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Antipsychotics in the maintenance phase for psychotic depression

Ahmed Al-Wandi¹ | Mikael Landén²,³ | Axel Nordenskjöld¹

¹University Health Care Research Centre, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
²Institute of Neuroscience and Physiology, the Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden
³Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Abstract

Objective: This study aimed to associate antidepressants with versus without antipsychotics with readmission and suicide in patients with psychotic unipolar depression.

Methods: Swedish national registers were used to identify inpatients with psychotic unipolar depression, treated 2007–2016. The participants collected antidepressants with or without antipsychotics from a pharmacy within 14 days after discharge and were followed up for 2 years. The primary outcome was hospital readmission due to any psychiatric disorder, suicide attempt, or completed suicide. Cox regression was used to analyze the data, which were adjusted for sex, age, prior admissions, comorbidity, electroconvulsive therapy, and other pharmacological treatments.

Results: We identified 4391 patients, of which 2972 were in the antidepressant + antipsychotic combination therapy group, and 1419 were in the antidepressant monotherapy group. After 2 years, 42.3% and 36.6% of patients were readmitted or committed suicide in the combination therapy and monotherapy group, respectively. Monotherapy was significantly associated with a lower risk of reaching the outcome in the main analysis (hazard ratio = 0.86; 95% confidence interval: 0.77–0.95). The results went in the same direction in all sensitivity analyses.

Conclusion: Our findings do not indicate any advantage of adding antipsychotics as adjunctive to antidepressants as maintenance treatment. Considering the wide use, known side effects, and the current lack of evidence supporting the benefit, further studies on the effect of antipsychotics in the maintenance phase of psychotic unipolar depression are urgently warranted.

KEYWORDS
antidepressants, antipsychotics, psychotic depression, readmission, relapse

1 | INTRODUCTION

In the 10th International Classification of Diseases (ICD-10), psychotic depression is defined as a severe depressive episode with concurrent hallucinations, delusions, or depressive stupor.¹ Psychotic depression is estimated to affect approximately 0.35%–1% of the population during their lifetime.² In a meta-analysis by

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Furthermore, some studies suggest a higher number of depressive episodes and hospitalizations in psychotic depression, though there are conflicting results. The American Psychiatric Association recommends a combination of antidepressants and antipsychotics as first-line treatment for psychotic depression alongside electroconvulsive therapy (ECT). In systematic reviews of acute pharmacological treatments by Farahani et al and Kruizinga et al, combination therapy with antidepressants and antipsychotics was superior to antidepressant monotherapy; however, this comparison was only examined in a small number of studies, limiting the confidence of the results. The existing data on maintenance treatment are even more scarce. Our group recently conducted a systematic review of maintenance treatment for preventing relapse in psychotic depression. We identified three studies comparing antidepressant + antipsychotic combination therapy with antidepressant monotherapy. In the largest of these studies, conducted by Flint et al, 126 patients were randomized under double-blind conditions to receive sertraline and olanzapine combination therapy or sertraline and placebo in the maintenance phase. After 36 weeks of follow-up, there was a statistically significant difference in favor of combination therapy; 23.2% of the participants finishing the study suffered a relapse in the combination group compared with 58.6% in the monotherapy group. But, when all three studies in our review were synthesized in meta-analysis, there was no significant difference between combination therapy and monotherapy; however, the evidence was of low quality due to substantial heterogeneity between the studies, small sample sizes, and few events.

If antipsychotics are to be used in the maintenance phase it is important to determine for how long the treatment should continue, since antipsychotics are associated with many potential side effects including metabolic, extrapyramidal, and anticholinergic side effects. In a study by Rothschild et al, they concluded that most patients do not need antipsychotic treatment for more than 4 months. However, this was an uncontrolled study with only 30 participants, and due to the open nature of the study, the authors concluded that their findings must be regarded as preliminary.

Due to the limited number of studies and the potential side effects of antipsychotics, further investigation is warranted to decide whether antipsychotics as an adjunctive to antidepressants are superior to antidepressants alone in the maintenance phase.

