Differential Associations of the Number of Comorbid Conditions and the Severity of Depression and Anxiety with Self-Reported Suicidal Ideation and Attempt in Major Depressive Disorder and Bipolar Disorder

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Abstract:

Background: Previous studies have shown that the number of comorbidity, depression and anxiety severity were associated with increased risk for suicidal behaviors. This study was to investigate the interaction of the number of comorbidities, depression and anxiety severity with self-reported suicidal ideation (SR-SI) and suicide attempt (SA) in patients with major depressive disorder (MDD) or bipolar disorder (BPD).

Methods: Three-hundred routine clinical outpatients were diagnosed with the MINI-STEP-BP version at the initial evaluation. Symptom-severity was measured with the 16-item Quick Inventory of Depressive Symptomatology-self-report (QIDS-SR-16) for depression, Zung Self-Rating Anxiety Scale (SAS), and Clinical Global Impressions-Severity (CGI-S) for overall severity. SR-SI was based on QIDS-SR-16 item 12 and SA was based on the MINI suicidality module. Chi-square, Fisher-exact, and linear regression were used for analyses.

Results: Of 103 patients with MDD and 147 with BPD, the SR-SI and SA was 23.3% and 17.5% for MDD, and 35.0% and 20.4% for BPD, respectively. SR-SI and SA were positively associated with the number of comorbidities in BPD, but not in MDD. SR-SI was positively associated with depressive severity and overall illness severity in both MDD and BPD. However, anxiety severity had a positive linear correlation with SR-SI only in BPD. Anxiety and depressive severity had additive effect on SR-SI in BPD, but had opposite effect on SR-SI in MDD.

Conclusion: These data suggest that suicide risk assessment should be disorder specific in patients with a mood disorder. Diagnosing all psychiatric disorders and measuring depression and anxiety severity is essential for managing suicidal behaviors.

Keywords: Suicidal ideation; Mood disorder; Comorbidity; Depression severity; Anxiety severity; Association

Introduction

Psychiatric disorders play a very important role in suicide attempt (SA) and suicide death [1,2]. Mood disorders were among the highest risk disorders for suicide [3] although the difference between major depressive disorder (MDD) and bipolar disorder (BPD) in suicide risk and suicidal behaviors continues debatable [4,5]. The results from cross-sectional studies comparing the suicidality between patients with BPD and those with MDD have also been inconsistent [6-9]. However, more and more data suggest that patients with MDD and those with BPD may have differences in suicidal behaviors. A clinical study found that bipolar patients with suicide attempts reported higher levels of aggression and impulsivity, but less hopelessness compared with MDD attempters although there were no significant differences in the number of suicide attempts, intent to die or suicidal ideation [6]. A National Comorbidity Survey – Replication study also found that a lifetime history of MDD was associated with increased risk for the onset of suicidal ideation, but not suicidal plan or attempts [2]. In contrast, a lifetime diagnosis related to impulse control including bipolar disorder was not only associated with an increased risk for suicidal ideation, but also an increased risk for suicidal ideators to make a plan and/or attempt.

Risk factors for suicidal behaviors including psychiatric disorders, comorbidity, demographics, and clinical correlates have been widely studied [1,2,10-12]. In contrast, there have been a limited number of studies on the relationship between the severity of depressive and anxiety symptoms and suicidal behavior in mood disorders [7,13-18]. The positive associations between severity of anxiety symptoms and increased risk for suicidal behaviors have been reported in patients with bipolar disorder [17], patients with different psychiatric disorders [14,15], patients with an anxiety disorder [19], and the general population [20]. Similarly, the severity of depressive symptoms was also associated with increased risk for suicidal behaviors in depressed adolescents [18], patients with bipolar disorder [21], a mixed group with a mood disorder [7,16], geriatric patients with depression [13],
depressed primary care patients [22], college students [23], and the general population [20].

However, there has never been a study to compare the relationship between the severity of depression and anxiety and suicidal behaviors or the relationship between the number of comorbidities and suicidal behaviors in patients with MDD and those with BPD. Previously, we found that patients with BPD had more complex patterns of comorbidity than those with MDD [24]. We also found that patients with BPD had higher rates of self-reported and clinician-ascertained suicidal ideations than those with MDD, but both groups had similar rates of disagreement between self-reported and clinician-ascertained suicidal ideations [25]. The disagreement was positively correlated to depression severity in both MDD and BPD, but was only positively correlated to anxiety severity in BPD.

