Effects of vilazodone on suicidal ideation and behavior in adults with major depressive disorder or generalized anxiety disorder: post-hoc analysis of randomized, double-blind, placebo-controlled trials

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Treatment-emergent suicidal ideation and behavior are ongoing concerns with antidepressants. Vilazodone, currently approved for the treatment of major depressive disorder (MDD) in adults, has also been evaluated in generalized anxiety disorder (GAD). Post-hoc analyses of vilazodone trials were carried out to examine its effects on suicidal ideation and behavior in adults with MDD or GAD. Data were pooled from vilazodone trials in MDD (four studies) and GAD (three studies). The incidence of suicide-related events was analyzed on the basis of treatment-emergent adverse event reporting and Columbia-Suicide Severity Rating Scale (C-SSRS) monitoring. Treatment-emergent suicidal ideation was analyzed on the basis of a C-SSRS category shift from no suicidal ideation/behavior (C-SSRS = 0) at baseline to suicide ideation (C-SSRS = 1–5) during treatment. In pooled safety populations (MDD, $n = 2233$; GAD, $n = 1475$), suicide-related treatment-emergent adverse events occurred in less than 1% of vilazodone-treated and placebo-treated patients. Incidences of C-SSRS suicidal ideation were as follows: MDD (vilazodone = 19.9%, placebo = 24.7%); GAD (vilazodone = 7.7%, placebo = 9.4%). Shifts from no suicidal ideation/behavior at baseline to suicidal ideation during treatment were as follows: MDD (vilazodone = 9.4%, placebo = 10.3%); GAD (vilazodone = 4.4%, placebo = 6.1%). Data from placebo-controlled studies indicate little or no risk of treatment-emergent suicidal ideation or behavior with vilazodone in adults with MDD or GAD. Nevertheless, all patients should be monitored for suicidal thoughts and behaviors during antidepressant treatment. *Int Clin Psychopharmacol* **32:281–288 Copyright © 2017 The Author (s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Many antidepressant medications are effective in treating the symptoms of major depressive disorder (MDD) and generalized anxiety disorder (GAD), but the issue of treatment-emergent suicidal ideation and behavior continues to be a concern. In a meta-analysis carried out by the US Food and Drug Administration (FDA) that was based on a reclassification of adverse events from antidepressant clinical trials, it was concluded that these medications were associated with a modest increase in the risk for suicidality in pediatric patients (Hammad *et al.*, 2006). These results contributed to the FDA's current requirement that all approved antidepressants carry a black-box warning of an increased risk for suicidal thoughts and behavior in children, adolescents, and young adults.

The FDA also requires clinical trials of new psychotropic drugs to include a prospective assessment of suicidal ideation and behavior using instruments such as the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner *et al.*, 2011). These instruments are generally more sensitive than reports of suicide-related treatment-emergent adverse events (TEAEs). Although such TEAE data are useful, patient reporting of TEAEs is not as comprehensive or as consistent as C-SSRS monitoring (Gassmann-Mayer *et al.*, 2011). The C-SSRS is an 11-category rating system that incorporates both individual patient responses and external sources (e.g. family, friends, health records) into the evaluation of a patient's suicide risk, thereby making it easier to identify potential concerns and distinguish between suicidal ideation and suicidal behavior (FDA, 2012).

These regulatory measures draw attention to a serious safety issue that warrants ongoing scrutiny, but there are some limitations and unintended consequences that should also be considered (Ho, 2012). First, several meta-analyses of clinical trial data have found no overall association between FDA-approved antidepressants and the emergence of suicidal ideation or behavior in adults, although some increase in risk has been observed in younger adults (≤24 years) (Khan *et al.*, 2003; Stone *et al.*, 2009; Gibbons *et al.*, 2012). In addition, an analysis of healthcare claims data found no significant increase in suicides or suicide attempts after initiation of antidepressant treatment; rather, the highest risk of suicide attempt occurred in the month before treatment initiation (Simon *et al.*, 2006). This finding, along with results from other claim-based analyses (Gibbons *et al.*, 2006; Gibbons *et al.*, 2007), points to the challenge of balancing the beneficial effects of antidepressants on suicidal thoughts and behaviors against the potential negative effects of these drugs. Finally, the FDA black-box warning may have contributed to an overall decline in the diagnosis and treatment of MDD (Libby *et al.*, 2009) and an increasing trend in adolescent suicides (Bridge *et al.*, 2008).