### Significant outcomes
- Adding antipsychotics as adjunctive to antidepressants as maintenance treatment was not associated with a decreased risk of readmission among patients with psychotic unipolar depression.

### Limitations
- We only had access to records of collected drugs from pharmacies. Information regarding compliance and what pharmacological treatment the patients received during the hospital stays was missing.
- Information about other signs of relapse except hospital readmissions and suicides was missing.
- The possibility of residual confounding cannot be excluded.

## 2 MATERIALS AND METHODS

### 2.1 Study design

The aim of this registry study was to assess the association of antidepressant monotherapy versus antidepressant + antipsychotic combination therapy with readmission and suicide among patients with psychotic unipolar depression (henceforth shortened to psychotic depression). The data used in this study were obtained by combining several Swedish registries. All permanent residents in Sweden receive a personal identity number through which the different registries used in this study were linked together by Statistics Sweden.

### 2.2 Participants

We identified individuals diagnosed with a main inpatient diagnosis of psychotic depression (F32.3 or F33.3) according to ICD-10 between January 1, 2007 and December 31, 2016. If individuals had more than one inpatient episode, we used the first. The first inpatient episode is henceforth referred to as the index episode. A list of the ICD-10 codes that were used to identify the different disorders and suicide attempts is presented in Table A1.

Subjects were excluded if they had a concomitant diagnosis of a psychotic disorder, bipolar disorder, or manic episode during the index episode; if there were
any previous inpatient episodes with the abovementioned diagnoses from January 1, 1997 up until the start of the index episode; if the subjects were younger than 18 years old; if the duration of the index episode was less than 1 day; and if the index episode overlapped with another psychiatric inpatient episode.

To be included in the final analysis, the subjects had to collect either ≥1 antidepressant without antipsychotics or ≥1 antidepressant and ≥1 antipsychotic from a pharmacy from 1 day after the start of the index episode to a maximum of 14 days after discharge. The anatomical therapeutic chemical (ATC) classification system was used to identify the different medications. A list of the ATC codes that were used is presented in Table A2.

2.3 | Outcome

The primary outcome was the composite of hospital readmission due to any psychiatric disorder as main diagnosis, readmission due to suicide attempt, or completed suicide (whichever came first) within 2 years of discharge. Subjects who died of other causes than suicide contributed with time in the analysis until their death.

2.4 | Data sources

Information about inpatient episodes was obtained from the Swedish National Inpatient Register. This mandatory register covers >99% of all somatic and psychiatric hospital discharges. Data on ECT were extracted from the Swedish National Inpatient Register and the Swedish National Quality Register for ECT (Q-ECT). In 2019, the Q-ECT covered 93% of all cases receiving ECT in Sweden. We extracted data on the collection of prescribed drugs from the Swedish National Prescribed Drug Register. Data on deaths and suicides were obtained from the Swedish Cause of Death Register.

2.5 | Other variables

In a systematic review and meta-synthesis by Buckman et al, childhood maltreatment, residual symptoms, and a history of prior episodes were identified as the strongest predictors for the recurrence of depression. However, we were unable to assess childhood maltreatment in the available registries. A history of previous hospitalizations due to a psychiatric disorder was used as a proxy for prior episodes.

Other potential confounders included as covariates in the statistical analyses were sex, age, ECT during the index episode; collection of lithium, lamotrigine, benzodiazepines, and other anxiolytics (aside from benzodiazepines) after admission (but before reaching the outcome); and an inpatient diagnosis of a personality disorder, anxiety disorder, alcohol use disorder, or substance use disorder either prior to or during the index episode.

2.6 | Statistical analyses

SAS Enterprise Guide 8.3 and IBM SPSS Statistics 27 were used for the statistical analyses. Patient characteristics were compared between the treatment groups by calculating the standardized mean difference. Cox regression was used to analyze the primary outcome, with a follow-up time of up to 2 years. The subjects who reached the primary outcome within the first 14 days after discharge were excluded from the analysis as they may not have had time to collect the prescribed treatment. The abovementioned covariates were assessed in univariable, multivariable, and multivariate stratified analyses and were also tested for interactions.

