Differences in antipsychotic treatment between depressive patients with and without a suicide attempt

Marie Asp a,b,*, Livia Ambrus a,b, Margareta Reis c, Sofie Manninen a, Johan Fernström a,b, Daniel Lindqvist a,d, Åsa Westrin a,d

a Department of Clinical Sciences Lund, Psychiatry, Lund University, Sweden
b Office of Psychiatry and Rehabilitation, Psychiatric Clinic Lund, Region Skåne, Sweden
c Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden
d Office for Psychiatry and Rehabilitation, Psychiatry Research Skåne, Region Skåne, Sweden

ARTICLE INFO

Keywords: Depression Suicidality Suicide attempt Antipsychotics Personality disorders Psychiatric comorbidity

ABSTRACT

Background: Depressed suicide attempters are, according to some earlier studies, treated more often with antipsychotics than depressive non-suicide attempters. Cluster B personality disorders, especially borderline personality disorders, are associated with a high suicide risk, and antipsychotics are commonly used for the reduction of symptoms. However, no previous study has taken comorbid personality disorders into account when assessing the use of antipsychotics in patients with unipolar depression. Therefore, the aim of this study was to investigate the clinical selection of pharmacotherapy in unipolar depression with and without a previous suicide attempt, taking into account potential confounders such as cluster B personality disorders.

Methods: The study sample consisted of 247 patients with unipolar depression. The study was approved by the Regional Ethical Review Board in Lund, Sweden. Study participants were recruited from 4 different secondary psychiatric care clinics in Sweden and were diagnosed according to the DSM-IV-TR with the MINI and SCID II. Previous and ongoing psychiatric treatments were investigated in detail and medical records were assessed.

Results: Thirty percent of the patients had made previous suicide attempts. Depressed suicide attempters underwent both lifetime treatment with antipsychotics and an ongoing antipsychotic treatment significantly more often than non-attempters. Significances remained after a regression analysis, adjusting for cluster B personality disorders, symptom severity, age at the onset of depression, and lifetime psychotic symptoms.

Conclusions: This is the first study to consider the effect of comorbidity with cluster B personality disorders when comparing treatment of depressive suicide and non-suicide attempters. Our findings suggest that suicide attempters are more frequently treated with antipsychotics compared to non-suicide attempters, regardless of cluster B personality disorder comorbidity. These findings are important for clinicians to consider and would also be relevant to future studies evaluating reduction of suicide risk with antipsychotics in patients with psychiatric comorbidity and a history of attempted suicide.

1. Introduction

The majority of suicide worldwide is assumed to be associated with depression, and approximately one-third of all depressed patients attempt suicide at some point in their lives [1]. Depressed suicide attempters are known to have worse short-term responses to antidepressant treatment as compared to those with no suicide attempts [2–4].

One strategy for depressive patients who do not respond to the first line of treatment is augmentation with second-generation antipsychotics (SGAs) [5–8]; there is some preliminary evidence that SGAs reduce suicidal behavior in patients with depression [9].

However, the clinical complexity of depressive patients with a prior suicide attempt may result in treatment difficulties. Patients with depression and a previous suicide attempt may more commonly display certain clinical characteristics than depressive patients without suicide attempts, such as earlier onset of disease and more severe symptoms [10–13]. Additionally, it is well known that personality disorders (PDs) are common in depressed patients [14] and associated with poor
Furthermore, patients with BPD display symptoms such as impulsivity disorder (BPD), confer an increased risk of suicidal behavior [22]. Antidepressant treatments since they, especially borderline personality comorbidities may be important factors to consider in selecting optimal medications during the current depressive episode. However, none of the previous studies included assessment of PDs. Such comorbidities may be ongoing unipolar or bipolar depression and an insufficient treatment response. These patients were referred to the study from four secondary psychiatric care clinics in southern Sweden. All patients participating in the study had an out-patient contact at one of the included clinics. The exclusion criteria were a body mass index of less than 15, pregnancy, and current liver disease. Insufficient treatment response was defined as not having achieved remission with the previous and ongoing treatments during the current depressive episode.

