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Research report

Lithium is associated with decrease in all-cause and suicide mortality in high-risk bipolar patients: A nationwide registry-based prospective cohort study

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ABSTRACT

Background: Mortality rates, in particular due to suicide, are especially high in bipolar patients. This nationwide, registry-based study analyses the associations of medication use with hospitalization due to attempted suicides, deaths from suicide, and overall mortality across different psychotropic agents in bipolar patients.

Method: Altogether 826 bipolar patients hospitalized in Finland between 1996-2003 because of a suicide attempt were followed-up for a mean of 3.5 years. The relative risk of suicide attempts leading to hospitalization, completed suicide, and overall mortality during lithium vs. no-lithium, antipsychotic vs. no-antipsychotic, valproic acid vs. no-valproic acid, antidepressant vs. no-antidepressant and benzodiazepine vs. no-benzodiazepine treatment was measured.

Results: The use of valproic acid (RR=1.53, 95% CI: 1.26–1.85, $p<0.001$), antidepressants (RR=1.49, 95% CI: 1.23–1.8, $p<0.001$) and benzodiazepines (RR=1.49, 95% CI: 1.23–1.80, $p<0.001$) was associated with increased risk of attempted suicide. Lithium was associated with a (non-significantly) lower risk of suicide attempts, and with significantly decreased suicide mortality in univariate (RR=0.39, 95% CI: 0.17–0.93, $p=0.03$), Cox (HR=0.37, 95% CI: 0.16–0.88, $p=0.02$) and marginal structural models (HR=0.31, 95% CI: 0.12–0.79, $p=0.02$). Moreover, lithium was related to decreased all-cause mortality by 49% (marginal structural models).

Limitations: Only high-risk bipolar patients hospitalized after a suicide attempt were studied. Diagnosis was not based on standardized diagnostic interviews; treatment regimens were uncontrolled.

Conclusions: Maintenance therapy with lithium, but not with other medications, is linked to decreased suicide and all-cause mortality in high-risk bipolar patients. Lithium should be considered for suicide prevention in high-risk bipolar patients.

1. Introduction

Bipolar disorders (BPD) are relatively common, often severe and disabling mental disorders that affect up to 4% of the population (Merikangas et al., 2007), although lower lifetime prevalence rates for bipolar I disorder (0.24–0.42%) have been reported in Finland (Perälä et al., 2007). BPD is potentially fatal largely due to suicidal risk. According to a Finnish cohort study, 80% of patients with BPD I or II exhibit suicidal behavior, and 51% attempt suicide during their lifetime (Valtonen et al., 2005). The mortality ratio for suicide in BPD has been estimated about 15–20 times higher than in the general population (Harris and Barraclough, 1997; Tondo et al., 2003). In addition to increased suicide mortality and attempted suicide rates, the all-cause mortality is also increased in BPD (Carlborg et al., 2014; Laursen et al., 2007; Laursen et al., 2013; Ösby et al., 2001).

Mood-stabilizing pharmacotherapy is a cornerstone of BPD treatment. According to the latest guidelines, lithium is recommended,

Abbreviations: BPD, bipolar disorder; HDR, hospital discharge register; MSM, marginal structural model; SGA, second generation antipsychotic

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alone or in combination with other psychotropic drugs, as a first- or second-line pharmacotherapy for the treatment of acute mania and bipolar depression, as well as a first-line maintenance treatment for BPD (National Institute for Health and Clinical Excellence, 2014; Yatham et al., 2013). In line with these evidence-based clinical guidelines, the efficacy of lithium in BPD, especially in preventing manic episodes, has been convincingly supported by several studies (Geddes et al., 2004; Geddes and Miklowitz, 2013; Gitlin and Frye, 2012; Severus et al., 2014). Additionally, a large systematic review has demonstrated the cost-effectiveness of lithium for the prevention of relapses in BPD (Soares-Weiser et al., 2007).

In addition to lithium, first-line pharmacological options for the treatment of acute mania or depression, as well as long-term maintenance therapy in bipolar patients include mood-stabilizing anticonvulsants like valproic acid, antipsychotics and antidepressants (National Institute for Health and Clinical Excellence, 2014; Yatham et al., 2013). Furthermore, benzodiazepines can be used as adjunctive therapy, especially in the case of acute mania, given their anxiolytic and sedative properties.

A growing body of evidence has shown that long-term treatment with lithium reduces the risk of suicide and suicide attempts in patients suffering from affective disorders (Baldessarini et al., 2006; Baldessarini and Tondo, 2008). Similarly, a recent systematic meta-analysis of randomized trials has shown the efficacy of lithium in terms of reduced suicides and all-cause deaths (but not deliberate self-harm) when compared with placebo in patients experiencing unipolar or bipolar depression (Cipriani et al., 2013). Additionally, when compared to other active drugs (antipsychotics, antidepressants and anticonvulsants), lithium was superior to carbamazepine in preventing deliberate self-harm (Baldessarini and Tondo, 2008). Similar results were obtained in two Danish nationwide cohort studies, where continued lithium treatment was associated with reduced risk of suicide, and lithium tended to be superior to anticonvulsants in terms of suicide prevention (Kessing et al., 2005; Søndergård et al., 2008).