2.7 | Sensitivity analyses

2.7.1 | Analysis at 365 days

Between 366 and 730 days after discharge, only 50.9% of the subjects in the combination therapy group collected a prescription of an antidepressant and an antipsychotic (see Table 3). We therefore performed an additional Cox regression analysis with a shortened follow-up time of 365 days.

2.7.2 | Exclusion of patients with prior treatment

It is possible that treatment prior to the index episode could confound the results. To adjust for this, we performed an analysis excluding subjects who had collected a prescription of antidepressants, antipsychotics, or lithium within 365 days before the start of the index episode. The subjects were also excluded if they had received any ECT treatment prior to the index episode.

2.7.3 | Analysis of patients in remission

A subgroup of patients receiving ECT was assessed with the Montgomery-Åsberg Depression Rating Scale in interview format (MADRS) and/or in self-rated format
(MADRS-S) registered in the Q-ECT.\textsuperscript{22} We performed a sensitivity analysis of the subjects having achieved remission, which was defined as scoring <10 points on either MADRS or MADRS-S at the end of the ECT treatment.\textsuperscript{23}

2.7.4 Analysis of patients that collected acute treatment

An early relapse after discharge may be due to insufficient acute treatment rather than failing maintenance treatment. We therefore conducted a sensitivity analysis of patients who survived 9 months past the date of admission. To ensure that the patients had obtained acute treatment for an adequate period of time, only patients who had collected a prescription of either antidepressants + antipsychotics or antidepressants alone 3–6 months past the date of admission were included in the analysis. Our analysis only included patients with index inpatient episodes of up to 3 months because of lacking information regarding which treatment the patient obtained in the hospital during the index episode. Finally, only patients who had collected a prescription of antidepressants + antipsychotics or antidepressants alone between 6 and 9 months past the date of admission were included as this was considered to be the maintenance treatment.

3 RESULTS

3.1 Patient characteristics at baseline

The final cohort consisted of 4391 subjects, of whom 1419 and 2972 were in the antidepressant monotherapy and combination group, respectively. A higher proportion of patients received ECT during the index episode in the monotherapy group (36.4%) than in the combination group (26.7%). Otherwise, there were similar distributions regarding sex, age, previous psychiatric hospitalizations, comorbitity, and treatment modalities in the monotherapy and combination groups, with no standardized mean difference exceeding 0.2. The patient characteristics are presented in Table 1.

3.2 Distribution of antidepressants and antipsychotics

The distributions of the most commonly collected antidepressants and antipsychotics are presented in Figure 1a,b. Mirtazapine was the most common antidepressant in both groups (collected by 43.8% and 41.3% of subjects in the monotherapy and combination group, respectively), followed by venlafaxine, escitalopram, sertraline, and citalopram.

Olanzapine was the most common antipsychotic in the combination group, collected by 50.7% of subjects, followed by risperidone (24.3%), quetiapine (11.2%), aripiprazole (6.9%), and haloperidol (6.6%).

3.3 Primary outcome

A Kaplan–Meier plot of the outcome rates is presented in Figure 2. A total of 1777 patients (40.5%) reached the outcome within 2 years. A significantly higher proportion of patients reached the outcome in the combination group (42.3% vs. 36.6%; \( p < 0.01 \)). The majority of the first events were readmissions, with a significantly higher proportion in the combination group (41.8% vs. 35.9%; \( p < 0.01 \)). There was a non-significantly higher proportion of suicides in the monotherapy group (0.8% vs. 0.5%; \( p = 0.35 \)). A significantly higher proportion of patients died from other causes in the combination group (3.5% vs. 2.4%; \( p = 0.04 \)).

Antidepressant monotherapy was associated with a reduced risk of the outcome in both univariable analysis (hazard ratio [HR] = 0.84; 95% confidence interval [CI]: 0.76–0.93) and multivariable analysis (HR = 0.86; 95% CI: 0.77–0.95). The results went in the same direction in all sensitivity analyses. The results of the main analysis and sensitivity analyses are presented in Table 2.