The current study sample was a subset of the GEN-D study, restricted to those patients with clinical unipolar depression who were enrolled between 2012 and 2018. Diagnoses categorized as clinical unipolar depression included major depressive disorder (MDD) with a single or recurrent episode, chronic depression, and dysthymia. Bipolar patients were excluded from this subset because they routinely receive antipsychotics as mood-stabilizing drugs. The current study sample consisted of 247 patients.

2.2. Measures

2.2.1. Diagnostic assessment

After inclusion in the study, patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV-TR). The diagnostic procedure was performed by a board certified psychiatrist or a resident in psychiatry with at least 3 years of psychiatric training, under the supervision of a senior colleague. Supervision involved the discussion of all diagnostic assessments. The diagnostic procedure for all patients included the Mini International Neuropsychiatric Interview (MINI) 6.0 [28] and the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II) [29].

2.2.2. Research protocol

A semi-structured research protocol was used to collect data on previous and current psychosocial circumstances, educational level, childhood circumstances, and traumatic life events. Detailed questions on previous and ongoing self-harm and suicidal behavior were asked. A suicide attempt was defined as a non-fatal, self-directed, potentially injurious behavior with any intent to die [30]. Self-harm was considered to refer to actions of self-injury or intoxication without the intent of death.

Variables considered normally distributed are presented with means and standard deviations (SDs), and variables not considered normally distributed are presented with medians and ranges (min–max). The MADRS scores and BSA scores were considered normally distributed, and an independent samples t-test was used to compare suicide attempters and non-suicide attempters. Pearson’s chi-square test was used to compare proportions, and for sample sizes less than five, Fisher’s exact test was used. For comparison of the number of antidepressants taken, current age, age at the onset of depressive symptoms, and years in mental health care, a Mann–Whitney U test was used.

3. Results

Patient characteristics for suicide and non-suicide attempters are presented in Table 1. Suicide attempters were significantly younger at the time of their first depressive episode (p < 0.05); had more current depressive symptoms, measured as total MADRS score (p < 0.05); and experienced the lifetime presence of psychotic symptoms significantly more often (p < 0.05). Cluster B personality disorder was more common among depressive
suicide attempters than depressive non-suicide attempters (p < 0.001).

Subgroups of PDs are given in Table 2.

No patient participating in the study had a primary psychotic disorder. Anxiety disorders were present in 64% of suicide attempters and 57% of non-suicide attempters, with no statistically significant difference between groups. Substance use disorders were present in 16% of suicide attempters and 2% of non-suicide attempters (p < 0.01).

Lifetime and current treatments for depression in suicide and non-suicide attempters are given in Table 3.

All patients in the study had used antidepressants during earlier treatment history, the date of their suicide attempt in relation to antipsychotic treatment was analyzed. Of them, 18% had already received antipsychotic treatment before the suicide attempt, 20% started treatment with antipsychotics within 1 month after the suicide attempt, 7.5% started within 2–6 months, 7.5% within 7–12 months, and 35% after more than 12 months. For 12% of such participants, data were missing regarding when the suicide attempt had occurred or when antipsychotic treatment was given.

The reasons for the prescription of antipsychotic medication, according to medical records, are given in Table 5.

The most commonly prescribed antipsychotic drugs were quetiapine, olanzapine, and aripiprazole, with no significant differences in frequency between suicide and non-suicide attempters.

4. Discussion

The aim of this naturalistic and descriptive study was to investigate the use of antipsychotic drugs in unipolar depressed patients with and without a history of attempted suicide, while also considering the influence of comorbidity with cluster B personality disorders; current depressive symptom severity, measured as total MADRS score; the age at suicide attempters.