The research on the efficacy of other active compounds in preventing suicidal behavior in bipolar patients has produced partially contradictory results. Even though valproic acid appeared to have a similar antisuicidal efficacy as lithium in some studies (Oquendo et al., 2011; Yerevanian et al., 2007a), results of several other works suggest that the suicide risk of bipolar patients is higher during treatment with valproic acid than with lithium (Collins et al., 2008; Goodwin et al., 2003).

Similarly, although second generation antipsychotics (SGA) were found to reduce the risk of suicide in patients suffering from schizophrenia (Altamura et al., 2003; Meltzer and Okayli, 1995), results regarding the suicide prevention properties of antipsychotics in bipolar patients are rather contradictory. Despite some suggestive findings of potential beneficial effects of olanzapine (Houston et al., 2006; Tohen et al., 2002), most of the research to date indicates higher risks of suicide attempts in bipolar patients treated with antipsychotics than with mood stabilizers (Yerevanian et al., 2007b). Specifically, first generation antipsychotics seem to be associated with higher risk of suicidal behavior than SGA (Koek et al., 2012), with no significant differences within the latter class (namely, risperidone, olanzapine and quetiapine). However, while the rates of suicidal behavior were higher in the case of monotherapy with SGA rather than mood stabilizers, they were significantly lower when the antipsychotics (either first or second generation) were combined with lithium or other mood stabilizers (Koek et al., 2012). Similarly, a 6-year retrospective study of veterans experiencing BPD (Ahearn et al., 2013) found the majority of attempted suicides (59%) to happen while patients were taking no medication, followed by periods when the patients were taking SGA (24%), valproic acid (21%) and lithium (15%); when considering the duration of exposure to the drug, the highest attempted suicide rates corresponded to the antipsychotic (alone or in combination) treatment phases (20.1/10000 months of exposure).

Despite the still-open debate regarding the benefits and risks of antidepressant therapy for BPD (Geddes and Miklowitz, 2013), antidepressants in combination with other agents are recommended as first-line treatment for bipolar depression (National Institute for Health and Clinical Excellence, 2014; Yatham et al., 2013). In a 27-year longitudinal study those with bipolar I disorder had a significant reduction in risk of suicidal behavior by 54% during periods of antidepressant exposure compared to propensity-matched unexposed intervals. In the same study the risk in bipolar II disorder was reduced by 35% (Leon et al., 2014). However, in a meta-analysis of randomized controlled trials on long-term antidepressant treatment in BPD, adjunctive antidepressants provided no clinical benefits compared to mood stabilizer monotherapy (Ghaemi et al., 2008). Similar results were yielded by a recent meta-analysis of double-blind randomized controlled trials, where the use of antidepressants in bipolar depression, although not associated with increased risk of affective switching, was not superior to placebo or other pharmacological agents in terms of short-term and long-term clinical efficacy (Zhang et al., 2013). In the same study, no difference in terms of suicidality was found between short-term or long-term antidepressant treatment and placebo in bipolar depression (Zhang et al., 2013). On the contrary, in their retrospective study of 405 bipolar patients Yerevanian et al. (2007c) found higher rates of suicidal behavior during treatment with antidepressants (alone or combined with a mood stabilizer) compared to treatment periods with mood stabilizers only. However, there is a general lack of studies focusing on the influence of antidepressants on suicidal risk in bipolar patients.

With a few exceptions (Kessing et al., 2005; Søndergård et al., 2008), most of the outcome studies of pharmacotherapy in bipolar patients have been conducted in restricted health-care settings (Collins and McFarland, 2008; Goodwin et al., 2003; Yerevanian et al., 2007a; Yerevanian et al., 2007b; Yerevanian et al., 2007c), therefore including only selected patient groups. To the best of our knowledge, there are no nationwide population-based studies comparing different pharmacological agents with regard to attempted suicide, completed suicide and overall mortality in BPD patients simultaneously. Thus, our current nationwide study was designed to provide long-term naturalistic data on the relationships between lithium, antipsychotics, valproic acid, antidepressants and benzodiazepines, and the risk of suicidal behavior and overall mortality in bipolar patients following a serious attempted suicide.

2. Methods

2.1. Study population and procedures

All the individuals who were hospitalized in Finland because of a suicide attempt (*International Classification of Diseases, 10th Revision* ICD-10 codes X600 to X840, Z728, or Z915) between January 1, 1996 and December 31, 2003, and in prospective screening had been hospitalized due to bipolar disorder (ICD-10 codes F30.0 to F30.9, F31.0 to F31.9) before the index attempt, were included in the study. The first hospital treatment period due to attempted suicide was considered the index period. Each individual was followed-up until December 2003 or up to death, if this occurred in the intervening time. Only individuals aged 16 years or older at the time of the index hospitalization were included. Participants were selected, through unique personal identification codes routinely used in Finnish registries, from the Hospital Discharge Register (HDR), which covers all public and private psychiatric and general hospitals, and community-care inpatient units in Finland. Information obtained from the national HDR