The stratified multivariate analysis did not reveal any subgroup where combination therapy was significantly associated with a lower risk of the outcome than monotherapy. In the monotherapy group, younger age (18–30 years) was associated with a markedly lower risk of the outcome (HR = 0.54; 95% CI: 0.39–0.74).

3.4 Covariates

The results of the univariable analysis and multivariable analysis of the covariates are presented in Table A3. Younger age was associated with an increased risk of the outcome. Psychiatric hospitalizations prior to the index episode were associated with an increased risk, especially for patients with more than 10 previous hospitalizations. Being diagnosed with a personality disorder, anxiety disorder, alcohol use disorder or substance use disorder was associated with an increased risk in the univariable analysis, whereas only a diagnosis of an anxiety disorder was statistically significant in the multivariable analysis. Lithium was associated with a lower risk of the outcome in both the univariable analysis (HR = 0.63; 95% CI: 0.48–0.82) and multivariable analysis (HR = 0.52; 95% CI: 0.40–0.68). The other treatments did not demonstrate any
statistically significant differences regarding the outcome, except for benzodiazepines, which were associated with an increased risk in the univariable analysis only.

### 3.5 Collection of prescribed medication during the follow-up time

The prescribed medications that the surviving patients in the monotherapy and combination group collected during the follow-up time are shown in Table 3. Among the patients designated to the monotherapy group, 63.8% collected a prescription of ≥1 antidepressant between days 91 and 180, 64.9% between days 181 and 365, and 59.1% between days 366 and 730. Among the patients designated to the combination therapy group, 60.1% collected a prescription of ≥1 antidepressant and ≥1 antipsychotic between days 91 and 180, 59.0% between days 181 and 365, and 50.9% between days 366 and 730.

### 4 DISCUSSION

This register study followed 4391 subjects for up to 2 years. Compared with combination therapy, antidepressant monotherapy was significantly associated with a
FIGURE 1  (a) Distribution of the most commonly collected antidepressants. (b) Distribution of the most commonly collected antipsychotics. The figures illustrate the antidepressants and antipsychotics that were collected by at least 1% of each treatment group within 14 days after discharge. A patient may have collected more than one antidepressant or antipsychotic, and thus the total percentage exceeds 100%.

FIGURE 2  Kaplan–Meier plot of the combined outcome of readmission and suicide. AD, antidepressant.
lower risk of the composite outcome (readmission due to a psychiatric disorder, suicide attempt, or completed suicide) in the main analysis, and the results went in the same direction in all sensitivity analyses.

An important question is whether the inferiority of combination therapy is due to confounding by indication, that is, were antipsychotics prescribed to sicker or more at-risk subjects?

Regarding the known prognostic factors for the recurrence of depression, we tried to account for the effect of residual symptoms by conducting a sensitivity analysis of patients in remission. The results were still in favor of monotherapy treatment. The number of previous psychiatric hospital admissions were also similar between the groups. Overall, the patient characteristics were similar at baseline, except that a higher proportion of patients in the monotherapy group received ECT during the index episode. As ECT is considered to be an effective treatment for psychotic depression, one may argue that the patients receiving ECT may have been better treated when discharged from the index episode and thus had a better long-term outcome. However, ECT during the