Ongoing efforts are needed to provide clinicians with information on the effects of antidepressants and other psychoactive drugs on suicidal ideation and behavior. Although clinical trial reports usually provide suicide-related results, such information may be limited as suicidal events are uncommon, particularly when trials specifically exclude patients with a current risk of suicide. Analysis of pooled data from multiple studies may provide a more robust approach for understanding the risk of treatment-emergent suicidal ideation and behavior. Therefore, a post-hoc analysis was carried out using suicide-related data from the clinical trials of vilazodone, a selective serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist that is approved by the FDA for the treatment of MDD in adults.

In addition to MDD trials (Rickels *et al.*, 2009; Khan *et al.*, 2011; Croft *et al.*, 2014; Mathews *et al.*, 2015), vilazodone has been investigated in adults with GAD (Gommoll *et al.*, 2015a, 2015b; Durgam *et al.*, 2016). Including both datasets in this post-hoc analysis provides an opportunity to evaluate the effects of vilazodone on suicidal ideation and behavior in two different patient populations, including subsets of younger adults (18–24 years).

Methods

Clinical studies

The vilazodone clinical trials are summarized in Table 1; detailed methods for all studies have been published previously. Five studies were carried out in adults with MDD, including four short-term (8 or 10 weeks), randomized, double-blind, placebo-controlled trials (Rickels *et al.*, 2009; Khan *et al.*, 2011; Croft *et al.*, 2014; Mathews *et al.*, 2015) and one long-term (52 weeks), open-label study (Robinson *et al.*, 2011). Three 8-week, randomized, double-blind, placebo-controlled studies were carried out in adults with GAD (Gommoll *et al.*, 2015a, 2015b; Durgam *et al.*, 2016). All studies were carried out in accordance with good clinical practice guidelines (FDA guidelines, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, and/or Declaration of Helsinki) and with the approval of the institutional review board for each study site.

Study participants

All participants in the vilazodone studies provided written and informed consent. Key eligibility criteria for the MDD studies included the following: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (DSM-IV-TR) criteria for MDD (APA, 2000); current major depressive episode with a duration of at least 4 weeks to up to 2 years (Rickels *et al.*, 2009; Khan *et al.*, 2011) or at least 8 weeks to up to 12 months (Croft *et al.*, 2014; Mathews *et al.*, 2015); 17-item Hamilton Depression Rating Scale ($HAMD_{17}$) total score ≥22 and item 1 (depressed mood) score ≥2 (Rickels *et al.*, 2009; Khan *et al.*, 2011); $HAMD_{17}$ total score ≥18 (Robinson *et al.*, 2011); and Montgomery-Åsberg Depression Rating Scale total score ≥26 (Croft *et al.*, 2014; Mathews *et al.*, 2015). Key eligibility criteria for all of the GAD studies (Gommoll *et al.*, 2015a, 2015b; Durgam *et al.*, 2016) included the following: DSM-IV-TR criteria for GAD; Hamilton Anxiety Rating Scale total score ≥20, item 1 (anxious mood) score ≥2, and item 2 (tension) score ≥2; Clinical Global Impressions-Severity of Illness score ≥4; and $HAMD_{17}$ total score ≤17.

For all MDD and GAD studies, patients with an axis I disorder other than the diagnosis required for eligibility (i.e. MDD or GAD for the respective studies) were not allowed to participate. In the GAD studies, patients who had comorbid depression were also excluded. Additional exclusion criteria included nonresponse to two or more previous antidepressants after adequate treatment duration at recommended doses and suicide risk on the basis of one or more of the following criteria: investigator judgment, previous suicide attempt, C-SSRS score, Montgomery-Åsberg Depression Rating Scale item 10 (suicidal thoughts) score ≥5, and/or $HAMD_{17}$ item 3 (suicide) score ≥3.

