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Hopelessness and Suicidal Ideation in Outpatients With Treatment-Resistant Depression: Prevalence and Impact on Treatment Outcome

Abstract: Depression and hopelessness are risk factors for suicide. The purpose of this study was to examine the extent of suicidal ideation and hopelessness in outpatients with treatment-resistant depression (TRD) and to study the impact of suicidal ideation and hopelessness on treatment with nortriptyline (NT). The degree of suicidal ideation and hopelessness was assessed during the screen visit with the use of items #3 and #30 of the Hamilton Depression Rating Scale (HAM-D) in 89 patients with TRD who entered a 6-week open trial of NT. Forty of these patients also completed the Beck Hopelessness Index (BHI) during the screen visit. In separate logistic regressions, the scores from the BHI and the two HAM-D items were then tested as predictors of clinical response to the 6-week trial with NT, controlling for the severity of depression. More than half of patients reported thoughts or wishes of death to self and significant hopelessness. A greater degree of hopelessness before treatment in completers, reflected by the score on the HAM-D item #30, predicted response to NT. More than half of patients with prominent hopelessness who completed the trial responded. Patients with TRD are more likely than not to report prominent suicidal ideation and hopelessness. Furthermore, a full 6-week trial of NT, a relatively noradrenergic tricyclic antidepressant, may be particularly useful in patients who have failed to respond to several antidepressants and also report significant hopelessness.

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Suicide is a major public health concern (Weller et al., 2001). Currently, suicide ranks as the third leading cause of death in adolescents, representing 12% of deaths (American Academy of Child and Adolescent Psychiatry, 2001). Both depression (Bostwick and Pankratz, 2000) and hopelessness (Beck et al., 1989) are risk factors for suicidal ideation and suicide. A study of 4000 patients reveals that in depression, the standardized mortality rate is double for all causes of death and 26-fold for death from suicide (Newman and Bland, 1991). Overall, the lifetime risk for suicide in depressed patients has been estimated at 2.2% (Bostwick and Pankratz, 2000).

In addition to suicide, hopelessness has also been shown to predict a variety of other adverse health outcomes in large epidemiological studies, such as incidents of myocardial infarctions, hypertension,

cancer, and an increase in all-cause mortality (Everson et al., 1996; Everson et al., 2000; Stern et al., 2001). In fact, the relationship between hopelessness and these adverse outcomes remains significant even after adjusting for other biological, socioeconomic, or behavioral risk factors such as depression, smoking, perceived health, or social support (Everson et al., 1996; Everson et al., 2000; Stern et al., 2001). In addition, patients with a high degree of hopelessness may also receive suboptimal care; the results of one study indicate that hopeless patients overestimate the risks and underestimate the benefits of potentially life-saving treatments (Ganzini et al., 1994). This finding is particularly important for patients with treatment-resistant depression (TRD), who have not responded to previous antidepressant treatments and typically require higher doses of medication, more aggressive treatment, or both in order to respond. In addition, after protracted treatment courses, TRD patients may experience an even greater tendency to underestimate the benefits of the next treatment.

It appears that 29% to 46% of depressed patients show only partial or no response to antidepressants (Fava and Davidson, 1996). TRD, which represents a more chronic and severe form of major depressive disorder (Kornstein and Schneider, 2001), is associated with higher disability, morbidity, and mortality (Greden, 2001). However, hopelessness or suicidal ideation has never been assessed systematically among patients with TRD in relationship to treatment outcome. Studying the extent of hopelessness or suicidal ideation in this population may help identify risk factors that would place these patients at higher risk for disability or death and help guide clinicians and their patients in their treatment decisions (Nierenberg and Amsterdam, 1990). The purpose of this study was to examine suicidal ideation and hopelessness in depressed patients who had not responded to one to five adequate antidepressant trials during the current depressive episode, and the relationship between these two symptoms of depression and treatment outcome.

