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Research report

Treatment and outcome of antidepressant treatment-associated hypomania in unipolar major depression: A 3-year follow-up study

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ABSTRACT

Background: The main aim of this study was to propose a standardized acute and maintenance/continuation treatment protocol for acute antidepressant treatment-associated hypomania (AAH) in major unipolar depression. The second objective was to describe outcomes at three-year follow-up in a cohort of patients with AAH who had been included in this standardized therapeutic protocol.
Methods: The study consisted of two distinct prospective phases: a 1-year follow-up first phase in which all consecutive patients with a diagnosis of moderate/severe unipolar depressive disorder received acute and continuation/maintenance antidepressant treatment; and a second phase, in which patients who had suffered AAH during the first phase were admitted to a 3-year follow-up with the authors-designed standardized acute and continuation/maintenance treatment protocol.
Results: In our patient sample, the reintroduction of antidepressant treatment according to the proposed protocol was not accompanied by new AAH episodes following 11–36 months of pharmacological antidepressant treatment. The second notable result was that no subject presented manic episodes or spontaneous hypomania (once antidepressant maintenance treatment had finished) during three years of follow-up.
Limitations: We should be cautious when generalizing these results to patients with mild major depressive episode or other type of unipolar affective disorder.
Conclusions: Based on these results, we should not refuse the prescription of antidepressant drugs to patients with unipolar depression and subsequent AAH. The treatment protocol which we describe in this study can serve as a basis for future studies and, in anticipation of future consensus, as a practical proposal for clinical psychiatrists.

1. Introduction

It is striking how little literature exists on hypomanic episodes in the context of the treatment of unipolar depression with antidepressant drugs (Chun and Dunner, 2004). Perhaps more surprising is the total absence of studies which assess the treatment and outcome of this clinical condition. The scarcity of existing research in this area does, however, explain current nosological uncertainty (Akiskal et al., 2003).

The sample finally assessed in this prospective study consisted of subjects diagnosed with unipolar major depression in whom a hypomanic index episode was detected coinciding with antidepressant drug treatment (antidepressant treatment-associated hypomania —AAH). This study had two aims. The main objective was, given the absence of clinical guidelines, to put forward a standardized therapeutic protocol for acute and maintenance/continuation treatment of AAH in unipolar major depression. The second aim was to describe the three-year outcome of a cohort of patients with AAH included in this standardized therapeutic protocol.

2. Methods

2.1. Study design

This study was conducted at the Unipolar Affective Program at Hospital Clínic, Barcelona. It involved a longitudinal design and was carried out between January, 2000 and December, 2012. The study consisted of two consecutive phases: a 1-year follow-up first phase in which all consecutive patients seen between January, 2000 and December, 2009 with a diagnosis of unipolar depressive disorder received acute and continuation/maintenance antidepressant treatment (in agreement with international clinical guidelines); and a second phase in which patients who had

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suffered AAH during the previous phase were admitted to a 3-year follow-up with an authors-designed standardized acute and continuation/maintenance treatment protocol.

The study was approved by the Ethics Committee at our hospital. Following a complete description of the study to the patients (or a close relative when there was a doubt about the patient's level of comprehension), written informed consent was obtained.

2.2. Patient selection

Both in- and outpatients with unipolar major depression aged over 17 years were included in the 1-year follow-up first phase. All met DSM-IV criteria (American Psychiatric Association, 1994) for acute major depressive episode.

The literature suggests that those patients affected by unipolar major depression and AAH may not be true unipolar depression patients but rather a subtype of bipolar patients. With the aim of ensuring, to the maximum degree possible, a pure sample of patients affected with unipolar major depression, it appeared essential to reduce as much as possible the chances of erroneously including patients suffering from other unipolar affective disorders, such dysthymia or adjustment disorders. With this aim (and bearing in mind that we were excluding patients affected by mild unipolar major depression) we introduced a further inclusion criterion; having a pre-treatment 17-item Hamilton depression rating scale (HDRS; Hamilton, 1960) score of 19 or greater. Those patients with a history of hypomania, mania or non-affective psychosis were excluded from the study.