Assessments and analyses

Study populations included in the present post-hoc analyses are as follows: the pooled MDD safety population, defined as all randomized patients in the four short-term MDD studies who received at least one dose of double-blind study medication and had at least one postbaseline safety assessment; the long-term MDD safety population, defined as all patients in the long-term

Table 1 Summary of vilazodone clinical trials

	Treatment duration	Safety population	C-SSRS available
MDD Study 1			
NCT00285376 (Rickels *et al.*, 2009)	8 weeks Double-blind	Placebo ($n = 204$) Vilazodone 40 mg/day ($n = 205$)	No
MDD Study 2			
NCT00683592 (Khan *et al.*, 2011)	8 weeks Double-blind	Placebo ($n = 233$) Vilazodone 40 mg/day ($n = 235$)	Yes
MDD Study 3			
NCT01473394 (Croft *et al.*, 2014)	8 weeks Double-blind	Placebo ($n = 253$) Vilazodone 40 mg/day ($n = 255$)	Yes
MDD Study 4			
NCT01473381 (Mathews *et al.*, 2015)	10 weeks Double-blind	Placebo ($n = 281$) Vilazodone 20 mg/day ($n = 288$) Vilazodone 40 mg/day ($n = 287$)	Yes
MDD Study 5			
NCT00644358 (Robinson *et al.*, 2011)	52 weeks Open-label	Vilazodone 40 mg/day ($n = 599$)	Yes
GAD Study 1			
NCT01629966 (Gommoll *et al.*, 2015a)	8 weeks Double-blind	Placebo ($n = 221$) Vilazodone 20 mg/day ($n = 227$) Vilazodone 40 mg/day ($n = 225$)	Yes
GAD Study 2			
NCT01766401 (Gommoll *et al.*, 2015b)	8 weeks Double-Blind	Placebo ($n = 198$) Vilazodone 20–40 mg/day ($n = 200$)	Yes
GAD Study 3			
NCT01844115 (Durgam *et al.*, 2016)	8 weeks Double-blind	Placebo ($n = 202$) Vilazodone 20–40 mg/day ($n = 202$)	Yes

C-SSRS, Columbia-Suicide Severity Rating Scale; GAD, generalized anxiety disorder; MDD, major depressive disorder.

MDD study who received at least one dose of open-label study medication and had at least one postbaseline safety assessment; and the pooled GAD safety population, defined as all randomized patients in the three short-term GAD studies who received at least one dose of double-blind study medication and had at least one postbaseline safety assessment.

Suicidal ideation and suicidal behavior were monitored on the basis of adverse event reporting (all studies) and C-SSRS responses [all studies except one short-term MDD trial (Rickels *et al.*, 2009)]. The incidence of suicide-related TEAEs was analyzed descriptively in the pooled safety populations (MDD, GAD) and in the long-term MDD population. MedDRA terms for suicide-related TEAEs included completed suicide, depression suicidal, intentional overdose (or overdose), intentional self-injury, multiple-drug overdose intentional, poisoning deliberate, self-injurious behavior, self-injurious ideation, suicidal behavior, suicidal ideation, and suicide attempt.

Suicidal ideation on the basis of C-SSRS data was defined as a 'yes' response to any one of the five suicidal ideation questions (categories 1–5 of the C-SSRS); suicidal behavior was defined as a 'yes' response to any one of the five suicidal behavior questions (categories 6–10 of the C-SSRS). Suicidal ideation or behavior (overall suicidality) was defined as a 'yes' response to any one of the 10 suicidal ideation or behavior questions (categories 1–10 of the C-SSRS). A score of zero was assigned if no ideation or behavior was present, as indicated by a 'no' response to all 10 C-SSRS ideation or behavior questions.