METHODS

Subjects were recruited at the Massachusetts General Hospital Depression Clinical and Research Program for the purposes of an outpatient clinical trial to assess the efficacy of lithium versus placebo augmentation of nortriptyline (NT) for subjects with TRD who had previously failed to respond to an open clinical trial of NT. This report is on the open phase of the study. Inclusion criteria were as follows: men and women age 18 to 70 years with MDD as diagnosed using the Structured Clinical Interview for DSM-III-R—patient edition (SCID-P; Spitzer et al., 1989) and a score on the 17-item Hamilton Depression Rating Scale (HAM-D-17; Hamilton, 1960) greater than or equal to 18. Treatment resistance was defined as at least one but no more than five adequate failed trials during the current episode. The adequacy of a trial was assessed using the Harvard Antidepressant Treatment History form (Nierenberg et al., 1991), which provides criteria specific to each antidepressant in terms of dose and duration for a trial to be considered adequate. Exclusion criteria for this trial were defined as follows: bipolar I or II disorder, psychotic disorders, a history of organic mental or seizure disorder, serious or unstable medical illness, substance abuse or dependence disorders active within the past 12 months, lactation, pregnancy, history of adverse reaction or allergy to the study medications, concomitant use of psychotropic medications, and clinical or laboratory evidence of thyroid abnormalities. Patients who were found to be imminently suicidal and in need of immediate containment, as assessed through clinical interview and using HAM-D-17 item #3 (score of 4), were excluded from the study.

The presence and extent of hopelessness during the screen visit were assessed with the Beck Hopelessness Inventory (BHI; Beck and Steer, 1988). Forty patients completed the BHI during the screen visit. Because of the relatively small sample size of those administered this instrument, the degree of hopelessness was also assessed during the screen visit with item #30 of the 31-item Hamilton Depression Rating Scale (HAM-D-31). Suicidal ideation was assessed during the screen visit with the use of item #3 of the HAM-D-31. A total of 92 outpatients were enrolled. We were able to locate the screen HAM-D-31 scales for all but three of these patients.

The HAM-D item #3 asks, "During the course of the past week, have you ever had any thoughts that life is not worth living, or that you'd be better off dead? What about thoughts of killing yourself?" and is rated as follows: 0, suicidal ideation is "absent"; 1, patient "feels that life is not worth living"; 2, patient "wishes he/she were dead or any thoughts of possible death to self"; 3, patient has "suicidal ideas or gesture"; 4, patient has "attempted suicide." The HAM-D item #30 asks, "Over the last week, do you feel hopeful that you will get better? Are you experiencing discouragement, despair, pessimism about the future?" and is rated as follows: 0, hopelessness is not present; 1, the patient has intermittent doubts that "things

will improve" but can be reassured; 2, the patient consistently feels "hopeless" but accepts reassurances; 3, the patient expresses feelings of discouragement, despair, pessimism about future, which cannot be dispelled; and 4, the patient spontaneously and inappropriately perseverates, "I'll never get well," or its equivalent.

Participants in this study signed an Institutional Review Board-approved informed consent form during the screen visit. Subjects returned 1 week later (baseline visit) and then started on 25 mg of NT. The NT dose was increased by 25 mg per day until an initial daily dose of 100 mg was reached, unless patients were unable to tolerate the dose increase because of side effects. Blood levels of NT were obtained at weeks 2 and 6, and dose adjustments were made after the second week if blood levels were 100 ng/ml or less. Subjects were then kept on their dose of NT for 6 weeks.

Study visits occurred at screen, at baseline, and then weekly for 6 weeks. The HAM-D-31, which allows the scoring of the HAM-D-17, was administered during the screen and baseline visits and at each study visit by experienced psychiatrists and psychologists. In our group, training in the use of instruments such as the HAM-D-17 and SCID-P is performed by peer review of videotaped interviews. Our interrater reliability for the use of the SCID-P was recently estimated as Kappa=.80 (Fava et al., 2000).

DEFINITION OF CLINICAL RESPONSE AND STATISTICAL TESTS USED

Response was measured by examining the change in HAM-D-17 score between baseline and week 6. Clinical response was defined as a 50% or greater reduction in the total HAM-D-17 score (baseline–endpoint). A completer analysis and an intent-to-treat (ITT) analysis were used. In the former, the analysis was limited to patients who completed the study. In the latter, the last recorded HAM-D-17 score substituted for the score at week 6 for patients who prematurely discontinued the study.

