

Pharmacological treatments and risk of readmission to hospital for unipolar depression in Finland: a nationwide cohort study



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Summary

Background Little is known about the comparative effectiveness of long-term pharmacological treatments for severe unipolar depression. We aimed to study the effectiveness of pharmacological treatments in relapse prevention in a nationwide cohort of patients who had been admitted to hospital at least once as a result of unipolar depression.

Methods Our nationwide cohort study investigated the risk of readmission to hospital in 1996–2012 in all patients in Finland who had been admitted to hospital at least once for unipolar depression (without a diagnosis of schizophrenia or bipolar disorder) in Finland between Jan 1, 1987, and Dec 31, 2012. We used nationwide databases to obtain data for hospital admission, mortality, and dispensed medications. Exposure and non-exposure periods for medications were established using the PRE2DUP method. The primary analysis was within-individual analysis of readmission to hospital in the total cohort, in which each individual was used as his or her own control to eliminate selection bias. Putative survival and protopathic biases were controlled in sensitivity analyses. Since 33 independent statistical comparisons were done for specific medications, the level of statistical significance was set at $p < 0.0015$.

Findings Data from 123 712 patients were included in the total cohort, with a mean follow-up time of 7.9 years (SD 5.3). Lithium use was associated with a lower risk of re-admission to hospital for mental illness than was no lithium use (hazard ratio [HR] 0.47 [95% CI 0.40–0.55]; $p < 0.0001$), whereas the groups of antidepressants (HR 1.10 [1.06–1.13]; $p < 0.0001$) and antipsychotics (HR 1.16 [1.12–1.20]; $p < 0.0001$) were not associated with a reduced risk of readmission to hospital. Risk of hospital readmission was lower during lithium therapy alone (HR 0.31 [0.21–0.47]; $p < 0.0001$) than during use of lithium with antidepressants (HR 0.50 [0.43–0.59]; $p < 0.0001$). After lithium, clozapine (HR 0.65 [0.46–0.90]; $p = 0.010$) and amitriptyline (HR 0.75 [0.70–0.81]; $p < 0.0001$) were the specific agents associated with the next lowest risk of readmission. In the sensitivity analyses controlling for survival and protopathic biases, all drugs were associated with lower rates of readmission to hospital than they were in the primary analysis, showing the same rank order in comparative effectiveness. The lowest mortality was observed during antidepressant use (HR 0.56 [0.54–0.58]; $p < 0.0001$).

Interpretation Our results indicate that lithium, especially without concomitant antidepressant use, is the pharmacological treatment associated with the lowest risk of hospital readmission for mental illness in patients with severe unipolar depression, and the outcomes for this measure related to antidepressants and antipsychotics are poorer than lithium. Lithium treatment should be considered for a wider population of severely depressed patients than those currently considered, taking into account its potential risks and side-effects.

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Introduction

Major depressive disorder is the second leading contributor towards years lived with disability worldwide.¹ Although the majority of patients recover from an acute episode of major depressive disorder, most of them have relapses during their life.² Randomised controlled trials (RCTs) have shown that non-pharmacological interventions² and antidepressant maintenance treatments reduce relapses by about 15–25 percentage points (corresponding to a number needed to treat of 5–6) compared with placebo or treatment as usual during 8–24-month follow-up.^{3–7} Although meta-analyses on maintenance treatments have shown that antidepressants reduce the 40% relapse rate with placebo to 20% with active treatment, no significant differences have previously been found between specific

compounds.^{4–7} Thus far, one small RCT has studied the efficacy of lithium versus placebo augmentation in relapse prevention in patients receiving antidepressants. Although seven of 15 patients with placebo relapsed, none of the 14 patients who received lithium relapsed.⁸ However, individuals participating in RCTs are only an atypical minority of the total patient population, since many patients are excluded from these studies for reasons such as substance abuse or non-adherence to the study procedure, and many decline to take part in research. To our knowledge, only antidepressants and lithium have been included in relapse prevention studies, and no data are available for antipsychotics. Further, the RCTs comparing the effectiveness of lithium versus antidepressants have been small, resulting in insufficient

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Research in context**Evidence before this study**

Antidepressants, lithium, and antipsychotics are used in the treatment of severe unipolar depression, but little is known about their comparative long-term effectiveness. We searched previous evidence on relapse prevention of unipolar depression from PubMed using the search terms “antidepressant”, “lithium”, “antipsychotic”, “unipolar”, “depression”, and “relapse”, published from Jan 1, 1980, to Dec 31, 2016. The only meta-analysis found reported a relative relapse risk of 0.40 in favour of lithium over a variety of antidepressants, but this finding did not reach statistical significance because of insufficient statistical power.