The incidences of C-SSRS suicidal ideation and suicidal behavior were analyzed descriptively in the overall pooled safety populations. However, to explore whether age was a potential risk factor for overall suicidality (C-SSRS = 1–10) and suicidal behavior (C-SSRS = 6–10), odds ratios (ORs) with 95% confidence intervals (CIs) for vilazodone versus placebo were calculated in subgroups of patients categorized by age (18–24 and ≥ 25 years) in the pooled MDD and GAD safety populations.

Shift analyses were carried out on the basis of the following C-SSRS categories: no suicidal/ideation behavior (C-SSRS = 0); suicidal ideation (C-SSRS = 1–5); and suicidal behavior (C-SSRS = 6–10). Worsening was defined as a shift from a less severe to a more severe C-SSRS category (e.g. from suicidal ideation at baseline to suicidal behavior at any time during double-blind treatment). Improvement was defined as a shift from a more severe to a less severe C-SSRS category (e.g. from suicidal ideation at baseline to no suicidal ideation during treatment). No change was defined as no shift in categories (e.g. no suicidal ideation at baseline and during treatment).

Results

Patient characteristics

In the pooled safety populations, baseline characteristics were similar between the vilazodone and the placebo groups (Table 2).

Suicide-related adverse events

No completed suicides occurred during any of the MDD or GAD studies. The incidence of suicide-related

Table 2 Baseline characteristics (pooled safety populations)

	Pooled MDD studies		Pooled GAD studies	
	Placebo ($n=967$)	Vilazodone ($n=1266$)	Placebo ($n=621$)	Vilazodone ($n=854$)
Age [mean (SD)] (years)	41.5 (12.9)	40.6 (12.6)	40.2 (13.4)	40.1 (13.3)
Women [*n* (%)]	551 (57.0)	727 (57.4)	411 (66.2)	563 (65.9)
White race [*n* (%)]	711 (73.5)	941 (74.3)	487 (78.4)	656 (76.8)
BMI [mean (SD)] (kg/m^2)	29.4 (6.1)	29.1 (6.5)	27.9 (5.4)	28.2 (5.5)
Age at disease onset [mean (SD)] (years)	31.2 (13.8)	30.7 (13.2)	27.1 (14.2)	26.8 (14.2)
C-SSRS suicidal ideation/behavior (*n*)[a]	767	1065	621	854
Lifetime suicidal ideation or behavior [*n* (%)]	379 (49.4)	556 (52.2)	190 (30.6)	266 (31.1)
Lifetime suicidal ideation [*n* (%)]	378 (49.3)	550 (51.6)	186 (30.0)	265 (31.0)
Lifetime suicidal behavior [*n* (%)]	111 (14.5)	169 (15.9)	54 (8.7)	78 (9.1)

Suicidal ideation/behavior was defined as follows: ideation or behavior, endorsement of any C-SSRS category (1–10); ideation, endorsement of any C-SSRS ideation category (1–5); behavior, endorsement of any C-SSRS behavior category (6–10). For this analysis, patients could have reported both ideation and behavior.
C-SSRS, Columbia-Suicide Severity Rating Scale; GAD, generalized anxiety disorder; MDD, major depressive disorder.
[a]C-SSRS lifetime history was not collected in one MDD study (Rickels *et al.*, 2009).

Table 3 Incidence of suicide-related treatment-emergent adverse events (safety populations)

	Pooled MDD studies [*n* (%)]		Pooled GAD studies [*n* (%)]		Long-term MDD study [*n* (%)]
TEAE[a]	Placebo ($n=967$)	Vilazodone ($n=1266$)	Placebo ($n=621$)	Vilazodone ($n=854$)	Vilazodone ($n=599$)
Suicidal ideation	5 (0.5)	3 (0.2)	2 (0.3)	3 (0.4)	5 (0.8)
Suicide attempt	0	2 (0.2)[b]	0	0	1 (0.2)[c]
Intentional self-injury	1 (0.1)	0	0	0	1 (0.2)
Intentional overdose	0	1 (<0.1)	0	0	1 (0.2)[d]

GAD, generalized anxiety disorder; MDD, major depressive disorder; TEAE, treatment-emergent adverse event.
[a]MedDRA preferred terms.
[b]One attempt includes the one patient with intentional overdose (sleeping medication). Although the other attempt also involved an overdose (acetaminophen), the event was not classified by the study investigator as an 'intentional overdose'.
[c]Includes the one patient with intentional self-injury (choking).
[d]Intentional overdose with diet pills.