These data suggest that depression and anxiety severity as well as the number comorbidity [2] may play a different role in suicidality among the patients with a mood disorder. The aim of this analysis was to compare the self-reported suicidal ideation (SR-SI) and SA in patients with MDD and those with BPD and their interactions with the severity of depressive and anxiety, and/or the number of Axis I comorbidities.

Methods

Subjects

All participants were routine clinical outpatients at the Mood & Anxiety Clinic in the Mood Disorders Program of the Department of Psychiatry at the University Hospitals Case Medical Center. The details of the diagnostic procedure and the measurements of depression and anxiety severity at the initial evaluation have been described previously [24,26]. Briefly, all new patients were evaluated with the Mini International Neuropsychiatric Interview Systematic Treatment Enhancement Program for Bipolar Disorder (MINI-STEP-BD version) [27] after a traditional “standardized” psychiatric interview. A modified suicidality module of the MINI was also administered [28]. Prior to the face-to-face interview, patients were asked to fill out the 16-Item Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR-16) [29], Zung Self-Rating Anxiety Scale (SAS) [30], and other self-reported questionnaires.

At the end of initial evaluation, subjects who agreed to participate in the study signed an informed consent form approved by the Institutional Review Board of the University Hospitals Case Medical Center. Afterwards, their data at the initial evaluation and follow-up visit(s) were used for future research purposes until they withdrew the consent. For those who decided not to participate in the study, their data were only used for clinical purposes.

Self-reported suicidal ideation and previous suicide attempt

The SR-SI was extracted from the QIDS-SR-16 item 12. In this item, there are four questions: 1) I don’t think of suicide or death (code 0 on severity); 2) I feel that life is empty or wonder if it’s worth living (code 1 on severity); 3) I think of suicide or death several times a week for several minutes (code 2 on severity); and 4) I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life (code 3 on severity). As other items of the QIDS-SR-16, it asks patients to check the one response “that best describes you for the past seven days.” The SA was based on the question #6 of the suicidality module of the MINI, “Did you ever make a SA?” If yes, a history of previous suicide attempted is established.

Baseline illness Severity

Overall illness severity at the initial evaluation was measured with the Clinical Global Impressions–Severity scale (CGI-S) [31]. Depression and anxiety severity at the initial evaluation were measured with QIDS-SR-16 and SAS, respectively.

Number of comorbidities

As previously described [24], the diagnoses with the MINI-STEP-BD version includes MDD, BPD, panic disorder with or without agoraphobia, social phobia, agoraphobia, obsessive-compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder (GAD), alcohol use disorder (AUD), drug use disorder (DUD), psychotic disorders, eating disorders (ED), and attention-deficit-hyperactivity disorder. Each anxiety disorder was counted separately, but AUD (abuse or dependence), DUD (abuse or dependence), and ED (anorexia or bulimia) were counted as one disorder. Therefore, the potential number(s) of comorbidities was the sum of aforementioned disorders.

Statistical analysis

Descriptive analysis was used for prevalence of SR-SI and suicide attempt. Chi-square or Fisher’s exact (n<5) was used for categorical data and t-test was used for continuous data. Odd ratio (OR) was used to estimate the risk with 95% confidence interval to reflect the magnitude of variance. The significance level was set at a level of 0.05. Due to the exploratory nature of the study, no adjustment for multiple comparisons was attempted.

The association between depression severity and SR-SI was analyzed based on the QIDS-SR-16 total scores i.e., 0-5 points (euthymic), 6-10 points (mild), 11-15 points (moderate), ≥16 (severe to very severe). The association between overall illness severity and SR-SI was based on the CGI-S scores i.e., CGI-S=1-2 (normal or closed to normal), 3 (mild), 4 (moderate), and ≥5 (severe to extreme severe).

Figure 1: Rates of self-reported suicidal ideation based on the item 12 of the 16 Item Quick Inventory of Depression Symptomatology Self-Report and lifetime suicide attempt based on the Suicidality Module of the Mini International Neuropsychiatric Interview in patients with major depressive disorder or bipolar disorder
The classification of anxiety severity was modified prior to the analysis because only 9 patients scored ≥ 75 points and met the original definition of severe anxiety. The 4 groups in the present study were normal or without anxiety (SAS=20-40 points), mild anxiety (SAS=41-50 points), moderate anxiety (SAS=51-60 points) and high anxiety ((≥61 points).

