Course of Major Depressive Disorder and Suicide Outcome: A Psychological Autopsy Study

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Background: There is considerable debate as to whether suicide is more likely to occur early in the course of major depressive disorder or by cumulative risk, with an increasing risk with each subsequent major depressive episode (MDE). By considering the number of MDEs among representative suicides, we aimed to further investigate the relationship between suicide outcome and the course of major depressive disorder.

Method: A psychological autopsy method with best informants was used to investigate 154 consecutive suicides who died in the context of a DSM-IV MDE. Proxy-based interviews were conducted by using the Structured Clinical Interview for DSM-III-R; the Structured Clinical Interview for DSM-IV Axis II; and a series of behavioral and personality-trait assessments. Second, 143 living depressed outpatients of comparable age to the suicide group were assessed for their history of MDEs. The study was conducted between 2000 and 2005.

Results: The distribution of MDEs among depressed suicide completers was as follows: first MDE, 74.7%; second MDE, 18.8%; more than 2 MDEs, 6.5%. This distribution is compared to 32.9% of depressed living outpatients with a single MDE. Increased levels of hostility were associated with single MDE suicide completers. The anxious trait of harm avoidance increased among multiple MDE suicide completers. Alcohol abuse increased among first MDE suicide completers.

Conclusions: Suicide in major depressive disorder is most likely to occur during the first MDE, and this appears to be related to increased levels of the impulsive-aggressive diathesis.

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The United States sees more than 30,000 suicide victims annually,[1] 50% of whom meet criteria for current depressive disorders.[2] Major depressive disorder is the primary psychiatric diagnosis associated with the greatest risk for suicide,[3] with approximately 5% of depressed individuals eventually dying by suicide.[4] Although major depressive disorder constitutes an important risk factor for suicide, the majority of those affected by major depressive episodes (MDEs) do not die by suicide.

In a seminal meta-analysis, Guze and Robins[5] reported that suicide was more likely to occur early in the course of depression, a finding that was based on the higher relative risk of suicide compared to other causes of death during this period. Prospective examinations subsequently confirmed a decreasing temporal relationship with suicide following psychiatric admission.[6–8]

Conversely, however, it has also been proposed that suicide occurs during periods of rapid change in the depressive state, such as at the onset and resolution of MDEs.[9] Risk would thus be constant or even a cumulative function of the number of MDEs. Support has also been obtained for this hypothesis, with a subpopulation of those meeting criteria for depressive disorders displaying constant risk across MDEs[10–12] while registry studies report increasing suicide risk with increasing number of psychiatric hospitalizations.[13]

A possible way to further investigate the relationship between the course of major depressive disorder and suicide outcome is to consider the number of MDEs among representative suicide completers. In this study, we investigated the relationship between number of MDEs and suicide. In addition, there has been increasing support for the claim that an impulsive-aggressive behavior diathesis,[14] which, when interacted with stressors such as psychiatric illness,[15] could result in suicide. One would therefore expect an inverse relationship between impulsive-aggressive behavior levels and number of MDEs among suicide completers, as individuals with high levels of impulsive-aggressive behavior diathesis would be more likely to act earlier on their suicidal ideation. Here we tested this hypothesis.

METHOD

Subjects

Through an ongoing collaboration with the Quebec Coroner's Office and the Montreal Central Morgue, our group (McGill Group for Suicide Studies, Montreal, Quebec, Canada) recruits consecutive suicides representative of suicides occurring in the region. Cases are assessed by psychological autopsy, a validated method[16–19] involving the individual best acquainted with the deceased serving as an informant. The participation acceptance rate by suicide families once referred by the coroner's office is 75%. Cases whose families choose not to participate do not differ with respect to age, race, or suicide method from cases whose families participate. For this study, we identified 154 (130 male) cases that met criteria for current major depressive disorder and died within the context of a proxy-reported DSM-IV MDE.