TEAEs was similar between the placebo and the vilazodone groups in each of the pooled safety populations (Table 3). In the short-term MDD studies, suicide attempt was reported as a TEAE in two vilazodone-treated patients; both attempts were also classified as on-therapy serious adverse events. These included a 20-year-old woman with an overdose of acetaminophen, who had hospital records of self-injurious behavior, but had denied any history of suicide attempt, and a 56-year-old woman with intentional overdose of sleeping medication, who stated that she had not intended to commit suicide. The long-term MDD study included one TEAE of suicide attempt (also classified as an on-therapy serious adverse event), reported in a 21-year-old man who attempted to choke himself (intentional self-injury), but aborted the attempt after calming himself down. One intentional overdose was also reported in a 31-year-old woman who ingested a combination of diet pills. Each of these patients was discontinued from his or her respective study. None of the suicide-related TEAEs were judged by the investigator as related to the study drug.

Columbia-Suicide Severity Rating Scale suicidal ideation and behavior

In the short-term studies, C-SSRS suicidal ideation and behavior occurred more frequently in the pooled MDD population than in the pooled GAD population (Table 4). In both pooled study populations, the incidence of any C-SSRS suicidal ideation or behavior was lower in the vilazodone group than in the placebo group.

Analyses in younger and older patients (18–24 and ≥ 25 years of age, respectively) suggested that younger age was not a risk factor for overall suicidality (C-SSRS = 1–10) or suicidal behavior (C-SSRS = 6–10) in the short-term studies (Fig. 1). In the MDD studies, the incidence of overall suicidality and suicidal behavior was lower in vilazodone-treated than in placebo-treated patients, irrespective of age. All ORs for these outcomes were less than 1, with the corresponding 95% CIs overlapping 1.00 (indicating no significant difference between vilazodone and placebo), except for the lower odds of overall suicidality with vilazodone relative to placebo in older patients (OR = 0.77, 95% CI = 0.61–0.98). In the GAD studies, the odds for overall suicidality and suicidal behavior were higher with vilazodone versus placebo in younger patients and lower with vilazodone versus placebo in older patients; however, 95% CIs for the ORs indicated that none of these outcomes were significant.

In the long-term, open-label MDD study, the incidence of C-SSRS suicidal ideation generally decreased over

Table 4 Columbia-Suicide Severity Rating Scale suicidal ideation and behavior during double-blind treatment

	Pooled MDD studies		Pooled GAD studies	
	Placebo ($n=765$)	Vilazodone ($n=1056$)	Placebo ($n=618$)	Vilazodone ($n=846$)
Any C-SSRS suicidal ideation[a]	189 (24.7)	210 (19.9)	58 (9.4)	65 (7.7)
Maximum suicidal ideation score [*n* (%)]				
1: wish to be dead	115 (15.0)	144 (13.6)	34 (5.5)	39 (4.6)
2: nonspecific active suicidal thoughts	22 (2.9)	25 (2.4)	7 (1.1)	15 (1.8)
3: active suicidal ideation with methods but no plan or intent to act	35 (4.6)	29 (2.7)	12 (1.9)	7 (0.8)
4: active suicidal ideation with no plan but some intent to act	14 (1.8)	10 (0.9)	4 (0.6)	3 (0.4)
5: active suicidal ideation with specific plan and intent to act	3 (0.4)	2 (0.2)	1 (0.2)	1 (0.1)
Any C-SSRS suicidal behavior[b]	28 (3.7)	22 (2.1)	8 (1.3)	10 (1.2)
Maximum suicidal behavior score [*n* (%)]				
6: preparatory acts or behavior	1 (0.1)	3 (0.3)	2 (0.3)	0
7: aborted attempt	11 (1.4)	8 (0.8)	2 (0.3)	2 (0.2)
8: interrupted attempt	13 (1.7)	8 (0.8)	4 (0.6)	6 (0.7)
9: actual (nonfatal) suicide attempt	3 (0.4)	3 (0.3)	0	2 (0.2)
10: completed suicide	0	0	0	0