The correlation between depression or anxiety severity and SR-SI was analyzed with linear logistic regression and R2 was used to reflect the strength of correlation. The incidence rate of SR-SI at each QIDS-16 or SAS score point was calculated with the SR-SI case(s) divided by the total case(s) at each score point. For the analyses of patients with MDD, BPD than those with MDD lived with family (43.5% versus 24.3%) and was analyzed with linear logistic regression and R2 was used to reflect the incidence rate of SR-SI at each score point. The analyses of interaction between depression and anxiety on SR-SI, only patients with moderate and severe/extreme depressive symptoms were used and the median of anxiety severity in each subgroup was used to further divide into low and high anxiety groups.

Results

Baseline demographics and historical correlates

Among the 300 patients, 103 with MDD and 147 with BPD were included in the study. About two-thirds of patients with MDD and a half of patients with BPD were female. Significantly more patients with BPD than those with MDD lived with family (43.5% versus 24.3%) and had a history of previous hospitalization (40.1% versus 18.4%). More patients with BPD had a history of verbal abuse than those with MDD (24.5% versus 14.6%). There were no significant differences between two groups in the mean age at the initial evaluation, educational level, marital and employment statues, other living arrangements, and physical or sexual abuse.

Self-reported suicidal ideation and suicide attempt

There were 17.5% of patients with MDD and 20.4% of patients with BPD having a history of previous SA (Figure 1). Of 103 patients with MDD, 23.3% endorsed any SR-SI with 19 patients of the severity of 1 point and 5 patient of severity of 2 points, but none was with severity of 3 points. Of 140 patients with BPD, 35.0% of them endorsed any SR-SI with 33 patients of the severity of 1 point, 14 of patients with 2 points, and 2 with 3 points. The rate of any SR-SI in BPD was significantly higher than that in MDD with an OR of 1.8 (95% CI 1.0 to 3.1 (Figure 1).

Association of the number of current and lifetime Axis I disorders with SR-SI and previous suicide attempt

As shown in Table 1, patients with BPD and 4 or more comorbidities had increased risk for current SR-SI compared to those without comorbidity with an OR of 6.5 (95% CI 1.8 to 22.5).

<table>
<thead>
<tr>
<th>Number of Current Comorbidity and SI</th>
<th>Number of Current Comorbidity and SA</th>
<th>Number of Lifetime Comorbidity and SA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bipolar Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>N of SI %</td>
<td>P Value</td>
</tr>
<tr>
<td>0 comorbidity</td>
<td>25 6 24 REF</td>
<td>25 2 8 REF</td>
</tr>
<tr>
<td>1 comorbidity</td>
<td>27 9 33.3 0.51122</td>
<td>29 5 17.2 0.2 15 2 13.3 0.38</td>
</tr>
<tr>
<td>2 comorbidities</td>
<td>32 10 31.2 0.54554</td>
<td>34 6 17.6 0.18 21 2 9.5 0.483</td>
</tr>
<tr>
<td>3 comorbidities</td>
<td>24 6 25 1</td>
<td>31 7 22.6 0.1 33 7 21.2 0.158</td>
</tr>
<tr>
<td>≥ 4 comorbidities</td>
<td>28 18 64.3 0.00327</td>
<td>28 10 35.7 0.01 69 19 27.5 0.069</td>
</tr>
<tr>
<td><strong>Major Depressive Disorders</strong></td>
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<td></td>
</tr>
<tr>
<td>0 comorbidity</td>
<td>18 3 16.7 REF</td>
<td>20 5 25 REF</td>
</tr>
<tr>
<td>1 comorbidity</td>
<td>38 9 23.7 0.23138</td>
<td>41 9 22 0.23 33 7 21.2 0.358</td>
</tr>
<tr>
<td>2 comorbidities</td>
<td>26 5 19.2 0.30286</td>
<td>23 2 8.7 0.08 25 3 12 0.44</td>
</tr>
<tr>
<td>≥ 3 comorbidities</td>
<td>20 7 35 0.13381</td>
<td>19 2 10.5 0.13 37 7 18.9 0.382</td>
</tr>
</tbody>
</table>

**Table 1:** Association of the Number of Current or Lifetime Axis I Comorbidity with Current Suicidal Ideation or Past Suicide Attempt in Patients with Bipolar Disorder or Major Depressive Disorder

Similarly, this group of patients with BPD also had significantly increased risk for SA compared those without comorbidity with an OR of 6.4 (95% CI, 1.2 to 32.9). In contrast, there was no significant association between SR-SI or SA and the number of comorbidity in patients with MDD.

