was achieved in 48 % of the patients. The tolerance was excellent. This study suggests the potential interest of duloxetine in some treatment-resistant depressed patients.

Key words: major depression – remission - SSRI – SNRI - duloxetine

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Introduction

Treatment resistance or partial remission in major depression remains a major public health problem. Complete remission is a very important issue in the treatment of depression. Indeed, partial remission is associated with a higher risk for relapse, a more chronic evolution, shorter intervals between episodes and a severe impact on quality of life. However, several acute depression trials suggest that less than 35% of the depressed patients will achieve remission with antidepressant monotherapy (Rush et al. 2006).

The management of treatment resistance in major depression is based on several strategies like switching to another antidepressant, augmentation or combination. Regarding the switching strategy, an increasing body of evidence is emerging suggesting that multi-action antidepressants such as venlafaxine and duloxetine might be more effective in treatment resistant depressed patients than single-action agents (Papakostas et al. 2007). Moreover, in a recent meta-analysis, switching from a SSRI to a dual-acting agent was more efficacious than switching from one SSRI to another (Papakostas et al. 2008). In this perspective, duloxetine could be an interesting agent to achieve full remission in case of failure with another antidepressant. Duloxetine is currently the agent with the most equally balanced dual reuptake inhibition and data supports its effectiveness in the acute and long-term treatment of MDD (Detke et al. 2004; Goldstein et al. 2004; Brecht et al. 2010).

In this context, the purpose of the present study was to assess the effectiveness of duloxetine in major depressed patients resistant to SSRIs or venlafaxine.

Methods

Data included in this study come from a retrospective chart review. Charts of outpatients

suffering from a major depressive disorder (DSM-IV) and treated between april 2006 and june 2007 were reviewed confidentially by the treating clinicians. We included patients who did not achieve full symptom remission (CGI-S (Clinical Global Impression – Severity) ≥ 3) after treatment of adequate dose and duration (more than 8 weeks) with at least either one SSRI or the SNRI venlafaxine. We excluded patients with a severe medical illness (mainly cardio-vascular and/or cerebro-vascular disorders) and/or a personality disorder according to DSM-IV criteria. CGI-S was used as a measure of symptom severity and administered before the prescription of duloxetine and 6 weeks later. We also used CGI-I (Improvement). Remission was defined as a CGI-S score of 1 (not currently depressed), and response as a CGI-I score less than 3 and a CGI-S score greater than 1. This retrospective review was done according to the rules of the local Ethics Committee of the University Hospital of Liège, Belgium. A paired t-test was used to compare CGI-S scores before and 6 weeks after the switch to duloxetine.

Results

The sample included 29 patients eligible for inclusion in our study. Sixteen patients had to be excluded due to severe physical illness including history of myocardial infarction (10 patients) and stroke (6 patients). Nine patients without severe physical illness were excluded because of a clear DSM-IV diagnosis of personality disorder. Baseline clinical characteristics included a number of previous episodes of 3.9 ± 2.6 . No patient fulfilled DSM-IV criteria for MDD with psychotic characteristics. Seven patients had atypical features and 17 were melancholics. All patients failed to respond to at least one trial with an SSRI or venlafaxine. The level of resistance to treatment was considered as

quite high. Indeed, 14 patients failed to achieve remission with more than one antidepressant and/or either combination or augmentation strategy. Twelve patients received one SSRI in monotherapy before switching to duloxetine and 8 patients were treated with at least either the combination venlafaxine/mirtazapine or an SSRI augmented with aripiprazole.

We observed a very significant decrease in CGI-S scores ($4,86 \pm 0,51$ to $2,17 \pm 1,44$, $p < 0.0001$) after treatment with duloxetine (dose between 60 and 120 mg, mean \pm SD = $78 \pm 29,0$). Remission was achieved in 48 % of the patients. The tolerance was excellent. Side effects were mainly nausea, sweating and sexual dysfunction.

Discussion

These results tend to support the potential interest of duloxetine in the management of major depressed patients resistant to SSRIs and/or venlafaxine. Indeed, 48% of the patients who failed to respond to previous agents or exhibited only partial remission remitted after the administration of duloxetine.

Several data support our results, and in particular the superiority of dual-acting agents over SSRIs (Brecht et al. 2010). There is also some evidence that duloxetine exhibits a particularly high level of efficacy. A meta-analysis of six randomized, double-blind, placebo-controlled studies, for example, revealed remission rates of 40% in the duloxetine group and 38% in the SSRI group compared to 28% in the placebo group (Papakostas et al. 2007). In more severely depressed patients, duloxetine was statistically superior in achieving remission compared to SSRIs (36% versus 29%, respectively). In a 52-week open-label study in outpatients, a remission rate of nearly 82% was reported for the duloxetine group (Papakostas et al. 2008). Moreover, duloxetine exhibits positive effects on painful physical symptoms that could explain the high remission rate associated with this agent (Raskin et al. 2003). The fact that duloxetine is currently the agent with the most equally balanced dual reuptake inhibition could also play a role to explain our results. However, these results do not mean that duloxetine is really more effective than venlafaxine or than some SSRI. But, this study only suggests that duloxetine is a valuable option for patients who failed to significantly improve with a previous antidepressant, particularly a SSRI or another SNRI.

In the interpretation of the data, several pitfalls have to be considered. First, our study is retrospective with the associated risks of considering data is not so accurate as in clinical trials. Secondly, our sample size is limited (only 29 patients), and hence it is difficult to draw real conclusions. Another possible limitation is the

lack of structured interview to make the diagnosis of depression. Due to the absence of a specific evaluation, we can not say if the improvement associated with the prescription of duloxetine is in relationship with an anti-nociceptive effect. Only few data are available concerning the clinical history of the patient, the symptomatology and comorbidities. Moreover, clinical improvement was assessed on the basis of one scale only (CGI). Other scales should have been used to score the clinical evolution. However, the data have been collected by well trained clinicians also involved in scientific programs. The experience of these psychiatrists could guarantee the reliability of the data.

In conclusion, duloxetine appeared very effective in the treatment of partial response or resistance to SSRIs and/or venlafaxine. These data suggest the usefulness of this switching strategy even in cases of failure with a previous SNRI or with other strategies such as augmentation or combination. However, these data are preliminary and should be re-examined using a larger sample.

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