Living individuals who met criteria for major depressive disorder were recruited from general psychiatric outpatient clinics associated with McGill University, Montreal, Quebec, Canada. In doing so, the control population exhibited MDEs that were severe enough to require follow-up in a specialized outpatient clinic and were of similar severity to depressed suicides.[20] To avoid the reporting of artifacts, we required that living depressed individuals name an informant for the interview process, and the participation acceptance rate for informants, once named, was 90%. Inclusion was dependent on proxy endorsement of DSM-IV criteria for an MDE. We recruited 143 living outpatients with MDEs who were of comparable age to the suicide cases (mean ± SD, 39.51 ± 11.23 years; men, 78.3% [N = 112]).

This study was approved by our local institutional review board; suicide families, living depressed individuals, and informants signed written informed consents. The study was conducted between 2000 and 2005.

Measures

Axis I and II DSM-IV disorders were assessed using the Structured Clinical Interview for DSM-III-R[21] and Structured Clinical Interview for DSM-IV Axis II[22]; lifetime MDEs were ascertained. Our group has very good levels of interrater reliability for depressive disorders ($\kappa = 0.87$). Within depressed individuals, specifically, we have excellent levels of agreement on key comorbid diagnoses ($1.0 > \kappa > .96$).[17]

Behavioral measures for this study were the Brown-Goodwin History of Aggression (BGHA),[23] to assess aggressive behaviors; the Barratt Impulsiveness Scale, version 11 (BIS-11),[24] to assess impulsive behaviors; the Buss-Durkee Hostility Inventory (BDHI),[25] to assess hostility; and the Temperament and Character Inventory (TCI),[26] to assess 4 basic temperaments. Internal consistency for these measures for the current study is as fol-

lows: BDHI, $\alpha = .84$; BGHA, $\alpha = .90$; BIS-11, $\alpha = .89$; and TCI subscales, $\alpha > .40$.

Validity of Proxy Information

We[17,27] and others[18,19] have previously reported highly consistent information between subjects and their informants, between multiple informants,[17] and for informants with different relationships to the subject.[28,29]

We compared the number of MDEs obtained from subject and informant ($N_{subject} = 16$) and found very good levels of symmetry ($\gamma = 0.75$, $p < .01$). Perfectly concordant histories of MDEs were reported in 62.5% of pairs, and only in 18.75% of pairs did 1 member of the dyad report a single MDE and the other, 2 or more MDEs.

Statistical Analyses

Statistical analyses were performed by using SPSS, version 11.5 (SPSS Inc., Chicago, Ill.). Analyses were restricted to suicide cases; only living controls' number of MDEs is reported.

First, we chose to determine the correlates of dying in the context of one's first MDE as opposed to a recurrent episode by using grouped analyses. Suicides who died in the context of their first MDE were compared to those with recurrent MDEs by using χ^2 tests (with exact limit test to evaluate the 95% CI) for categorical variables and t tests for continuous variables.

To test whether factors associated with suicide later in the course of major depressive disorder in grouped analyses offset lethal suicidal behavior, concomitant psychopathology and behavioral characteristics were also predicted by continuous number of MDEs by using multiple logistic or linear regressions. Testing incremental variation in predictors with increasing number of MDEs is a strong argument for its role when, during the course of the disorder, suicide occurs.

Greater emphasis and confidence in the findings is thus placed on factors significantly differentiating suicides as a function of number of MDEs by using both analytic approaches.

RESULTS

Distribution of MDEs

Among depressed suicide cases, 74.7% died within the first MDE, while 18.8% within their second and only 6.5% after a history of more than 2 MDEs (Figure 1). This is in stark contrast with the distribution of MDEs among living depressed outpatients, in which 32.9% (N = 47) had a history of single MDE.