Three separate multiple regressions were then performed to test whether the HAM-D items #3 and #30 or the BHI scores at screening predicted the severity of depression at screening, as reflected by the HAM-D-17. Three separate logistic regressions were performed to test whether any of these four scores predicted clinical response to NT in the completer analysis, controlling for depression severity during the screen visit, as reflected by the HAM-D-17 total score. Three separate logistic regressions were then performed to test whether any of these four scores predicted clinical response to NT in the ITT analysis, controlling for depression severity during the screen visit, as reflected by the HAM-D-17 total score.

Paired *t*-tests were used to test whether there was a statistically significant difference in the change in HAM-D item #30 or item #3 during the course of the trial (endpoint–screen) between responders and nonresponders in the completer analysis and the ITT analysis.

RESULTS

Ninety-two patients were enrolled in the trial. None of the patients screened were excluded because of a HAM-D item #3 score of 4. We were able to locate the screen HAM-D-31 scales for all but three of these patients. The results of the open NT trial are reported elsewhere (Nierenberg et al., In Press). Briefly, the mean age of our sample was 41.1±11.7 years, and 50% were females. The mean age of onset of depression was 22.4±14.1 years, the mean duration of the current major depressive episode was 96.2±114.4 months, and the mean HAM-D-17 score during the screen visit was 21.3±3.9. For our sample, the mean number of failed trials during the current depressive episode was 2.3±1.5. Thirty-one patients had failed to respond to one medication, 18 had failed to respond to two, 15 had failed to respond to three, 16 had failed to respond to four, and 12 had failed to respond to five. There were no significant differences in the NT dosage or level between responders and nonresponders at week 6. Only five patients with blood NT levels less than 100 ng/ml at week 2 could not tolerate the minimal target NT daily dose of 100 mg because of side effects. Two of these patients responded to NT.

The mean BHI score during the screening visit was 13.0±5.0 (*N*=40). Furthermore, during screening, 27 (30.3%) patients scored 0 on item 3 of the HAM-D, 15 (16.8%) scored 1, 19 (21.3%) scored 2, and 28 (31.4%) scored 3. Of the patients, 52.7% reported significant suicidal ideation, defined as a score of 2 or greater on this item. Also during this visit, 28 (31.4%) patients scored 0 on item 30 of the HAM-D, 13 (14.6%) scored 1, 14 (15.7%) scored 2, and 34 (38.2%) scored 3. Of the patients, 53.9% reported significant hopelessness, defined as a score of 2 or greater on this item.

None of these three scores (BHI and HAM-D-31 items #3 and #30) predicted depression severity during the screen visit (p ranged from .5 to .6). In addition, we did not find the degree of suicidal ideation during the screen visit, as reflected by the score on the HAM-D item #3, to predict clinical response to NT in the completer or ITT analyses

(p>.05). However, scores on the HAM-D item #30 during the screen visit did predict clinical response, with higher scores predicting good response in the completer analysis (p=.03, chi-square=4.9, odds ratio=2.2, 95% confidence interval=1.1 to 2.3). With respect to completers, approximately 23.5% (4/17) with a HAM-D item #30 score of 0 during screening responded, 33.3% (3/9) with a score of 1 responded, 55.5% (5/9) with a score of 2 responded, and 50.0% (13/26) with a score of 3 responded. Furthermore, there was a trend toward statistical significance for the BHI score during the screen visit to predict clinical response in the completer analysis (p=.09, chi-square=2.7, odds ratio=1.6, 95% confidence interval=1.0 to 1.4), with higher scores predicting a higher likelihood of response in the completer analysis. The mean HAM-D item #30 scores during the screen visit for responders and nonresponders in the completer analysis were 2.1±1.3 and 1.4±1.7, respectively. The mean BHI scores during the screen visit for responders and nonresponders in the completer analysis were 15.5±24.0 and 12.2±25.8, respectively.

Scores on the HAM-D scale item #30 during the screen visit or scores on the BHI during the screen visit did not significantly predict treatment response in the ITT analysis (p>.05). With respect to all patients (ITT), approximately 40.7% (11/27) with a HAM-D item #30 score of 0 during screening responded, 53.3% (8/15) with a score of 1 responded, 31.6% (6/19) with a score of 2 responded, and 39.3% (11/28) with a score of 3 responded.