**Table 2:** Comparison of the Number of Current or Lifetime Axis I Comorbidity and Suicide Attempt in Patients with Bipolar Disorder or Major Depressive Disorder

Association of current SR-SI and past suicide attempt

Overall, there was a significant association between current SR-SI and previous SA in patients with a mood disorder (Table 2). Patients with MDD and current SI only had numerical increases in previous SA (Table 2). Compared to bipolar patients without any SR-SI, patients...
with BPD and any SR-SI had a significantly increased risk for previous SA (Table 2).

**Association of depression and overall illness severity with current SR-SI**

As shown in Table 3, there was a positive association between SR-SI and the QIDS-SR-16 total scores in MDD and BPD. There was also a positive association between current SR-SI and CGI-S total scores in MDD and BPD (Table 3). Linear regression analysis demonstrated that depression severity in MDD was positively correlated to the increased risk of SR-SI with \( R^2=0.64 \) (Figure 2B). Depression severity in BPD was also positively correlated to the increased risk of any SR-SI with a correlation coefficient \( R^2=0.91 \) (Figure 2C).

<table>
<thead>
<tr>
<th>Association of anxiety severity with current SR-SI</th>
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</table>

As shown in Table 3, the association between current SR-SI and the increase in anxiety severity was not similar in patients with MDD and those with BPD. In MDD, mild anxiety was significantly associated with increased risk for current SR-SI compared to those without anxiety, but the increase in anxiety severity did not further increase the risk for current SR-SI.

<table>
<thead>
<tr>
<th>Interaction between severity of depression and anxiety on SI</th>
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Among those with MDD and moderate depressive severity, low anxiety (SAS ≤ 51) (n=15) was associated with increased rate of SR-SI compared to those with high anxiety (SAS ≥ 52) (n=13), 53.3% versus 23.1%.

Similarly, among those with MDD and severe/extreme depressive symptoms, low anxiety (SAS ≤ 56) (n=10) was associated with increased rate of SR-SI compared to those with high anxiety (SAS ≥ 57) (n=10), 60.0% versus 40.0%. In contrast, patients with BPD, moderate depression, and low anxiety (SAS ≤ 51) (n=17) were associated a lower rate of SR-SI compared to those with higher anxiety (SAS ≥ 52) (n=17), 35.3% versus 47.5%.

Similarly, among those with severe/extreme severe depressive symptoms, lower anxiety (SAS ≤ 57) (n=19) was associated with a lower rate of SR-SI compared to those with higher anxiety (SAS ≥ 58) (n=19), 63.2% versus 84.2%.

**Discussion**

To our knowledge, this is the first study using self-reported depressive and anxiety severity to separately investigate the relationship between current SR-SI and depressive and anxiety severity in patients with MDD and those with BPD. We found that depression severity had a positive association with increased risk for SR-SI in both patients with MDD and those with BPD although the magnitude of correlation was stronger in BPD than in MDD with \( R^2=0.91 \) versus \( R^2=0.64 \) (Figure 2B and 2C).

In contrast, anxiety severity had differential associations with current SR-SI in MDD and BPD with no overall significant correlation.

between anxiety severity and current SR-SI in MDD (Figure 2B1), but significant linear correlation in BPD (Figure 2C1).

The finding of positive correlation between depressive symptom severity and current SR-SI is consistent with previous studies in different populations [7,13,22,23,32-36]. A stronger correlation between depressive severity and current SR-SI in BPD than in MDD in the present study supports previous findings that differences in suicidality may exist between patients with MDD and those with BPD [3,6,8,9]. The differences include a higher suicide rate in BPD than in MDD [3] and more lethal suicide attempts in BPD than in MDD, especially in males [8,9].

The positive correlation between anxiety symptom severity and current SR-SI in BPD is expected, but lack of correlation between anxiety symptom severity and current SR-SI in MDD is somewhat unexpected. These findings are not contradictory to most previous studies. As shown in Figure 2A, if analyzed the correlation between anxiety severity and current SR-SI as one group, the finding is consistent previous studies, i.e., levels of anxiety are associated with suicidal ideation [15] and anxiety disorder increased risk for suicidal behavior [2,14,26,37-44]. However, a previous clinical study in patients with BPD found that patients with or without anxiety...
disorders had no difference in the rate of previous suicide [45]. Anxiety disorder was not associated with past suicide attempts or the severity of suicidal ideations. The inconsistency among these previous studies could be due to the studied population. More importantly, the majority of previous studies used lifetime anxiety disorder as a risk factor(s) [2,11,21,26]. Only a few used anxiety severity [14]. Some studies were cross-sectional [2,11,14,45]; some were prospective [26]; and others were retrospective [42,43]. Clearly, it is difficult, if not impossible, to compare the results from these studies. Meanwhile, in present study SAS only includes symptoms of generalized anxiety and panic attacks, the symptoms of other anxiety disorders could not be measured.