Some authors have arbitrarily suggested that AAH occurring during the first 8 weeks after starting or dose-adjusting the antidepressant treatment would correspond to a "psychotoxic" effect of the anti-depressive treatment, whereas if it occurs after these 8 weeks, it would be attributable to a "latent" bipolar disorder. In the absence of consistent data that allows adequate differentiation of AAH subtypes (not being an aim of this study), the authors preferred to disregard this debate in the design of the present study. So, for the second phase, the inclusion criterion was to have switched to AAH during the 1-year follow-up first phase. Hypomania was defined according to DSM-IV criteria; to reduce the chance of diagnostic error, to be categorized as AAH, these criteria must have been met in two consecutive visits (over a two-day interval).

2.3. Assessments

With the aim of defining the baseline clinical characteristics of the patient sample, depressive symptoms were quantified through the 17-item HDRS. Sub-classification of psychotic versus non-psychotic was determined through the presence or otherwise of delusions at baseline assessment. Evaluation of delusions was carried out throughout the clinical interview.

During the first phase, visits were conducted fortnightly during acute depression, monthly during the first six months after remission (or stabilized partial response) and, subsequently, quarterly until completion of 1-year follow-up.

During AAH-phase, visits were conducted weekly during hypomania, fortnightly during the first 3-months after remission and, subsequently, monthly until completion of the 3-year follow-up (with the proviso, in both phases, that each time a new symptom was suspected for the patient, an extra visit could be scheduled). Manic symptoms were quantified through the Young mania rating scale (YMRS; Young et al., 1978).

2.4. First phase treatment protocol

The treatment prescribed to patients was adjusted in line with that established in our hospital's Unipolar Depression Program Clinical Guide. This Clinical Guide is essentially structured according to depression symptom severity (please see Navarro et al., 2013) and is in agreement with international clinical guides. Depending on baseline severity, the initial treatment proposed is a selective serotonin reuptake inhibitor (SSRI), specifically, fluoxetine (20–40 mg/day) or escitalopram (10–30 mg/day), a serotonin–norepinephrine reuptake inhibitor (SNRI) (venlafaxine extended-release, 75–300 mg/day or, in recent years, duloxetine 60–120 mg/day), or a tricyclic antidepressant (TCA), particularly imipramine or nortriptyline (dose based on plasma levels). In some very severe patients, another option suggested by our Clinical Guide is electroconvulsive therapy (ECT).

According to our Clinical Guide, all patients should remain in remission for a minimum of 6 months (preferably 12 months)

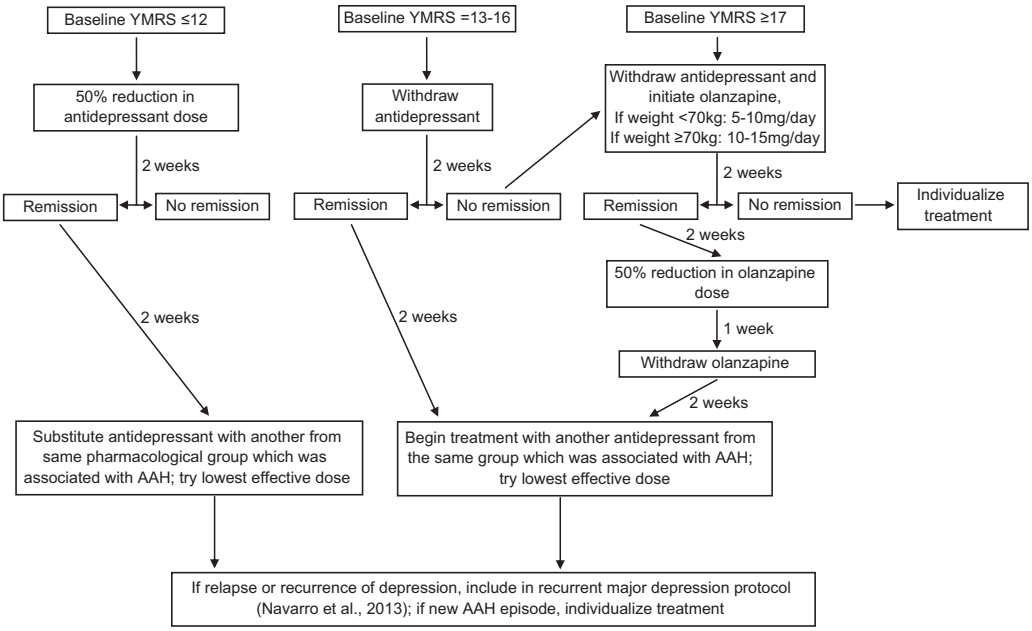

Fig. 1. Acute and continuation/maintenance treatment of AAH in unipolar major depression.