When completers alone were examined, there was a statistically significant difference in the change in HAM-D item #30 at week 6 compared with the screen visit between responders and nonresponders (–1.500 *vs.* .176, p=.0001). Specifically, responders experienced a mean decrease in HAM-D item #30 scores, whereas nonresponders experienced a mean increase. For completers, there was also a statistically significant difference in the change in HAM-D item #3 at week 6 compared with the screen visit between responders and nonresponders (–1.250 *vs.* –0.083, p=.004). Although both groups experienced a mean decrease in HAM-D item #3 scores during treatment, responders experienced a greater mean decrease in scores than nonresponders. When all patients were examined (ITT), there was a statistically significant difference in the change between HAM-D item #30 during the last recorded visit compared with the screen visit between responders and nonresponders (–1.308 *vs.* .229, p=.0004). Again, responders experienced a mean decrease in HAM-D item #30 scores, whereas nonresponders experienced a mean increase. For all patients (ITT), there was also a statistically significant difference in the change in HAM-D item #3 at endpoint compared with the screen visit between responders and nonresponders (–1.212 *vs.* –0.023, p<.001). Although both groups experienced a mean decrease in HAM-D item #3 scores during treatment, responders experienced a greater mean decrease in scores than nonresponders.

Discussion

The results of the present study indicate that more than half of patients with TRD reported thoughts of death to self, whereas approximately one third reported significant suicidal ideas or gestures. At the same time, more than half of TRD patients reported significant hopelessness or despair, whereas more than one third expressed despair and could not be reassured. Furthermore, we found that a greater degree of hopelessness predicted a favorable response to NT in patients who received the full 6 weeks of treatment, and this response was independent of the severity of the depressive episode. In fact, approximately half of patients reporting significant hopelessness who completed the trial responded. Although we did not find that hopelessness scores during the screen visit predicted response to the ITT analysis, this result may have been caused by the greater likelihood of hopeless patients to discontinue the study prematurely. In fact, Rifai et al. (1994) have reported that depressed patients with prominent hopelessness were more likely to discontinue treatment with NT prematurely.

With respect to suicide, our results are significant in that the presence and extent of suicidal thoughts have been shown to have a negative impact on the course of depression in a number of studies. A suicide attempt is a strong predictor of future suicidal behavior among patients with mood disorders (Nordstrom et al., 1995), whereas depressed patients with suicidal ideation are at higher risk of relapse (Szanto et al., 2001), of discontinuing treatment (Rifai et al., 1994), of experiencing a chronic course of illness (Moos and Cronkite, 1999), and of scoring lower on quality of life measures (Goldney et al., 2001), and are more likely to make use of mental health services than depressed patients without suicidal ideation (Pirkis et al., 2001).

The impact of hopelessness on the presentation, treatment, and course of major depressive disorder, however, is relatively understudied. In a study of 107 depressed adolescents who underwent a brief trial of psychotherapy, higher levels of hopelessness predicted persistence of depression after treatment (Brent et al., 1998). In a similar fashion, results of

a multicenter study involving 293 depressed outpatients randomized to a 16-week trial of interpersonal psychotherapy, cognitive behavioral therapy, imipramine, or placebo revealed that a higher degree of expectation of improvement predicted clinical response in the placebo and imipramine groups and across all treatment groups (Sotsky et al., 1991).