Regardless, our results do suggest that anxiety symptom severity had differential associations with current SR-SI in patients with MDD and those with BPD, i.e., a “plateau” effect in MDD and a “linear” effect in BPD (Table 3 and Figure 2). Because there were only a small number of patients with severe anxiety symptoms in MDD, it remain unclear if higher anxiety symptoms would cause a decrease in current SR-SI compared to those with mild anxiety symptoms. Increase in anxiety severity with decreased risk for suicide attempt was speculated in an epidemiological study [46].

<table>
<thead>
<tr>
<th>Patients</th>
<th>Normal vs. the Rest</th>
<th>Mild vs. the Rest</th>
<th>Moderate vs. Severe</th>
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<tr>
<td></td>
<td>Total N</td>
<td>No. of SI</td>
<td>SI %</td>
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<tr>
<td><strong>Bipolar Disorders</strong></td>
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<tr>
<td>QIDS-SR-16 total</td>
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<tr>
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<td>0</td>
<td>0</td>
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<tr>
<td>QIDS-16 6-10</td>
<td>36</td>
<td>5</td>
<td>13.9</td>
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<tr>
<td>QIDS-16 11-15</td>
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<td>14</td>
<td>43.8</td>
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<tr>
<td>CGI-S scores</td>
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<td>10</td>
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appeared to contradict these findings. Some epidemiological studies previous studies have shown that patients with MDD had a fewer [2,11]. In MDD, ≥ 3 comorbidities were associated with numerical suicidality in BPD as previously reported in epidemiological studies degree of worry might decrease the likelihood of carrying out the and higher SAS scores having a lower rate of SR-SI than those with a suicide attempt among ideators, which was speculated that the high number of comorbidities than those with BPD [24]. Fewer comorbidities in MDD and the “nonlinear” association of anxiety severity with current SR-SI in MDD are consistent with a lower rate of current SI in MDD than in BPD in the present study (Figure 1).

However, the similar rates of past SA in MDD and BPD (Figure 1) appeared to contradict these findings. Some epidemiological studies found that impulsivity and anxiety turned suicidal ideation to SA [2,47]. In a study of the World Mental Health Surveys, parental generalized anxiety and depression were the only predictors of the onset and persistence of suicidal plans among offspring with ideation, whereas parental antisocial personality and panic disorder were the only predictors the onset of persistence of suicide attempts among ideators [46]. Parental GAD had protective effect against planned suicide attempt among ideators, which was speculated that the high degree of worry might decrease the likelihood of carrying out the planned suicidal behavior. In the present study, patients with MDD and higher SAS scores having a lower rate of SR-SI than those with a lower SAS scores appeared to be consistent with this previous observation. It is possible that anxiety severity may also play different roles in other suicidal behaviors including SA in patients with MDD and those with BPD.

Our results suggest that the assessment of suicidality should be disease specific, especially when severe anxiety is a major concern. For patients with BPD, aggressive treatment of anxiety symptoms may reduce suicidal ideation, a precursor of most suicide attempt and suicide [2,10]. For patients with MDD, attention should be paid to those even with mild anxiety symptoms. Since depressive symptoms had positive correlation with SI in both MDD and BPD, aggressive treatments of depression and anxiety may reduce the risk of suicidal ideation and other suicidal behavior [48].

**Limitations**

The sample size of this study is relatively small. There were a limited number of patients with high severity of anxiety and depression symptoms so that the interaction between anxiety and depression symptoms could not be fairly studied. SAS only measures symptoms related to generalized anxiety disorder and panic attack. The other domains of anxiety disorder(s) could not be measured. The patients were from a tertiary medical center. Therefore, the results from the study may not be generable to other populations.

**Conclusions**

The number of comorbid conditions, depression and anxiety severity had stronger association with SR-SI and/or SA in patients with BPD than those with MDD. The differential associations of these variables with SR-SI/SA in patients with MDD or BPD suggest that a disorder specific assessment of suicidality in patients with MDD or BPD is essential for suicide risk management of patients with a mood disorder.

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**References**