C-SSRS, Columbia-Suicide Severity Rating Scale; GAD, generalized anxiety disorder; MDD, major depressive disorder; *n*, number of patients with at least 1 postbaseline C-SSRS assessment.
[a]Patients were only counted once on the basis of their most severe suicidal ideation score (C-SSRS category 1–5).
[b]Patients were only counted once on the basis of their most severe suicidal behavior score (C-SSRS category 6–10).

time, with 0 to less than 1% of patients reporting serious suicidal ideation (C-SSRS = 4 or 5) (Nilsson *et al.*, 2013) at all study visits (Fig. 2). C-SSRS suicidal behavior (C-SSRS = 6–10) was reported by six patients during the first week of treatment, three patients at an unscheduled study visit, and four patients at an early termination visit.

Columbia-Suicide Severity Rating Scale category shifts

Among patients in the pooled MDD and GAD safety populations with no suicidal ideation or behavior at baseline (C-SSRS = 0), more than 85% continued to have no suicidal ideation or behavior during double-blind treatment (Table 5). The percentage of patients who worsened to any suicidal ideation (C-SSRS = 1–5) or any suicidal behavior (C-SSRS = 6–10) was similar between the vilazodone and the placebo groups.

The majority of patients who had any suicidal ideation at baseline were in the lowest ideation category [C-SSRS = 1 (wish to be dead): MDD, 71.2% (250/351); GAD, 71.0% (44/62)]. Among patients with suicidal ideation at baseline, ~30% or more improved to no suicidal ideation during double-blind treatment, with the highest rate of improvement found in GAD patients who received vilazodone (44.7%). Some patients experienced worsening from suicidal ideation to suicidal behavior; this occurred more frequently in the GAD studies (vilazodone, 5.3%; placebo, 8.3%) than in the MDD studies (vilazodone, 1.1%; placebo, 1.8%).