These last findings contrast with the present results, which report a favorable outcome in hopeless patients who complete the trial. A possible reason for the discrepancy is the difference in the populations studied. Hope and the expectation of improvement are features that increase the likelihood of a patient experiencing a placebo response (Brown, 1994). However, patients with TRD have been reported to have low placebo response rates compared with non-TRD patients, which some estimate as low as 10% (Thase et al., 1992). The inherently low placebo response rate in our sample may explain why the traditional relationship between expectation of improvement, by way of the degree of hopelessness, and placebo response is not seen. Hopelessness per se may be a marker of an underlying biological process, and the low placebo response rates in TRD would be less likely to obscure an effect of NT on an underlying biological process. In a study of suicidal inpatients, for instance, Russ et al. (2000) report that the genotype frequency for the serotonin transporter (5HTT) was significantly related to BHI scores at screening. Specifically, patients with high BHI scores were more likely to have the long allele of 5HTT (5HTT-l), which has a higher transcriptional activity than the short allele (5HTT-s). The latter allele has been found to predict poor response to treatment with selective serotonin reuptake inhibitors (SSRIs) in MDD (Zanardi et al., 2001), whereas depressed patients homozygous for the 5HTT-l allele may respond sooner than those possessing a 5HTT-s allele (Pollock et al., 2000). Unfortunately, no studies have been published focusing on the role of the 5HTT alleles in predicting clinical response to agents that have a significant effect on the noradrenergic system; such studies would aid in confirming this relationship for NT.

Alternatively, there is some evidence to suggest that tricyclic antidepressants (TCAs) may actually be more effective than SSRIs in the treatment of certain depressive subtypes, such as melancholic and poststroke depression (Georgotas et al., 1986; Perry et al., 1996; Robinson et al., 2000; Roose et al., 1994). Patients with endogenous depression respond preferentially to clomipramine compared with SSRIs, a finding that may be caused by the dual effect of clomipramine on both the noradrenergic and the serotonergic systems (Danish University Antidepressant Group, 1986; Danish University Antidepressant Group, 1990). Similar to clomipramine, NT also has a significant effect on the noradrenergic system (Nyback et al., 1975). Thus, it is quite possible that patients with a greater degree of hopelessness who completed the 6-week trial were more likely to respond to treatment because of the use of TCA. In addition, it is also possible that clinicians were inadvertently more encouraging or supportive to very hopeless or suicidal patients, although the effect of support and encouragement on clinical response would have been rather small given the low placebo response rate in this population. In addition, this open trial was designed to generate nonresponders for the second phase of the study (placebo-controlled trial of lithium augmentation); if any bias were present, it would be toward minimizing response to NT to generate more subjects for the second phase of the study.

LIMITATIONS

Although the relationship between hopelessness and response to NT in TRD may represent a chance finding, the degree of significance (p=.02) and the fact that there was a similar trend when a second, independent measure of hopelessness was used (BHI) make this seem unlikely. One limitation of our study is the use of a dichotomous classification of clinical response. Another limitation is that of sampling bias. Clinical trials have a number of inclusion and exclusion criteria, and as a result, patients in clinical trials do not directly reflect the typical outpatient population with MDD. This factor is particularly important for the present study, because depressed patients who were imminently suicidal were excluded. Thus, it would be difficult to generalize the present findings to patients with chronic and severe suicidal ideation. In addition, our study did not involve a placebo arm, which would have afforded us the opportunity to compare the effect of hopelessness on treatment response in both the active drug and placebo groups. Finally, our assessment of hopelessness during the screen visit, pertaining to the week immediately before the screen visit, provides a cross-sectional measure of severity and is not informative about possible heterogeneous patterns of hopelessness during the course of illness. There may be patients whose level of hopelessness is static, for example, and others whose level of hopelessness fluctuates frequently according to life events. Our results do not address the relative like-

lihood of NT response for patients in these two hypothetical groups. Future studies addressing these limitations are necessary to shed light on the relationship among suicidal ideation, hopelessness, and treatment response in MDD.

CONCLUSIONS

Our findings demonstrate that in a sample of outpatients with well characterized TRD, patients are more likely than not to report prominent suicidal ideation and hopelessness. In addition, for patients with TRD prospectively treated with open-label NT who completed the trial, the presence of hopelessness appeared to be associated with a significantly greater chance of response to antidepressant treatment. In fact, approximately half of these patients with prominent hopelessness responded. The degree of expectation of improvement, indirectly measured by the degree of hopelessness, has traditionally been thought to be related to the placebo response. A possible reason for our finding may include the low placebo response rates in TRD, which would be less likely to obscure an effect of NT on an underlying biological process in patients with TRD and a greater degree of hopelessness. These results suggest that a full, 6-week trial of NT, a relatively noradrenergic TCA, may be particularly useful among patients who have failed to respond to several antidepressants and also present with significant hopelessness.

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