Suicide Characteristics as a Function of MDE History

Analyses with respect to number of MDEs and cases' characteristics are presented in Table 1. Single MDE

Figure 1. Distribution of Major Depressive Episodes (MDEs) Among Depressed Suicide Cases and Depressed Living Outpatients
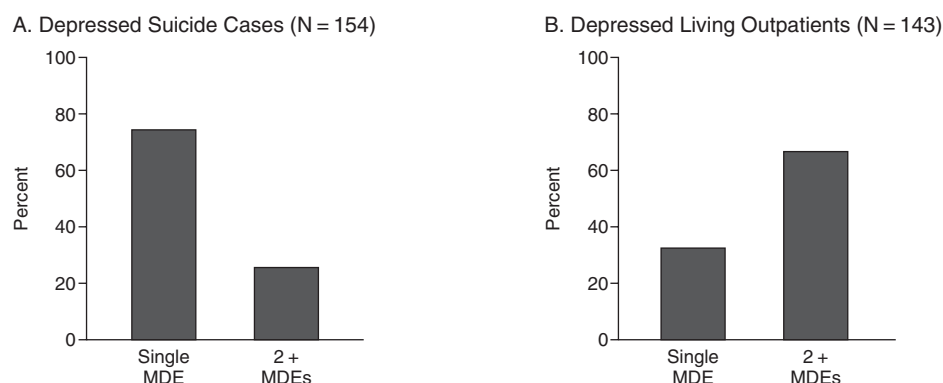

Table 1. Comparison of Suicide Completers Who Died Within Their First MDE Versus Multiple MDEs as Well as Across MDEs

Variable	Single MDE (N = 115)	At Least 1 Previous MDE (N = 39)	Single vs Multiple MDEs		Continuous No. of MDEs		
			p	t or OR (95% CI)	p	β or OR	95% CI
Demographic							
Age, mean ± SD, y	41.86 ± 13.95	43.08 ± 11.16	.622	–0.49	.144	0.01[a]	–0.00 to 0.02
Male, N (%)	101 (87.5)	29 (74.4)	.053	2.41 (0.97 to 6.00)	.105	1.27[b]	0.95 to 1.69
Married, N (%)	48 (42.9)	17 (43.6)	.937	1.03 (0.49 to 2.14)	.849	1.02[b]	0.78 to 1.34
University education, N (%)	10 (9.0)	7 (17.9)	.130	2.20 (0.77 to 6.27)	.628	1.08[b]	0.77 to 1.54
Illness characteristic							
Age at onset, mean ± SD, y	39.56 ± 13.82	35.28 ± 12.10	.139	1.48	.287	–1.16[a]	–3.32 to 0.99
Antidepressant medication, N (%)	23 (22.3)	17 (47.2)	.005	3.11 (1.39 to 6.94)	.045	1.48[b]	1.01 to 2.19
Current Axis I, N (%)							
Alcohol abuse	40 (34.8)	6 (15.4)	.022	2.93 (1.13 to 7.59)	.055	0.60[b]	0.36 to 1.01
Drug abuse	20 (17.4)	4 (10.3)	.288	1.84 (0.58 to 5.76)	.484	0.83[b]	0.50 to 1.37
Anxiety disorder	18 (15.7)	8 (20.5)	.484	0.71 (0.28 to 1.81)	.656	1.07[b]	0.77 to 1.50
Lifetime Axis I, N (%)							
Alcohol abuse	53 (46.1)	12 (30.8)	.094	1.92 (0.88 to 4.16)	.132	0.76[b]	0.54 to 1.08
Drug abuse	17 (14.8)	8 (20.5)	.402	0.67 (0.26 to 1.70)	.884	0.97[b]	0.66 to 1.41
Anxiety disorder	16 (13.9)	8 (20.5)	.326	0.62 (0.24 to 1.60)	.809	1.04[b]	0.75 to 1.44
Axis II, N (%)							
Cluster A	8 (7.4)	5 (13.2)	.284	0.52 (0.16 to 1.72)	.027	1.45[b]	1.04 to 2.02
Cluster B	24 (22.2)	11 (28.9)	.404	0.70 (0.30 to 1.61)	.719	1.05[b]	0.78 to 1.42
Cluster C	19 (17.6)	6 (15.8)	.800	1.13 (0.41 to 3.10)	.630	1.08[b]	0.78 to 1.50
BIS-11 score, mean ± SD	66.94 ± 12.97	64.95 ± 16.41	.501	0.67	.215	–1.77[a]	–4.58 to 1.03
BGHA score, mean ± SD	11.20 ± 13.20	6.94 ± 9.89	.092	1.69	.199	–1.12[a]	–2.85 to 0.60
BDHI score, mean ± SD	38.84 ± 13.22	33.64 ± 13.82	.073	1.81	.039	–2.74[a]	–5.34 to –0.14
TCI temperament score, mean ± SD							
Novelty seeking	20.45 ± 7.12	19.00 ± 7.86	.362	0.91	.166	–0.98[a]	–2.38 to 0.41
Harm avoidance	17.86 ± 7.09	21.59 ± 6.62	.015	–2.47	.033	1.50[a]	0.12 to 2.88
Reward dependence	13.07 ± 4.41	14.38 ± 4.82	.183	–1.33	.033	0.94[a]	0.07 to 1.80
Persistence	5.37 ± 2.24	4.86 ± 2.18	.290	1.06	.918	–0.02[a]	–0.47 to 0.43