Table 1

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics for suicide and non-suicide attempters.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicide attempters</td>
<td>Non-suicide attempters</td>
</tr>
<tr>
<td>n = 75</td>
<td>n = 172</td>
</tr>
<tr>
<td>Gender, men/women, n (%)</td>
<td>24 (51%) (32%)/ 66/106 (38%)/62%</td>
</tr>
<tr>
<td>Age, median (min–max)</td>
<td>35 (18–77)</td>
</tr>
<tr>
<td>Age when depressive symptoms started, median (min–max)</td>
<td>16 (7–48)</td>
</tr>
<tr>
<td>Years in mental health care, median (min–max)</td>
<td>12 (0–45)</td>
</tr>
<tr>
<td>Depression type, uniepisodic/multiepisodic, n (%)</td>
<td>16/59 (21%)/79%</td>
</tr>
<tr>
<td>Lifetime presence of psychotic symptoms, n (%)</td>
<td>7 (9.3%)</td>
</tr>
<tr>
<td>MADRS total score, mean ± SD</td>
<td>23 ± 8.2</td>
</tr>
<tr>
<td>BSI score, mean ± SD</td>
<td>6.6 ± 2.9</td>
</tr>
</tbody>
</table>

* Data regarding depression type (uniepisodic or multiepisodic) were missing for two non-suicide attempters.

Table 2

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Comorbid personality disorder diagnoses for depressive suicide and non-suicide attempters.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicide attempters</td>
<td>Non-suicide attempters</td>
</tr>
<tr>
<td>n = 75</td>
<td>n = 172</td>
</tr>
<tr>
<td>Any personality disorder, n (%)</td>
<td>41 (55%)</td>
</tr>
<tr>
<td>Cluster A personality disorder, n (%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Cluster B personality disorder, n (%)</td>
<td>23 (31%)</td>
</tr>
<tr>
<td>Cluster C personality disorder, n (%)</td>
<td>16 (21%)</td>
</tr>
<tr>
<td>Personality disorder not otherwise specified, n (%)</td>
<td>4 (5%)</td>
</tr>
</tbody>
</table>

* Patients could be assigned more than one personality disorder diagnosis.

Table 3

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Lifetime and current treatments for depression in suicide and non-suicide attempters.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicide attempters</td>
<td>Non-suicide attempters</td>
</tr>
<tr>
<td>n = 75</td>
<td>n = 172</td>
</tr>
<tr>
<td>Lithium treatment, n (%)</td>
<td>11 (15%)</td>
</tr>
<tr>
<td>ECT, n (%)</td>
<td>18 (25%)</td>
</tr>
<tr>
<td>Antipsychotic treatment, n (%)</td>
<td>56 (75%)</td>
</tr>
<tr>
<td>Antidepressant treatment, n (%)</td>
<td>17 (23%)</td>
</tr>
<tr>
<td>Lithium treatment, n (%)</td>
<td>1 (1.3%)</td>
</tr>
</tbody>
</table>

was no significant difference in antipsychotic treatment history for suicide versus non-suicide attempters.

In the binary logistic regression presented in Table 4, antipsychotic treatment remained more common among suicide attempters to a statistically significant degree, both for lifetime treatment (p < 0.05) and current treatment (p < 0.05).

For those suicide attempters with antipsychotics in their lifetime treatment history, the date of their suicide attempt in relation to antipsychotic treatment was analyzed. Of them, 18% had already received antipsychotic treatment before the suicide attempt, 20% started treatment with antipsychotics within 1 month after the suicide attempt, 7.5% started within 2–6 months, 7.5% within 7–12 months, and 35% after more than 12 months. For 12% of such participants, data were missing regarding when the suicide attempt had occurred or when antipsychotic treatment was given.

The reasons for the prescription of antipsychotic medication, according to medical records, are given in Table 5.

The most commonly prescribed antipsychotic drugs were quetiapine, olanzapine, and aripiprazole, with no significant differences in frequency between suicide and non-suicide attempters.

Table 4

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Binary logistic regression, with lifetime and current antipsychotic treatment as outcome variables.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicide attempt</td>
<td>Cluster B personality disorder</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.93</td>
</tr>
<tr>
<td>95% CI for odds ratio</td>
<td>1.03–3.59</td>
</tr>
<tr>
<td>p-Value</td>
<td>0.039</td>
</tr>
</tbody>
</table>

4. Discussion

The aim of this naturalistic and descriptive study was to investigate the use of antipsychotic drugs in unipolar depressed patients with and without a history of attempted suicide, while also considering the influence of comorbidity with cluster B personality disorders; current depressive symptom severity, measured as total MADRS score; the age at suicide attempters.
which depressive symptoms began; and the lifetime presence of psychotic symptoms.