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Association of antidepressant monotherapy versus antidepressant + antipsychotic combination therapy with the composite of readmissions and suicide.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis</td>
<td>N</td>
</tr>
<tr>
<td>Main analysis</td>
<td>4391</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>365 days of follow-up time</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Patients in remission</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>No pharmacological treatment 1 year prior to the index episode and no prior ECT treatment</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Patients who survived 270 days past the date of admission</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio. 
Note: Combination therapy is used as reference. Values of less than 1 indicate a better outcome in the monotherapy group.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Collection of medication during follow-up time among surviving patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collection of medication between days 91 and 180 among patients surviving past 90 days</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>AD monotherapy</td>
</tr>
<tr>
<td>Initial AD monotherapy</td>
<td>274 (22.5%)</td>
</tr>
<tr>
<td>Initial combination therapy</td>
<td>370 (14.5%)</td>
</tr>
<tr>
<td>Collection of medication between days 181 and 365 among patients surviving past 180 days</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>AD monotherapy</td>
</tr>
<tr>
<td>Initial AD monotherapy</td>
<td>227 (20.5%)</td>
</tr>
<tr>
<td>Initial combination therapy</td>
<td>332 (14.5%)</td>
</tr>
<tr>
<td>Collection of medication between days 366 and 730 among patients surviving past 365 days</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>AD monotherapy</td>
</tr>
<tr>
<td>Initial AD monotherapy</td>
<td>246 (25.1%)</td>
</tr>
<tr>
<td>Initial combination therapy</td>
<td>330 (17.1%)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, antidepressant; AP, antipsychotic. 
Note: Collection of an antidepressant or an antipsychotic after reaching the outcome was not accounted for.
index episode was not significantly associated with a differential risk of reaching the outcome, nor was there any interaction effect of ECT on the association between treatment group and outcome. Taken together, we found no evidence suggesting confounding by indication.

To date, there are limited data for comparison with our results. In our previous systematic review of maintenance treatment for psychotic depression, we only identified one high-quality study, conducted by Flint et al.\textsuperscript{10,11} They randomized patients who achieved remission with sertraline and olanzapine to either continue with the same treatment or replace olanzapine with placebo treatment. Among the patients who finished the study after 36 weeks of follow-up, 34/58 (58.6\%) had relapsed in the sertraline monotherapy group, compared with only 13/56 patients (23.2\%) in the combination group.

It is uncertain whether the results of Flint et al, can be generalized to patients receiving other forms of acute treatment than combination therapy. For instance, a patient who has achieved remission with combination therapy and then has the antipsychotic removed (e.g., the monotherapy group in the study by Flint et al) may be more prone to relapse than a patient having achieved remission with monotherapy who continues to receive monotherapy as maintenance treatment.

At present, there does not seem to be a clear consensus among clinical practitioners about what the first-line of acute treatment should be. In a study by Leadholm et al, a questionnaire was distributed among Danish psychiatrists, asking “What is your first choice of treatment for an unipolar psychotic depressive patient suffering from delusions of disease and death?” For non-suicidal psychotic depression, 42\% answered antidepressant + antipsychotic combination therapy, 31\% answered antipsychotic monotherapy and 21\% answered ECT.\textsuperscript{25} In a study by Patel et al, they reviewed which pharmacological treatments 163 patients were prescribed after \textgeq1 acute course of ECT, at four medical centers in Canada and the United States. Antidepressant + antipsychotic combination therapy was the most commonly prescribed pharmacotherapy ranging between 61.9\% and 85.5\% of patients across the medical centers.\textsuperscript{26}

The comparison of combination therapy and antidepressant monotherapy in the acute phase has been examined in two systematic reviews, by Farahani et al, and Kruizinga et al.\textsuperscript{8,9} In the review by Farahani et al, combination therapy demonstrated superiority, but the authors concluded that “... the number of studies and of the tested combinations was quite limited”.\textsuperscript{8} In the review by Kruizinga et al, the authors concluded that “Psychotic depression is heavily under-studied, limiting confidence in the conclusions drawn. Some evidence indicates that combination therapy with an antidepressant plus an antipsychotic is more effective than either treatment alone or placebo.”\textsuperscript{29}

In summary, there is some evidence favoring combination therapy over antidepressant monotherapy in the acute phase but antidepressant monotherapy and ECT are also used as acute treatment options. It is uncertain if the findings by Flint et al can be generalized to patients receiving monotherapy or ECT in the acute phase. Although our study lacks information regarding which drugs the patients may have received during the index episode, we know that 36.4\% and 26.7\% of patients in the monotherapy and combination group, respectively, received ECT during the index episode. Thus, we can conclude that our study population differs from that of Flint et al, which may at least partially account for the different results.

