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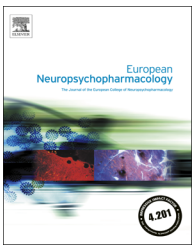

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Poor response to antidepressants predicts new suicidal ideas and behavior in depressed outpatients

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Abstract
Background: Only a few studies have investigated the factors associated with suicidal behavior after antidepressant treatment onset in adults. We examined the specific predictors of *de novo* suicidal ideas or attempts among depressed patients in the community, including subjects potentially at risk of suicidal behaviors, who initiated a new antidepressant treatment.
Methods: A large set of GPs and psychiatrists throughout France followed-up, for 6 weeks, 4357 outpatients for whom an antidepressant drug was prescribed. Dimensions related with antidepressant-induced suicidal events, such as depression, anxiety or hopelessness, were assessed longitudinally using univariate and multivariate approaches among subjects with treatment-emergent suicide ideation or attempts.
Results: New suicidal ideas were observed in 9% of patients with no suicidal ideation at baseline (n=81), while suicidal attempts were reported for 1.7% of the sample during the 6-week observation period (n=75). The onset of suicidal ideas and attempts was associated with the initial features of the patients (baseline level of anxiety, past history of suicide attempts and alcohol misuse) and the non-improvement of depression. Worsening of depressive symptoms during the follow-up increased the onset of new suicidal ideas (OR=5.67, $p<0.001$) and attempts (OR=2.60, p=0.002), corresponding to 67.5% and 56.5% of attributable risk respectively.

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Conclusions: When the analyses are restricted to the occurrence of suicidal ideas or attempts, the link between antidepressants and suicide risk might be more adequately explained by a poor response to antidepressant treatment rather than by a direct trigger-effect. This naturalistic study is limited by the use of non-structured diagnoses and self-report outcomes.

1. Introduction

Having a mood disorder, one of the main causes of disease burden worldwide (Catalá-López et al., 2013), is the main risk factor for suicidal ideation (SI) and suicide attempts (SA). The population attributable risk of mood disorders for a first occurrence of SI or SA has been estimated at 51% and 44% respectively (Nock et al., 2010). Thus, reducing the duration of depressive episodes might have a major impact on suicidal risk. In a 5-year follow-up study of patients treated for a major depressive episode (MDE), the incidence rate of SA was 21-fold during full symptomatic depression, and 4-fold during partial remission, compared to full remission (Holma et al., 2010). Moreover, physician's education programs targeting depression recognition and treatment reported increased prescription of antidepressants and substantial declines in suicide rates (Mann, 2005). Observational studies have also shown an inverse correlation between antidepressant prescriptions and suicide rates (Isacsson et al., 2009; Hamilton et al., 2007). Unfortunately, major depression is often inadequately treated (Oquendo et al., 2002).

Regulatory bodies have warned about the use of antidepressants in young adults, particularly during the first weeks of treatment. A recent meta-analysis of 372 double blind placebo controlled randomized clinical trials (RCTs) of antidepressants in adults confirmed that young participants (below 25 years of age) with a psychiatric indication had a significantly increased risk of suicidal behavior (OR=2.30) (Stone et al., 2009). However, RCTs usually apply the term "suicidality" to spontaneously declared suicidal events, preventing researchers to examine the risk of specific suicidal behaviors during antidepressant treatment (Meyer et al., 2010; Brent, 2009). Moreover, the warnings may have diminished the propensity to diagnose and treat major depression with antidepressants in patients under 18 years of age (Valuck et al., 2007; Libby et al., 2009) and subsequently increased the suicide rates among children and teenagers in several countries (Gibbons et al., 2007; Katz et al., 2008). This controversy might increase the confusion around the beneficial effects of antidepressants (Meyer et al., 2010).

To the best of our knowledge, few studies investigated the risk of well-defined SI or SA in adults treated with antidepressants. This was a secondary topic of four large trials: the GENDEP (Perroud et al., 2009), the STAR*D (Zisook et al., 2009), the "Multicenter Trial of Fluoxetine" (Perlis et al., 2007) and the German research network' study (Seemüller et al., 2008). In these studies, SI emerged in up to 20% of patients associated with several risk factors, including depression severity, younger age at onset and higher number of depressive episodes, and history of SA. However, most of these studies restricted the analyses to a limited number of antidepressants and detected very few SAs (30 in 6000 patients), which impeded the identification of specific predictors of SI versus SAs. Finally, these trials did not include some important markers according to the "stress diathesis" model (Mann et al., 1999), such as subjective reports of depression severity (excepting GENDEP) or hopelessness.

In order to investigate the origin of SI and suicidal behavior during the first weeks of antidepressant treatment, there is a need to assess the different components of the suicidal process, and their respective predictors (Meyer et al., 2010). The emergence of new suicidal ideas (i.e. in patients with no SI at the onset of treatment) is a potential marker of future suicidal acts and treatment-associated risk. Indeed, the occurrence of SI may be triggered by the effects of antidepressants, whereas the worsening of SI already present at the onset of treatment may be contaminated by other factors such as time variations of depression severity (Nock et al., 2010). In this study, we aim to investigate prospectively the association between treatment-emergent SI and treatment response in a large cohort of outpatients starting during the first six weeks of antidepressant treatment for a MDE. Secondarily, we will explore the course and predictors of SI and SA. We hypothesize that suicidal outcomes will be related with low treatment efficacy.

2. Experimental procedures

2.1. Sample

Participants were recruited from primary and psychiatric care clinical settings across France. A list of 3000 medical doctors was contacted by mail, as previously published (Gorwood et al., 2008) but on a new and independent sample. They were asked to participate in a short-term follow-up protocol to which 69.6% physicians agreed. Each clinician was contacted at least twice (usually by phone): i) to explain the instruments before starting the protocol; and ii) to check the received data at the end of the trial entry. By the end of the study, 1186 clinicians (39.5%) had included at least one patient (a maximum of 5 was requested to avoid center effects), followed-up for at least 6 weeks between the first and the second visit.

Clinicians were asked to include, during a 3-month interval, consecutive patients for whom a new or different prescription of antidepressant had to be made for a MDE. To enhance generalizability, self-declared outpatients seeking medical care were eligible and a checklist of DSM-IV criteria confirmed the diagnosis of MDE. Patients were required to