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Treatment -Emergent Suicidal Ideation During 4 Months of Acute Management of Unipolar Major Depression with SSRI Pharmacotherapy or Interpersonal Psychotherapy in a Randomized Clinical Trial

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Abstract

Background—To date, few randomized controlled trials (RCT) of major depression have examined suicidal ideation as an outcome measure. Our aim is to determine the incidence of treatment-emergent suicidal ideation (ESI) and behaviors during the acute phase of treatment with an SSRI antidepressant or interpersonal psychotherapy (IPT) in patients with unipolar major depression.

Methods—In a two-site RCT, 291 adult outpatients with non-psychotic major depression and a Hamilton Depression Rating Scale (HDRS) score ≥ 15 were randomly allocated to IPT or SSRI. Participants who did not remit with monotherapy received augmentation with the other treatment. ESI was defined as a post-baseline HDRS suicidality item score ≥ 2 or a post-baseline Quick Inventory of Depressive Symptomatology (QIDS) score ≥ 2 in patients with a baseline score ≤ 1 .

Results—Of the 231 participants who had no suicidal ideation at baseline, 32 (13.8%) subsequently exhibited ESI on at least one post-baseline visit. Time to suicidal ideation was significantly longer in patients allocated to SSRI compared to those allocated to IPT (HR=2.21, 95% CI 1.04-4.66, $p=0.038$), even after controlling for treatment augmentation, benzodiazepine use and comorbidity with anxiety disorders. Worsening of suicidal ideation occurred in 7/60 patients who had suicidal ideation at baseline. In the large majority of cases, suicidal ideation was successfully managed with the study protocol.

Conclusions—In the context of careful monitoring and frequent contact, SSRI was associated with a lower risk of ESI than IPT and both SSRI and IPT appeared to be safe treatments for patients with past suicide attempts, none of whom exhibited ESI during the study.

Keywords

depression; suicidal ideation; interpersonal psychotherapy; SSRI; suicide; randomized clinical trial

Introduction

Depression is an important risk factor for suicide-related phenomena (suicidal ideation, plans, attempts) [1]. More than 50% of patients with major depressive disorder may experience suicidal ideation during an index episode [2]. On October 15, 2004, the US Food and Drug Administration issued a public advisory, ordering manufacturers of antidepressant drugs to adopt a boxed warning to alert doctors of a greater risk of suicidality in children and adolescents treated with these medications, given that, in these special populations, some antidepressant treatments may at least transiently be associated with an increase of suicidal ideation [3]. In adult or late-life patients treated with SSRI, treatment-emergent suicidal ideation varied between 4% and 20%, depending on the sample characteristics and the definition of suicidal ideation [4-10]. In the GENDEP study, a peak of 6.6% was found at the 5th treatment week, with a higher risk associated with nortriptyline compared with escitalopram in men [11].

Less is known about treatment-emergent suicidal ideation in the context of psychotherapy because suicide risk is generally an exclusion criterion for clinical trials, and emergent suicidality is considered a serious adverse event. To our knowledge, only one study examined emergent suicidality in a psychotherapy trial for adolescent depression and found an incidence of 12.5% [12]. To date, a few randomized controlled trials (RCTs) of major depression were carried out in which suicidal ideation was an outcome measure [11] and none have compared psychotherapy with antidepressant treatment. Moreover, except for two studies [10,11], the assessment of emergent suicidality relied only on a self-report or an interview-based measure.

Below we report on the emergence of and increase in suicidal ideation and behaviors during 16 weeks of acute treatment with SSRI antidepressant or interpersonal psychotherapy (IPT) [13,14] in patients with major depression participating in the trial 'Depression: The Search for Treatment-Relevant Phenotypes' [15]. In order to use all available data, we combined weekly assessments of suicidality based on Item 3 of the Hamilton Depression Rating Scale (HDRS, [16]) and Item 12 of the Quick Inventory of Depressive Symptomatology – Self-report (QIDS, [17]).