Regarding maintenance treatment for major depressive disorder, there is strong evidence supporting the continuation of antidepressant treatment. In a meta-analysis conducted by Kato et al, the risk of relapse was approximately 20\% lower among subjects who, after having responded to an antidepressant continued to receive the same antidepressant, compared with changing to placebo.\textsuperscript{27} By contrast, the evidence supporting antipsychotics as maintenance treatment is limited. In a systematic review conducted by Chen et al, three studies were identified examining second-generation antipsychotics as maintenance treatment.\textsuperscript{28} All three studies indicated a prolonged time to relapse among the patients receiving antipsychotic treatment\textsuperscript{29–31}, however, only one study, conducted by Liebowitz et al, demonstrated statistical significance of antipsychotic monotherapy compared with placebo treatment.\textsuperscript{31}

Lithium has been suggested to have a preventive effect on relapse and suicides among patients with unipolar depression as a whole.\textsuperscript{32–34} Although only 192 of the 4391 participants in our study collected a lithium prescription, lithium was associated with a significantly better outcome in both the univariable and multivariable analyses. It is not clear why these patients received lithium. Since this is a study encompassing patients from all of Sweden, the indications for lithium may differ due to local traditions. These findings must be interpreted with caution, but they may indicate a preventive effect of lithium in psychotic depression. More studies on lithium as maintenance treatment for psychotic depression are warranted.

It is worth noting that between 91 and 180 days, only 60\% of the surviving participants initially designated to each treatment group collected the same treatment; 22.5\% and 14.5\% in the monotherapy group and combination group respectively did not collect any treatment at all. Thus, one may wonder how well this limited...
exposure among some of the participants relates to a follow-up time of 2 years. However, the results went in the same direction with a shortened follow-up time of 365 days. Also, approximately half of all relapses occur within the first 6 months, after that, the rate of relapses decreases. Thus, it seems that the majority of the patients have collected treatment during the most critical period. An option would have been to limit the participants to those who collected medication for the whole period of follow-up. However, we believe that this could have introduced bias since it may be that the patients who continuously collect medication had more symptoms than those with a more limited exposure. At present, the optimal duration of maintenance treatment remains uncertain and may vary depending on which acute treatment the patients have received. Further studies to decide the optimal duration of maintenance treatment are needed, preferably by also considering which treatment is used to achieve remission.

Our study has several strengths. Having access to high-quality registries enabled a large sample size. Furthermore, we conducted several sensitivity analyses where we shortened the follow-up time, excluded patients with prior treatment, delayed the start of follow-up time, and assessed only patients in remission. The results exhibited similar trends in all these analyses, strengthening the validity of our findings.

Our study also has limitations that should be mentioned. First, we only have information about which medication the patients collected from pharmacies. We do not have information about whether the patients were compliant with the medications. Information is also missing about what pharmacological treatment the patients may have received during the index episode, and these treatments may have affected the long-term outcomes.

Second, we were unable to assess any history of childhood maltreatment, which has been associated with a higher risk of recurrence of depression. We also cannot exclude that other residual confounding factors may have affected the results.

Third, different drug dosages may have affected the results, the effect of which is difficult to assess. For instance, it is not uncommon that patients with prescriptions of lower dosages are prescribed to take more than one tablet and vice versa. Furthermore, the patients may have had their medication uptitrated during the follow-up time. For these reasons, we did not deem it meaningful to compare different expedited dosages.

Fourth, a high number of different types of prescribed antidepressants and antipsychotics were collected by the patients and most of these have not been examined in patients with psychotic depression. Although the proportions of the collected antidepressants were similar between the treatment groups, various antipsychotics were collected by the combination therapy group. To our knowledge, there are only a few antipsychotics that have been examined as part of antidepressant + antipsychotic combination therapy in randomized controlled studies, namely, olanzapine, quetiapine, perphenazine, and haloperidol. In our study 50.7% of the patients collected olanzapine, 11.2% quetiapine, 6.6% haloperidol, and 1.5% perphenazine. Thus, a considerable minority collected a prescription of other antipsychotics than those previously studied, which may have affected the outcome.

Fifth, a relapse may occur without being readmitted or committing suicide. A patient may for instance suffer a relapse in their home, not seeking hospital care. Our registries will not detect these patients. However, among the patients that suffer the most severe forms of relapses, many will be readmitted or commit suicide.