Added value of this study

Our results are the first showing statistically significant superiority of lithium compared with antidepressants or antipsychotics in relapse prevention of unipolar depression. The risk of psychiatric readmission to hospital associated with the most widely used treatments (antidepressants, aripiprazole, and quetiapine) is higher than the risk associated with lithium.

Implications of all the available evidence

Lithium treatment should be considered for a wider population of severely depressed patients, taking into account its potential risks and side-effects.

statistical power in meta-analysis,⁹ and how the treatments retain their effectiveness beyond 1–3-year study periods is unknown. Therefore, the comparative real-world effectiveness of treatments for relapse prevention has remained unclear. Since the most severely ill patients and those with comorbidity are often not included in RCTs, the only way to study the representative patient population is via observational studies. We aimed to study the effectiveness of pharmacological treatments in relapse prevention in a nationwide cohort of patients in Finland who had been admitted to hospital at least once as a result of unipolar depression. Since the mid 1980s, the number of available beds in psychiatric hospitals in Finland has decreased by 80%;¹⁰ and only the most severely ill patients with depression are now admitted to hospital. Therefore, the study cohort consists of patients with the most severe cases of unipolar depression. Lithium, aripiprazole, and quetiapine are considered the most effective add-on treatments on top of antidepressants in treatment-resistant unipolar depression,^{11–14} and were chosen as the primary treatments of interest in our study.

Methods**Study design and data sources**

In this observational cohort study, we used national Finnish databases on mortality, admissions to hospital, and medications dispensed from pharmacies to study the comparative effectiveness of some psychotropic medications in relapse prevention of severe unipolar depression. In Finland, each person has a unique person identification number that enables the tracing of all individuals over time. The study cohort was identified from the Finnish National Hospital Discharge Register, which is administrated by the National Institute for Health and Welfare of Finland. The register was used to determine the incidence of readmission to hospital, and time spent in hospital (ie, hospital treatment periods), which was omitted from the time-at-risk measurement. The National Prescription Register was used to obtain information on dispensed prescriptions, and the National Mortality Register was used to retrieve mortality data. The data

sources have been described in more detail in our previous pharmacoepidemiological studies.^{15–18} This study included all participants who had been admitted to hospital at least once with a diagnosis of unipolar depression (ICD-10 diagnosis of F32–33, and Finnish ICD-9 1987 classification of 2961) between Jan 1, 1987, and Dec 31, 2012, without any diagnosis of schizophrenia or other non-mood psychotic disorders (ICD-10 F20–29; ICD-9 295, 2971A, 2973A, 2988A, 2989X, or 3012C) or mania or bipolar disorder (ICD-10 F30–31; ICD-9 2962–2964 or 2967A). For patients with a diagnosis of unipolar depression before 1996, the follow-up started on Jan 1, 1996 (that date from which medication use data became available), and for patients with no diagnosis before 1996, the follow-up started at the time of first discharge from hospital with a diagnosis of unipolar depression. To avoid survival bias, we also did an analysis in a subpopulation of new patients; this incident cohort included patients whose follow-up started after Dec 31, 1996, and had not been admitted to hospital with any mental disorder (ICD-10 F; ICD-9 290–319, 3310A, 3334A, 4378A, 0788B, 0461A, 1390A, or 6484X) before the start of follow-up and who had not used any antidepressant, mood stabiliser, or antipsychotic treatment in out-patient care within 1 year before the start of follow-up.

The research project was approved by the ethics committee of the National Institute for Health and Welfare of Finland (Dec 4, 2013, 8/2013). Further permissions were granted by pertinent institutional authorities at the National Institute for Health and Welfare of Finland (permission THL/1466/6.02.00/2013), the Social Insurance Institution of Finland (34/522/2013), and Statistics Finland (TK53–305–13).

Procedures

We studied the risk of psychiatric readmission to hospital for any mental disorder (excluding admissions for schizophrenia and other non-affective psychoses [ICD-10 F20–29] and mania and bipolar disorder [F30–31]) in all patients who had been admitted to hospital for unipolar depression at least once between 1987 and 2012 as

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