Methods

This study was carried out at the Western Psychiatric Institute and Clinic of the University of Pittsburgh and the outpatient clinic of the Ospedale Santa Chiara of the University of Pisa between April 2003 and April 2008 [15]. Study procedures are described in detail elsewhere [21]. In summary, patients between 18 and 66 years of age with a non-psychotic major depressive episode according to DSM-IV and a HRSD score ≥ 15 were randomly allocated to SSRI pharmacotherapy (escitalopram) or psychotherapy (IPT). Experienced interviewers with specific training carried out the diagnostic assessment using the SCID [18] and administered the HRSD. Exclusion criteria were previous manic or hypomanic episodes, current primary diagnosis of anorexia or bulimia nervosa, anti-social personality disorder, substance abuse or dependence in the past 3 months, planned or current pregnancy, significant medical illness, inability to tolerate study interventions, and depressive symptom severity or suicidality necessitating hospitalization. The acute treatment phase of the study involved weekly treatment visits and assessments, with three triage points at weeks 6, 12, and 20. Response was defined as a 50% in baseline HDRS score and remission as a mean HDRS ≤ 7 over 3 weeks. When remission was achieved, patients entered the continuation phase and were seen biweekly and then monthly for a total of 6 additional months.

Escitalopram was started at a dose of 10 mg and titrated when possible to 20 mg/day. IPT was added at week 6 for participants not yet showing a response and at week 12 for participants not in remission. Similarly, SSRI was added at the same time points for participants assigned to IPT who did not evidence response or remission. Participants assigned to either condition who complained of sleep difficulties were allowed to receive up to 4 mg of lorazepam until sleep difficulties resolved.

Study procedures were approved by the Ethics Committees of the two institutions and all patients signed a written informed consent to participate.

Outcome measures

To evaluate treatment emergent suicidal ideation, we combined information from self-report and interview-based measures about recurrent thoughts or suicide, plans and acts. We chose an approach combining these two methods because the literature indicates that each type of assessment frequently provides different information [10] and we assumed that endorsement of suicidal ideation on either instrument was a valid indicator of its presence. Specifically, suicidality was evaluated weekly during the acute phase using Item 3 of the HDRS (rated as 0 = no thoughts of death, 1 = life is empty or not worth living, 2 = recurrent thoughts of death or suicide, 3 = suicide plans, 4 = suicide attempts) and item 12 of the QIDS (rated as 0 = no thoughts of suicide or death, 1 = life is empty or not worth living, 2 = recurrent thoughts of death or suicide, 3 = suicide plans or attempts). Emergent suicidal ideation was defined as a HDRS suicide item score of ≥ 2 or a QIDS score ≥ 2 on any post-baseline visit for participants whose baseline score was 0 or 1, in line with the criteria used in [4,5] to define ESI. The onset of suicidal ideation was defined as the earliest date in which a patient had a score ≥ 2 on the QIDS or the HDRS.

Past suicidality was evaluated at intake and at the triage points of the protocol using the Interview on Suicidal Feelings (ISF [20]). Patients whose suicidality was deemed too severe to be managed in the context of their protocol treatment were immediately withdrawn from the study and offered appropriate alternative treatment.

Statistical methods

Patients with treatment-emergent suicidality were compared with those without treatment-emergent suicidality on baseline demographic and clinical characteristics and outcome variables using the χ^2 or the t-test when appropriate. Kaplan-Meier survival estimates and Cox regression models were used to analyze the hazard of emergent suicidality in patients allocated to IPT, compared to those allocated to SSRI. The time period considered in the survival analyses was 4 months of acute treatment, in order to examine the effect of adjunctive treatment and, therefore, data were censored at 4 months. Analyses were carried out using SPSS, version 15.0 and STATA, version 9.0 (STATA Corporation, Houston, TX, USA).

Results

Figure 1 presents participant flow through the study. 318 outpatients with unipolar depression were randomized and 291 received the allocated intervention, 153 at Pittsburgh and 138 at Pisa. Participants were recruited beginning in April 2003. Of the 291 study participants (149 assigned to IPT, 142 to SSRI), 210 (72%) were female, 113 (38.8%) married; mean age was 39.3 years and educational level was on average 13.8 years. Ninety (30.9%) participants were in their first episode of illness, while 201 (69.1%) had 2 or more episodes of depression. Mean HRSD-17 score at baseline was 20.1 (SD=4.0, range 15-35); 149 were randomized to IPT, 142 to SSRI (Table 1).

Participants at Pittsburgh were more frequently male, unemployed, had a higher educational level, more previous depressive episodes, a longer duration of illness and higher scores on lifetime measures of mood and anxiety spectrum psychopathology [21].