Finally, some studies have shown that less than 50% of patients diagnosed with psychotic depression retain their diagnosis at follow-up. The stratified analysis in our results revealed a greater disparity (in favor of antidepressant monotherapy) among younger patients. It is possible that a greater proportion of patients who received combination therapy in our sample will later be diagnosed with another condition.

To conclude, our results do not suggest an added benefit of adding antipsychotics as an adjunctive to antidepressants as maintenance treatment for psychotic unipolar depression. Since antipsychotics are used frequently, are known for several side effects, and there currently is a lack of studies supporting the usage of antipsychotics as an adjunctive to antidepressants, more clinical studies comparing antidepressant monotherapy and combination therapy are needed, preferably by also including lithium treatment.

CONFLICT OF INTEREST STATEMENT
Axel Nordenskjöld and Mikael Landén have received lecture honoraria from Lundbeck pharmaceuticals. No other disclosures were reported.

PEER REVIEW
The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/acps.13628.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.
ETHICS STATEMENT
Approval for this study was granted by the regional ethical review board in Uppsala, Sweden (2014/174), and the Swedish Ethical Review Authority (2020-05154). Informed consent was waived because this was a registry-based study in which the participants could not be identified at any time.

ORCID
Ahmed Al-Wandi https://orcid.org/0000-0003-1042-0730
Mikael Landén https://orcid.org/0000-0002-4496-6451
Axel Nordenskjöld https://orcid.org/0000-0001-7454-3065

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APPENDIX

<table>
<thead>
<tr>
<th>TABLE A1</th>
<th>ICD-10 codes used to identify disorders.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorder</td>
<td>ICD-10 codes</td>
</tr>
<tr>
<td>Psychotic depression</td>
<td>F32.3 and F33.3</td>
</tr>
<tr>
<td>Alcohol use disorder</td>
<td>F10 (except F10.6)</td>
</tr>
<tr>
<td>Substance use disorder</td>
<td>F11–F16, F18–F19</td>
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<tr>
<td>Anxiety disorder</td>
<td>F40–F42, F43.0–F43.2</td>
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<tr>
<td>Personality disorder</td>
<td>F60–F61</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>F20–F29, F04, F06.2, F07.9, F10.6</td>
</tr>
<tr>
<td>Bipolar disorder and mania</td>
<td>F30–F31</td>
</tr>
<tr>
<td>All psychiatric disorders</td>
<td>All F-codes*</td>
</tr>
<tr>
<td>Suicide/suicidal attempt</td>
<td>X60–X84</td>
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Electroconvulsive therapy (ECT) V9218, DA006, DA024, DA025

<table>
<thead>
<tr>
<th>TABLE A2</th>
<th>ATC codes used to identify medications.</th>
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<tbody>
<tr>
<td>Antidepressants</td>
<td>N06A</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>N05A (except N05AN)</td>
</tr>
<tr>
<td>Lithium</td>
<td>N05AN</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>N03AE, N05BA, N05CD*</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>N03AX09</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>R06AD01, R06AD02, N05BB01, N05BE01</td>
</tr>
</tbody>
</table>

Abbreviation: ATC, Anatomical Therapeutic Chemical (ATC) classification system.

*All ATC codes with characters after the given prefix are included, for example, N06A includes N06AA01, N06AA01, and so forth.

Abbreviation: ICD-10, International Classification of Diseases, 10th revision.
*All ICD-codes with numbers after the given prefix are included, for example, F10 includes F10.0, F10.1, and so forth.

*Psychiatric disorders were defined as all conditions where F is used as the initial prefix in the diagnosis code.

*In Sweden, a subset of codes known as action codes (KVÅ-koder in Swedish) are used to register different actions and procedures. Data on ECT treatment were extracted using these action codes.
### TABLE A3  Primary outcome of covariates in the main analysis.