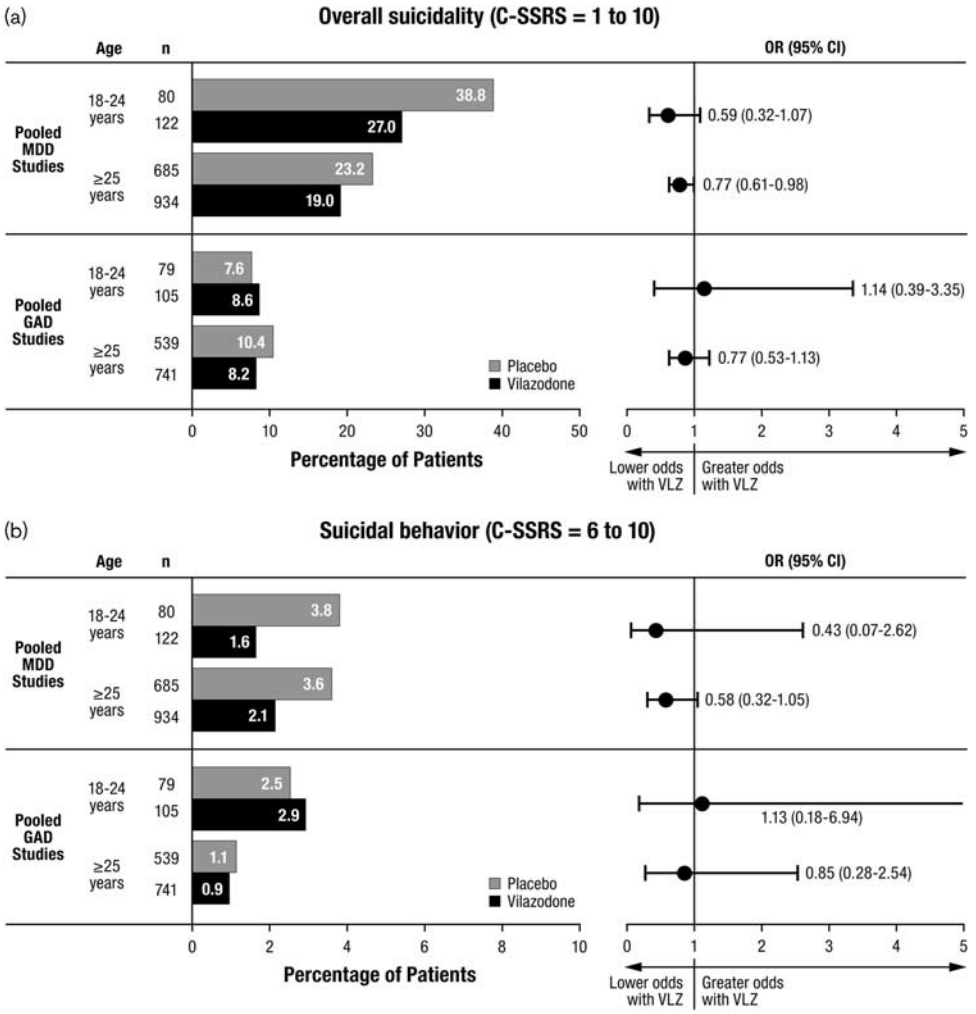
Discussion

In this post-hoc analysis of data pooled from seven short-term (8 or 10 weeks), double-blind, placebo-controlled trials, vilazodone was found to have similar or smaller effects on suicide-related events than placebo. Results from a 52-week, open-label study in adults with MDD did not show an increased risk of suicidal ideation or behavior with longer vilazodone treatment.

In the pooled MDD and GAD safety populations, suicide-related TEAEs (suicidal ideation, suicide attempt, intentional self-injury, intentional overdose) occurred in less than 1% of patients in the vilazodone and placebo groups. Both populations had higher incidences of C-SSRS suicidal ideation and suicidal behavior, which was expected as regular administration of the C-SSRS is a more sensitive method for detecting suicide-related events than spontaneous reporting of TEAEs by patients. The incidence of C-SSRS suicidal ideation during treatment was higher in the pooled MDD population (vilazodone and placebo groups combined, 21.9%) than in the pooled GAD population (8.4%). Such results were not unexpected, given the lifetime histories of suicidal ideation and behavior in these studies (Table 1) and the higher 12-month prevalence of suicidal ideation seen with MDD (39% to 42%) compared with GAD (12%) in the USA general population (Kessler *et al.*, 2005).

C-SSRS suicidal ideation occurred less frequently with active treatment than with placebo both in the pooled MDD population (vilazodone, 19.9%; placebo, 24.7%) and in the pooled GAD population (vilazodone, 7.7%; placebo, 9.4%). The incidence of C-SSRS suicidal behavior was also lower with vilazodone relative to placebo in the pooled MDD population (vilazodone, 2.1%; placebo, 3.7%). In the pooled GAD population, the incidence of suicidal behavior was similarly low in both treatment groups (vilazodone, 1.2%; placebo, 1.3%). Along with the C-SSRS shift analyses, which showed higher rates of improvement with vilazodone relative to placebo in GAD and MDD patients with suicidal ideation at baseline (Table 5), these lower incidences of C-SSRS suicidal ideation and behavior with vilazodone

Fig. 1



Overall suicidality and suicidal behavior in younger and older adults. Analyzed in patients from the pooled safety population who had at least one available postbaseline C-SSRS assessment, with incidence on the basis of each patient's maximum C-SSRS score during double-blind treatment. Overall suicidality (a) was defined as an endorsement of any suicidal ideation or behavior category (maximum C-SSRS score of 1–10). Suicidal behavior (b) was defined as an endorsement of any suicidal behavior category (maximum C-SSRS score of 6–10). CI, confidence interval; C-SSRS, Columbia-Suicide Severity Rating Scale; GAD, generalized anxiety disorder; MDD, major depressive disorder; OR, odds ratio; VLZ, vilazodone.