Suicidal ideation was absent at pre-treatment baseline visits in 231 study participants (79.4%) and present in 60 (20.6%) participants, of whom 59 (25.5%) had a score of 2 (recurrent thoughts of death/suicide) and 1 (0.4%) had a score of 3 (suicide plans).

Treatment-emergent suicidal ideation (ESI)

Of the 231 participants who had no suicidal ideation at baseline 32 (13.8%) subsequently exhibited ESI on at least one post-treatment visit. Ten such patients were identified by the QIDS, 10 by the HDRS (n=10) and 12 by both. The percentage agreement between the two instruments was 76% and Cohen's kappa, measuring the agreement beyond chance, was 0.40. In 4 of the 12 cases identified by the HDRS and the QIDS, a score ≥ 2 on the suicidality item was reached on both instruments on the same date, the other 8/12 patients endorsed suicidality on the self-report (QIDS) at least one week earlier than they did when queried directly by the interviewer (HDRS).

Of the 32 patients with ESI, 22 (18.8%=22/117) had been initially randomized to IPT and 10 (8.8%=10/114) had been initially randomized to SSRI. Participants with ESI did not differ from those without ESI on age, sex, education, marital status, duration of illness, baseline HDRS score and number of total lifetime depressive episodes. However, they were more likely to report wishes to die at baseline (61.3% vs. 37.4%, $\chi^2=6.3$, $p=0.012$), mostly in the previous month and *less* likely to have a history of suicidal behavior (0% vs. 10.6%, $\chi^2=3.7$, $p=0.053$). Of note, none of the 21 participants with a past history of suicide attempts developed ESI during treatment.

Onset and Duration of ESI

Treatment at onset of suicidal ideation was IPT in 18 participants, SSRI in 6 participants, SSRI+IPT in 4 participants and IPT+SSRI in 4 participants. With respect to timing of suicidal ideation, 13 (40.6%) of episodes occurred within 4 weeks of beginning treatment, 9 (28.2%) between 5-8 weeks of beginning treatment, and 10 (31.2%) after 8 weeks. In the 8 patients who experienced emergent suicidal ideation during combination treatment, only in 3 instances did this happen within a month of beginning the combination (0 and 14 days after starting adjunctive IPT, 6 days after starting SSRI). In the other 5 participants, emergent suicidal ideation started between 25 and 58 days later. Time to suicidal ideation was significantly longer in patients allocated to the SSRI sequence compared to those allocated the IPT sequence (log-rank 4.54, $p=0.033$, HR=2.21, 95% CI 1.04-4.66, $p=0.038$) (Fig. 2).

We then examined whether treatment augmentation, the number of days spent in augmentation, the presence of comorbidity with anxiety disorders, the use of benzodiazepines and past wishes to die confounded the effect of treatment assignment on ESI in a Cox regression model. Time to suicidal ideation remained longer in patients assigned to SSRI compared to those assigned to IPT (HR=2.22, 95% CI 1.00-4.94, $p=0.05$), after adjusting for these variables. Of note, treatment-emergent suicidal ideation was, in 25 (25/231, 10.8%) participants, transient and was endorsed at one visit only. However, in 7 cases, ideation lasted for more than one week. When it persisted, it was successfully managed within the treatment protocol, with the exception of 2 patients who were discontinued from the study in order to receive a higher level of treatment.

In order to determine whether ESI was a unique signal or a proxy measure of depression overall worsening, we examined the change in total HDRS or QIDS scores from baseline to

ESI. Eighteen of the 32 patients with ESI had an increase in the severity of depression and 14 a decrease.

Worsening of suicidal ideation

Seven patients (11.7%) had a worsening of pre-existing suicidal ideation (a score of 3 on the HDRS or the QIDS suicidality item) during the first 4 months of acute treatment. When this occurred, 2 patients were in treatment with IPT, 1 with SSRI 4 with the combination (2 IPT + SSRI, 2 SSRI+IPT). Four of these patients completed the study, while a 28 year-old woman and a 30-year-old man were discontinued from the protocol and referred to higher level of treatment, and a 44 year-old man dropped out. There were no suicide attempts or completed suicides during the study.