<table>
<thead>
<tr>
<th></th>
<th>Univariable analysis</th>
<th></th>
<th>Multivariable analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td></td>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Sex (female)</td>
<td>1.13 (1.03–1.24)</td>
<td></td>
<td>1.07 (0.97–1.18)</td>
<td></td>
</tr>
<tr>
<td>Age (reference: 18–30 years)</td>
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</tr>
<tr>
<td>31–40 years</td>
<td>0.99 (0.83–1.18)</td>
<td>31–40 years</td>
<td>0.96 (0.81–1.15)</td>
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<tr>
<td>41–50 years</td>
<td>0.71 (0.60–0.85)</td>
<td>41–50 years</td>
<td>0.67 (0.56–0.80)</td>
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</tr>
<tr>
<td>51–60 years</td>
<td>0.64 (0.54–0.77)</td>
<td>51–60 years</td>
<td>0.61 (0.51–0.73)</td>
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<tr>
<td>61–70 years</td>
<td>0.66 (0.56–0.78)</td>
<td>61–70 years</td>
<td>0.62 (0.52–0.74)</td>
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</tr>
<tr>
<td>&gt;70 years</td>
<td>0.77 (0.66–0.90)</td>
<td>&gt;70 years</td>
<td>0.72 (0.61–0.85)</td>
<td></td>
</tr>
<tr>
<td>Number of psychiatric hospitalizations before index episode (reference: 0 episodes)</td>
<td></td>
<td></td>
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<tr>
<td>1–2 episodes</td>
<td>1.25 (1.12–1.39)</td>
<td>1–2 episodes</td>
<td>1.24 (1.10–1.38)</td>
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</tr>
<tr>
<td>3–5 episodes</td>
<td>1.58 (1.36–1.83)</td>
<td>3–5 episodes</td>
<td>1.56 (1.33–1.84)</td>
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<tr>
<td>6–10 episodes</td>
<td>2.57 (2.07–3.18)</td>
<td>6–10 episodes</td>
<td>2.45 (1.93–3.12)</td>
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<tr>
<td>11–20 episodes</td>
<td>4.24 (3.09–5.82)</td>
<td>11–20 episodes</td>
<td>4.18 (2.92–5.98)</td>
<td></td>
</tr>
<tr>
<td>&gt;20 episodes</td>
<td>4.37 (2.77–6.89)</td>
<td>&gt;20 episodes</td>
<td>3.52 (2.13–5.82)</td>
<td></td>
</tr>
<tr>
<td>Personality disorder</td>
<td>1.97 (1.61–2.42)</td>
<td>Personality disorder</td>
<td>1.18 (0.94–1.48)</td>
<td></td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>1.51 (1.36–1.69)</td>
<td>Anxiety disorder</td>
<td>1.14 (1.01–1.29)</td>
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<tr>
<td>Alcohol use disorder</td>
<td>1.26 (1.03–1.54)</td>
<td>Alcohol use disorder</td>
<td>0.88 (0.71–1.10)</td>
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<tr>
<td>Substance use disorder</td>
<td>1.85 (1.54–2.23)</td>
<td>Substance use disorder</td>
<td>1.13 (0.92–1.39)</td>
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</tr>
<tr>
<td>ECT during index episode</td>
<td>1.01 (0.92–1.12)</td>
<td>ECT during index episode</td>
<td>1.08 (0.97–1.20)</td>
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</tr>
<tr>
<td>Lithium collected after start of index episode</td>
<td>0.63 (0.48–0.82)</td>
<td>Lithium collected after start of index episode</td>
<td>0.52 (0.40–0.68)</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines collected after start of index episode</td>
<td>1.10 (1.00–1.21)</td>
<td>Benzodiazepines collected after start of index episode</td>
<td>1.06 (0.96–1.16)</td>
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</tr>
<tr>
<td>Lamotrigine collected after start of index episode</td>
<td>1.21 (0.98–1.49)</td>
<td>Lamotrigine collected after start of index episode</td>
<td>0.99 (0.80–1.23)</td>
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</tr>
<tr>
<td>Anxiolytics collected after start of index episode</td>
<td>1.07 (0.97–1.18)</td>
<td>Anxiolytics collected after start of index episode</td>
<td>0.94 (0.85–1.05)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.