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Journal of Affective Disorders 106 (2008) 279–284

JOURNAL OF AFFECTIVE DISORDERS

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Research report

Risk of psychosis exacerbation by tricyclic antidepressants in unipolar Major Depressive Disorder with psychotic features

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Received 29 November 2006; received in revised form 20 June 2007; accepted 11 July 2007
Available online 31 August 2007

Abstract

Background: We conducted a systematic review of the published trials in unipolar Major Depressive Disorder with psychotic features (MDDP) to examine the risk of psychosis exacerbation by antidepressants.
Methods: We searched Medline, Cochrane Central Register of Controlled Trials, PsychINFO, and EMBASE for English language, controlled, open or retrospective acute antidepressant and/or antipsychotic treatment studies of unipolar MDDP. Studies without a clear delineation of treatment course or between bipolar disorder and unipolar MDDP were excluded. We evaluated studies for the number of subjects with psychosis exacerbation, and contacted the corresponding author for ambiguous cases. Studies in which we were unable to determine rates of psychosis exacerbation were excluded. Psychosis exacerbation was determined on a categorical basis, and analyzed with Fisher's exact test, a modified Wald confidence interval and odds ratio.
Results: 20 studies meeting criteria provided sufficient adverse event reporting for inclusion. 15 of 177 subjects (8.5%) on antidepressant monotherapy had a psychosis exacerbation, 8 of whom were on tricyclics. 2 of 129 subjects on either antipsychotic or combination treatment had a psychosis exacerbation. Tricyclic monotherapy was significantly more likely to be temporally associated with psychosis exacerbation ($p=0.007$).
Limitations: Limitations include the small number of placebo-controlled trials, and numerous studies in which the relevant information was missing. Additionally, most trials were designed as treatment outcome studies, and not to determine the rate of psychosis exacerbation.
Conclusions: Although rare, the present study indicates that tricyclic monotherapy may be temporally associated with an exacerbation of psychotic symptoms in patients with unipolar MDDP, potentially worsening prognosis.

Keywords: Major depression with psychotic features; Psychotic depression; Delusional depression; Antidepressant side effects; Pharmacologically induced psychosis

1. Introduction

The risk of psychosis exacerbation by antidepressants in unipolar Major Depressive Disorder with psychotic features (MDDP) was first reported almost thirty years ago (Nelson et al., 1979), in 3 cases of MDDP with worsening psychosis temporally related to initiation of monotherapy with a tricyclic antidepressant. Similar

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doi:10.1016/j.jad.2007.07.012

findings have been reported with serotonergic antidepressants (Lauterbach, 1991; Narayan et al., 1995).

There is also evidence that MDDP is qualitatively unlike other affective disorders (Roose et al., 1983; Schatzberg and Rothschild, 1992), and therefore might respond differently to antidepressants, when compared to uncomplicated unipolar depression. The presence of delusions in the index episode of depression is associated with a five-fold increased risk of suicide (Roose et al., 1983), making treatment that risks worsening delusions dangerous.

Despite the seriousness of this potential risk, only limited attention has been given to the risk of antidepressant exacerbation by antidepressants in the literature recently. Furthermore, the optimal treatment for MDDP remains controversial. A recent systematic review (Wijkstra et al., 2005) on the pharmacological treatment of MDDP found no conclusive evidence that combined antipsychotic and antidepressant combination treatment is more effective than antidepressant monotherapy. However, the conclusion was limited (Wijkstra et al., 2005) by a small number of studies with relatively few patients. Conversely, a recent attempt to create an algorithm for MDDP found improved effectiveness with first-line combined antidepressant and antipsychotic treatment (Trivedi et al., 2004). Neither of these reports examined psychosis exacerbation with antidepressant treatment, nor have there been any double-blind studies that have directly investigated this risk.

A retrospective study (Preda et al., 2001), however, found that over a 14-month period, 8.1% of admissions to a general inpatient psychiatric hospital were due to antidepressant-associated mania or psychosis. 8 (18.6%) of these patients were diagnosed with MDDP. Subsequently, a prospective study (Bowers et al., 2003) followed 16 consecutive admissions for manic or psychotic symptoms, 5 of whom had unipolar MDDP. Each patient's regimens initially included a serotonergic antidepressant, in addition to various other psychotropics. Antidepressants were discontinued on admission, and the initial mean BPRS of 53.8 fell to a mean of 28 at discharge. These reports are limited by their case series design, which restricts the ability to distinguish between cause and correlation, and magnitude of effect.

To evaluate the available literature regarding the potential risk of antidepressant exacerbation of psychosis in MDDP, we conducted a systematic review of the published trials in this field to determine whether this risk holds true when all the studies are examined collectively. We hypothesize that in comparison to treatment including an antipsychotic, there will be a small, but significantly increased number of MDDP patients on antidepressant monotherapy who experience psychosis exacerbation.

2. Methods

2.1. Data sources and study selection

We performed a comprehensive literature search in Medline, Cochrane Central Register of Controlled Trials, PsychINFO, and EMBASE for studies from January, 1980 through July, 2005. Search terms were "psychotic depression", "delusional depression", "depression with psychosis", "depression and psychosis", "depressive psychosis", "depressive disorder and psychosis" and "psychotic disorder and depressive disorder". We also manually searched the reference lists of studies meeting our inclusion criteria (specified below).

Inclusion criteria included: (i) English language, (ii) acute, (iii) controlled, open or retrospective acute antidepressant and/or antipsychotic treatment studies of unipolar MDDP (criteria used were ICD-9 and 10, DSM III through DSM IV-R, or RDC).

Exclusion criteria included: (i) Case reports, (ii) non-English language studies, (iii) non-acute trials (defined as a trial focusing on follow-up after initial response to treatment), (iv) trials of medications other than antidepressants or antipsychotics, and (v) studies without a clear delineation of treatment course or (vi) between bipolar disorder and unipolar MDDP.

2.2. Data extraction

Studies meeting criteria were evaluated by both authors for a report of the number of patients in whom psychosis worsened, and the corresponding author was contacted via e-mail in ambiguous cases. Psychosis exacerbation was considered present or absent if explicitly stated in the manuscript, or if the contacted author provided information to this effect. Studies in which we were unable to determine if there were any patients experiencing exacerbation of psychosis were not included in this review. Psychosis exacerbation was determined on a categorical basis.

The subjects of the studies were then divided into 2 groups; those receiving acute monotherapy with antidepressants, and those receiving acute treatment therapy including an antipsychotic medication, i.e. antipsychotic monotherapy or antidepressant + antipsychotic (combination) treatment. A two-tailed Fisher's exact test was used to analyze the data, and results were considered significant at p value < 0.05. Additionally, odd ratios (OR) were calculated, and confidence intervals (CI) were calculated by a modified Wald method.