The main finding was that antipsychotics were more frequently used in patients with a previous suicide attempt than non-suicide attempters. This finding was confirmed for patients undergoing both lifetime and current antipsychotic treatment. These findings remained even after adjusting for the above-mentioned variables. All of these factors were estimated to increase the likelihood of antipsychotic treatment. As expected, we also found a significantly higher frequency of suicide attempts in BPD patients compared to those without BPD.

Our conclusion that suicide attempters are more frequently treated with antipsychotics is in line with earlier studies, though these did not take PDs into account. Baldessarini et al. showed that antipsychotic medication was overrepresented among suicide attempters [19]. The study included both MDD and bipolar disorder and included an assessment of comorbid ADHD, anxiety disorders, and substance use disorders. Ruengorn et al. [20] also found that suicide attempters were more commonly treated with antipsychotics, though psychotic symptoms were more frequently present in that study than our study, which may partially explain the results. In the Northern Finland Birth Cohort study, higher antipsychotic doses were associated with increased suicidal ideation in patients with non-psychotic disorders [21].

PDs were prevalent in this study, and BPD was particularly common in the suicide attempters group. It is well known that attempted suicide is common in patients with BPD, especially among patients with BPD and concurrent depressive disorder [24,38–41]. The overall frequencies of PDs in the present study are well in accordance with other out-patient study samples [42–44]. Furthermore, the high frequency of BPD among the suicide attempters can also be seen in other studies of unipolar depression and BPD [45–48].

To our knowledge, this is the first study comparing antipsychotic treatment for depressive patients with and without suicide attempts that takes into account the potential confounding effect of, above all, BPD. This was important to control for because psychotropic medications are often used in the treatment of PDs [36,49]. In particular, the use of SGAs in cases of BPD is increasing [50]. Prescription patterns between 2009 and 2011 show that almost 50% of BPD patients are prescribed an SGA during the same time period was 20% [51].

There is a need for more Randomized Controlled Trials (RCT) on the use of pharmacological treatment in PDs, since most of the research so far has focused specifically on BPD, many studies are underpowered and include short treatment duration [49]. However, the results from our study are mainly in line with the established literature showing benefit of antipsychotics on BPD. Montgomery et al. reported, in a sample of patients with PDs, that depot flupenthixol was associated with fewer suicidal acts, compared to placebo, over a 6 month follow-up period after an index suicide attempt [52,53]. In a subsequent study on patients with BPD on methadone maintenance therapy, add-on olanzapine was associated with a reduction in self injurious behavior compared to add-on sertraline [54]. This effect has not been replicated in other studies of olanzapine in BPD, but studies have shown improvement on global functioning, anxiety, interpersonal sensitivity and impulsive-aggressive behavior [55]. In an RCT, aripiprazole was shown to reduce psychotic symptoms, impulsivity and interpersonal problems in patients with BPD [56]. Findings from uncontrolled trials of risperidone on BPD suggested an effect on impulsivity, aggressiveness, affective instability and anxiety [55] and one RCT showed effect on paranoid ideations [57]. Finally, an open-label uncontrolled study provided preliminary evidence that quetiapine has beneficial effects on cognitive symptoms of BPD including executive functioning [58]. Thus, antipsychotics may be an important tool in the treatment of BPD, targeting several key symptoms [59–61]. However, no medication is indicated to treat the global psychopathology of BPD and treatment should preferably be restricted to more severe symptoms and short-term use to reduce side-effects and avoid polypharmacy [49,59,62].

After a review of the medical records, we could not find evidence that the majority of antipsychotic treatment was prescribed as a result of a suicide attempt. Only 20% of prescriptions were started within 1 month after a suicide attempt. Only one earlier study had assessed the relationship between antipsychotic prescription history and suicide attempts, and those assessments were performed directly after suicide attempts and thus only accounted for prescriptions begun before the suicide attempt [63].

When investigating the reasons for the prescription of antipsychotics, we found that anxiety was a more common reason for prescription among non-suicide attempters, which was an unexpected result. Moreover, we were able to identify several off-label indications for the prescribed SGAs for both suicide and non-suicide attempters. Off-label prescriptions are common among psychiatric patients and their use has been debated in earlier research [64–67]. However, no earlier study has assessed the reasons for the prescription of antipsychotic treatments in depressed suicide attempters and non-suicide attempters in such a detailed way.