[a]β.
[b]OR.
Abbreviations: BDHI = Buss-Durkee Hostility Inventory; BGHA = Brown-Goodwin History of Aggression; BIS-11 = Barratt Impulsiveness Scale, version 11; MDE = major depressive episode; TCI = Temperament and Character Inventory.

suicide cases were marginally more likely than recurrent MDD cases to be male (OR = 2.41, 95% CI = 0.97 to 6.00). Antidepressant medication was more common among multiple MDE cases (OR = 3.11, 95% CI = 1.39 to 6.94), and this association held when considering continuous number of MDEs (OR = 1.48, 95% CI = 1.01 to 2.19).

Single MDE suicide cases were more likely to meet criteria for alcohol abuse (OR = 2.93, 95% CI = 1.13 to

7.59), with marginally fewer cases meeting criteria with each successive episode (OR = 0.60, 95% CI = 0.36 to 1.01). There was a trend toward higher BDHI mean ± SD scores in single MDE cases (38.84 ± 13.22 vs. 33.64 ± 13.82), and these scores significantly decreased with increasing number of MDEs (β = –2.74, 95% CI = –5.34 to –0.14). Conversely, higher mean ± SD scores on the harm avoidance dimension of the TCI were observed in multiple MDE suicide cases (21.59 ± 6.62 vs.

17.86 ± 7.09) and increased with number of MDEs (β = 1.50, 95% CI = 0.12 to 2.88). When considering continuous number of MDEs, increasing number of MDEs was associated with an increasing prevalence of cluster A personality disorders (OR = 1.45, 95% CI = 1.04 to 2.02). Similarly, a negative relationship was observed between number of MDEs and levels of reward dependence, as measured by the TCI (β = 0.94, 95% CI = 0.07 to 1.80). There were no statistically significant relationships between number of MDEs and any other clinical, demographic, or behavioral dimensions among cases.

DISCUSSION

Major depressive disorder has consistently emerged as an important risk factor for suicide, and important research has gone into refining suicide risk within this group. In this study, we tested the stage of the illness, defined as number of depressive episodes, at which suicide occurs in DSM-IV major depressive disorder among 154 depressed individuals drawn from consecutive (representative) suicides. Our results suggest that suicide in major depressive dissorder is most likely to occur during an individual's first MDE.

Although previous studies have demonstrated that the risk for suicide decreases with time following admission in psychiatric samples,[5–8] no study has yet formally tested the relationship between course of illness, in terms of number of MDEs, and likelihood of dying by suicide. Further, our examination provides the first test of suicide and the course of major depressive disorder among representative suicides.

Previous studies have been limited to clinical samples, yet it is clear that the proportion of depressed individuals receiving psychiatric care who go on to die by suicide is limited,[4] and many individuals who die by suicide do not come into contact with psychiatric service providers.[30] Our study suggests that those who die by suicide after a first depressive episode were more likely to have benefited from psychiatric services, but that these individuals constitute a minority of depressed individuals who die by suicide. The majority of depressed suicides die within their first MDE, prior to receiving psychiatric attention. Although expected, this conclusion provides insight into inconsistent findings regarding the course of major depressive disorder and suicide, with studies having reported constant risk emerging primarily from studies of psychiatric populations. More specifically, studies reporting constant risk have examined psychiatric populations, and, therefore, samples consisting of those having resisted acting on suicidal ideas long enough to receive psychiatric attention, perhaps as a direct result of lower levels of vulnerability. Without minimizing the importance of lifelong treatment in those individuals who

exhibit constant risk for suicide across MDEs, this population clearly constitutes a minority of depressed suicide completers.