Discussion

In this randomized controlled study, the rates of emergent suicidal ideation in adult patients with moderate to severe depression and no suicidal ideation at baseline were 18.8% in a treatment sequence beginning with IPT and 8.8% in a treatment sequence beginning with SSRI. These rates are consistent with previously published pharmacotherapy trials, in which ESI rates ranged between 4% to 20%.[4-11]. Also, consistent with Perlis et al.[5], we found that ESI tended to be transient and to occur during the first month of treatment in 40.6% of participants who experienced it. When suicidal ideation started during treatment, it was successfully managed within the treatment protocol and required referral to a higher level of care only in 2 cases.

Furthermore, augmentation of IPT with SSRI led to no greater incidence of emergent suicidal ideation than did augmentation of SSRI with IPT.

Of note, 57.4% of the overall sample with moderately severe depression did endorse thoughts of death at baseline and 13.7% had previously made a suicide attempt. In line with Perlis et al. [5] information about past suicidal thinking contributed to the prediction of suicidal ideation during the protocol in participants who had no suicidality at baseline; however, these investigators also found an increased risk of ESI in females, younger patients and in patients exhibiting insomnia, activation and anxiety during treatment with fluoxetine and Zisook et al. [9] reported that drug abuse, severe depression and melancholic features are additional risk factors in patients treated with citalopram. We did not confirm these findings. One of the reasons might be the small number of patients with ESI in the present protocol, compared with the above-mentioned studies, and the broader definition of emergent suicidal ideation used in the STAR*D study [9], that includes also feelings that life is empty and not worth leaving.

Our results suggest that the strategy of combining information from self-report and clinician-rated instruments improved the detection of cases with ESI. Moreover, on the occasions when both instruments indicated the presence of ESI, suicidal ideation had been previously endorsed on the self-report measure. Evidence from studies using self-reported and observer rated scales of depression [24,25] suggest moderate correlations between measures. Other studies demonstrated that demographic and clinical characteristics may be associated with underreporting or overreporting of suicidality. Interestingly, Seemuller [10] found that suicidality items from two different clinician-rated scales (HDRS and MADRS) actually identify a different number of cases with ESI. Our strategy tries to obviate the shortcoming of relying on one measure only.

The use of adjunctive lorazepam (or equivalent) for insomnia was allowed in the present protocol and was more frequent among patients treated with SSRI. This might have reduced

the anxiety levels or regulated the sleep of these participants, thereby lowering the risk of suicidal ideation in patients assigned to SSRI. However, our results indicate that even when use of benzodiazepines was controlled for, the IPT treatment strategy continued to be associated with a higher risk of suicidal ideation.

When we examined the change from baseline in total HDRS and QIDS scores in the 32 patients with ESI, we found that in 18 cases there was a global worsening of the scores and in 14 cases the increase in suicidal item occurred in the face of falling composite depression scores. Therefore, we submit that ESI is not necessarily a proxy of global worsening but may be in some cases a suicide-specific signal.

Although the absence of suicide attempts and completed suicides in both the SSRI and the IPT groups in our study prevents the drawing of any conclusions on the effects of the treatments on the risk of committing/attempting suicide, our findings indicate that suicidality was generally transient and only 4 patients who exhibited suicidal thoughts and plans needed to be referred to a higher level of care. Several factors may have contributed to this outcome, including the frequency of visits to the clinic (once a week during the acute phase, with the possibility of more frequent visits when necessary), specific attention to ensuring whenever possible that patients did not have access to lethal means (particularly large quantities of medication and firearms), the involvement of family members and friends through inclusion in patients' initial evaluation and in a psychoeducational workshop on depression and the goals of the study, and the availability of a phone emergency service that gave each patient the possibility of speaking with a study clinician (most often his/her own treating clinician) 24 hours a day. Although the protocol provided a safety net to all patients, those whose suicidal ideation worsened received an even higher level of attention, including extra visits and/or phone sessions, the prescription of medications to treat insomnia or anxiety, the possibility of adding the augmentation treatment (psychotherapy or SSRI pharmacotherapy) earlier than mandated by the study protocol and, if necessary, a referral to a higher level care.

Limitations

Generalization of our findings to settings or circumstances other than those in which our study was carried out should be made with caution. First, we excluded patients with psychotic depression, active suicidal ideation with plan, current alcohol or drug abuse, current eating disorders, and newly diagnosed and unstable physical illness. Still, the large portion of participants reporting some level of suicidal ideation at baseline or a past suicide attempt, the presence of 9% of patients with a HDRS-17 score in the 27 to 35 range at baseline, and the proportion of patients with recurrent illness at least partially mitigates concerns about the external validity of our findings. Second, we conducted a structured clinical interview (SCID) to exclude patients with bipolar disorder (including those with Bipolar Disorder NOS, who may be more difficult to diagnose correctly outside a research setting), thus reducing the risk of SSRI-induced mixed symptoms (usually associated with increased suicidality).