This study has several limitations. The most significant limitation is recall bias, meaning that patients may have had difficulty remembering earlier treatments. We attempted to minimize this by conducting a thorough review of patients’ medical records to complement the research-grade clinical assessment. However, we could not access medical records from all primary caregivers and all private practitioners. There were also difficulties in assessing compliance, which is known to be a considerable challenge in the treatment of depression [68,69]. We have also identified a limitation in the diagnostic assessment, where mixed depression was not specifically considered. Mixed depression carries an increased suicide risk [70] and could also be more common in BPD [71]. Furthermore, anxiety is a common symptom of mixed depression, [72] for which antipsychotics may be a more adequate treatment strategy than antidepressants [73]. Additionally, we did not adjust for multiple comparisons in the statistical analysis. Thus our findings need to be replicated in independent cohorts. Moreover, a limited sample size is a notable limitation of the study. Finally, this study must be considered hypothesis-generating, providing no causal explanations for why suicide attempters receive more antipsychotic treatment.

Despite the above-mentioned limitations, we can also identify several strengths, such as the naturalistic design, which identified treatment attempts for a clinically representative psychiatric sample of patients with difficult-to-treat depression. Furthermore, the study offered a rigorous diagnostic assessment of all patients, providing detailed information about comorbidities, which enabled us to study the impact of PDs on medication prescriptions.

Our results suggest that suicide attempters are more difficult to treat and that there is a need for studies approaching this problem with the

---

**Table 5 Reasons for prescription of antipsychotic treatment.**

<table>
<thead>
<tr>
<th>Reasons for prescription of antipsychotic treatment</th>
<th>Number of antipsychotics used among suicide attempters</th>
<th>Number of antipsychotics used among non-suicide attempters</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression, n (%)</td>
<td>23 (32%)</td>
<td>32 (40%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sleep disturbances, n (%)</td>
<td>9 (13%)</td>
<td>12 (15%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Anxiety, n (%)</td>
<td>10 (14%)</td>
<td>22 (27%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Mood-stabilizing effect, n (%)</td>
<td>15 (21%)</td>
<td>6 (7%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Psychotic symptoms, n (%)</td>
<td>9 (13%)</td>
<td>2 (2%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Other reasons, n (%)</td>
<td>3 (4%)</td>
<td>4 (5%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Missing, n (%)</td>
<td>3 (4%)</td>
<td>3 (4%)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

* Some patients received more than one antipsychotic drug.
help of personalized medicine. In a future study, we would like to further investigate dosages, drug concentrations, effects, and side-effects of ongoing treatment of psychotropic drugs, allowing for a more detailed therapeutic drug monitoring approach to the treatment of depressive suicide attempters. Also, in future research regarding clinical depression and suicide risk, it will be important to identify factors, including combinations of treatments, that could reduce the risk of future suicide attempts.

5. Conclusions

In conclusion, our findings suggest that suicide attempters are more frequently treated with antipsychotics than non-suicide attempters, regardless of cluster B personality disorder comorbidity. These findings are important for clinicians to consider and would also be of importance in future studies evaluating the reduction of suicide risk with antipsychotics in patients with psychiatric comorbidity and a history of attempted suicide. Furthermore, the findings may represent an adequate treatment strategy. There is increasing evidence that antipsychotics are an effective augmentation treatment [5–8], and although more studies are needed on their potential antisuicidal properties, especially in subgroups with various psychiatric comorbidities, the approach is promising [9].

Declaration of competing interest

None.

Acknowledgements

The authors sincerely thank Johan Olsson and Linda Hanson, research nurses at the Science Center Region Skåne, for their work on the patient recruitment process and the processing of the research data.

References

[22] Paris J. Suicidality in borderline personality disorder. Medicina (Kaunas) 2019;55,55.
[34] Crosby Alex EOL, Cindi Melanson. Self-directed violence surveillance; uniform definitions and recommended data elements. National Center for Injury Prevention and Control (U.S.), Division of Violence Prevention; 2011.