In addition, our results support the implication of an impulsive-aggressive behavior diathesis-stress interaction. Several indicators of elevated levels of impulsive-aggressive behaviors, including aggression, hostility, and alcohol abuse, were associated with suicide earlier in the course of MDD. The diathesis-stress framework suggests that (1) high levels of impulsive-aggressive behavior increase the probability of individuals engaging in lethal suicidal behavior and (2) high levels of impulsive-aggressive behavior that leads to suicide vulnerability require fewer or lesser stressors than lower levels of the vulnerability so that (3) the probability of vulnerable individuals' engaging in lethal suicidal behavior is considerable during the first MDE.

It is also interesting to note that the proportion of women who die by suicide increases after the first MDE. This is interesting, for it supports the suggestion that while completed female suicide, but not suicide attempts,[31] could in many cases also likely result from the impulsive-aggressive diathesis, other mechanisms, such as hopelessness or yet unidentified mechanisms, appear to play a larger role among female suicides than among male suicides.[32]

How does one reconcile the finding that suicide is most likely to occur in the first MDE and, due to the gender difference in major depressive disorder, that women are more likely to experience a first MDE, yet one does not see an excess of first MDE female suicides? In line with previous findings, we know that death by suicide is a predominantly male phenomenon,[33] while suicide attempters are more often women. On this basis alone, one would expect the relationship that we report and could hypothesize that suicide attempts may also be more likely in the first MDE and may exhibit an excess of female attempters. Moreover, our findings suggest that the stage of the illness at which suicide occurs may be attributable to an individual's level of impulsive-aggressive diathesis. We know that women who die by suicide have, on average, lower levels of impulsivity than men who die by suicide and that impulsivity among female suicides appears to be bimodal.[32] In other words, the proportion of highly impulsive female suicides is comparable to the proportion of highly impulsive male suicides, yet, unlike male suicides, the remainder of suicides displays levels of impulsivity at and below levels encountered in nonsuicidal populations. This suggests that, for a significant portion of women who die by suicide, the behavioral traits that may have predisposed them to suicide may be unrelated to the impulsive-aggressive predisposition. It is therefore reasonable to expect that men, who appear to be more heavily predisposed than women to suicide via the impulsive-aggressive diathesis, would be present in excess among first MDE

suicides despite the fact that they are less likely to meet criteria for major depressive disorder. Women, on the other hand, would be more likely to exhibit constant risk across MDEs.

LIMITATIONS

The limitations of our study are inherent to retrospective, proxy-based postmortem studies. While prospective follow-up of patients at risk would be preferable, the rarity of suicides in this population renders such studies underpowered and uninformative. Concerning limitations of proxy-based assessments, we found that the number of MDEs reported by proxies and subjects themselves is consistent. Family members of the deceased may exaggerate or distort information, yet if this takes place, it would not be a function of number of MDEs. The design of our study does not allow us to determine whether antidepressant dosage differs between suicides at various stages of the illness, whether antidepressant treatment directly decreased the risk of dying by suicide, or whether personality differences influence treatment-seeking behaviors.

CONCLUSION

Suicide in major depressive disorder is most likely to occur in the first MDE, and this appears to be related to higher levels of the impulsive-aggressive behavior diathesis. Individuals who die by suicide later in the course of major depressive dissorder appear to have previously benefited from psychiatric services, while at the same time exhibiting lower levels of the impulsive-aggressive diathesis. Greater emphasis must be placed on early identification of major depressive disorder, and levels of impulsive-aggressive behaviors should be taken into account when assessing suicide risk.

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