In conclusion, we submit that in the context of careful, measurement-based assessment and weekly contact with experienced clinicians both SSRI and IPT are safe treatments for patients with unipolar depression who report past suicide attempts, none of whom exhibited ESI during the present study. In this particular context we observed that, contrary to current concerns about the safety of SSRIs, they were actually associated with a lower risk of ESI than interpersonal psychotherapy.

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Figure 1. Participant flow

Fig. 2.
Kaplan-Maier estimates of time to suicidal ideation in patients assigned to IPT and those assigned to SSRI.

Table 1
Demographic and Clinical Characteristics of Study Participants

	Total (N=291)	IPT (N=149)	SSRI (N=142)	Test and p-value
Age, Mean (SD)	39.6 (12.1)	39.3 (12.7)	39.8 (11.4)	t = -0.38, p = 0.71
Gender F (%)	72.2	71.1	73.2	$\chi^2 = 0.16$, p = 0.690
Educational Level, Mean (SD)	13.8 (3.4)	14.1 (3.0)	13.5 (3.8)	t = 1.53, p = 0.13
Married or Living with Partner (%)	38.8	35.6	42.3	$\chi^2 = 1.37$, p = 0.24
Working Status (%)				
Employed	64.9	67.8	62.0	$\chi^2 = 2.71$, p = 0.44
Home Maker	9.3	6.7	12.0	
Unemployed	9.6	10.1	9.2	
Other	16.2	15.4	16.9	
Median # Children	1 [0-6]	1 [0-4]	0 [0-6]	z = -0.75, p = 0.45
Mean Age at Onset	27.6 (13.0)	27.5 (12.8)	27.8 (13.1)	t = -0.19, p = 0.85
Median # Depressive Episodes	2 [1-39]	2 [1-10]	3 [1-39]	z = -0.14, p = 0.89
17-item baseline Hamilton Rating Scale for Depression	20.1(4.0)	19.8 (4.0)	20.4 (4.1)	t = -1.31, p = 0.19
Median Duration of Illness (Years)	8.0 [0-51]	3.5 [0-47]	10.8 [0-51]	z = -5.32, p < 0.001
Any previous drug treatment, N (%)	187 (74.3)	93 (62.4)	94 (66.2)	$\chi^2 = 0.45$, p = 0.50
Mood Spectrum Assessments (MOODS-SR) Lifetime Depressive Component	33.7 (12.1)	33.6 (12.1)	33.9 (12.1)	t = -0.23, p = 0.82
Lifetime Manic Component	19.8 (10.6)	19.9 (11.3)	19.7 (10.0)	t = 0.17, p = 0.87
Anxiety Spectrum Assessments				
Lifetime OBS-SR	44.4 (24.4)	44.3 (23.7)	45.0 (25.3)	t = -0.25, p = 0.80
Lifetime PAS- SR	33.2 (19.9)	30.7 (18.8)	35.9 (20.7)	t = -2.24, p = 0.026
Lifetime SHY-SR	54.3 (36.6)	51.4 (34.6)	57.4 (38.5)	t = -1.40, p = 0.16

Cox regression model predicting the effect of treatment assignment, adjunctive treatments and past wishes to die on treatment emergent suicidal ideation.

Table 2

	b	SE(b)	Wald	df	p	Exp(b)	95.0% CI for Exp(b)	
							Lower	Upper
Treatment (IPT vs. SSRI)	.798	.408	3.837	1	.050	2.222	.999	4.939
Past wishes to die	.884	.373	5.609	1	.018	2.422	1.165	5.035
Comorbidity with anxiety disorders	.012	.368	.001	1	.974	1.012	.492	2.082
Benzodiazepines	.342	.381	.805	1	.370	1.407	.667	2.969
Adjunctive treatment with IPT or SSRI	-2.011	1.510	1.774	1	.183	.134	.007	2.582
Days with adjunctive treatment	.017	.020	.672	1	.412	1.017	.977	1.058