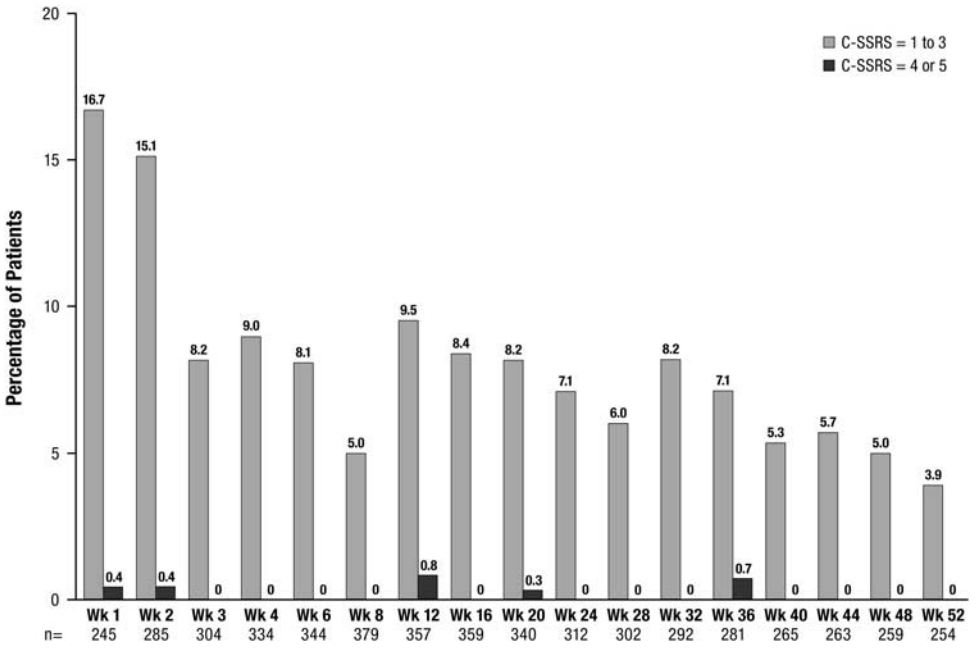
relative to placebo are consistent with other studies that have shown approved antidepressants to have protective effects on suicidality in adults (Barbui *et al.*, 2009; Gibbons *et al.*, 2012). It should be noted, however, that the high rate of improvement observed with vilazodone in the C-SSRS shift analysis of GAD studies (44.7%) was based on relatively small numbers of patients (vilazodone, $n = 38$; placebo, $n = 24$) and this outcome should be interpreted with some caution.

As some increased risk of suicidality among younger adults has been found in other antidepressant trials (Stone *et al.*, 2009), post-hoc analyses of overall suicidality and suicidal behavior were carried out using data from younger adults (18–24 years) who participated in the vilazodone studies. These patients represented ~10 and 15% of the pooled MDD and GAD populations, respectively. In the MDD studies, younger patients had lower odds with vilazodone relative to placebo for both overall suicidality (OR = 0.59) and suicidal behavior (OR = 0.43). In the GAD studies, however, the odds among younger patients were slightly higher with vilazodone versus placebo for overall suicidality (OR = 1.14) and suicidal behavior (OR = 1.13). For all of these outcomes, however, the 95% CI had a lower limit less than 1 and a higher limit greater than 1, indicating no significant difference between vilazodone and placebo in younger adults.

Limitations

The primary limitation of this post-hoc analysis is that the studies excluded patients who fulfilled any of the criteria for suicide risk. In addition, patients with comorbid

Fig. 2



Incidence of C-SSRS suicidal ideation by visit (long-term major depressive disorder study population). All patients in this study were treated with open-label vilazodone. Analysis carried out in patients who had an available C-SSRS assessment at the relevant study visit. No patient was counted more than once per study visit. C-SSRS, Columbia-Suicide Severity Rating Scale; Wk, week.

Table 5 Columbia-Suicide Severity Rating Scale category shifts[a]

	Pooled MDD studies [*n* (%)]		Pooled GAD studies [*n* (%)]	
	Placebo	Vilazodone	Placebo	Vilazodone
No suicidal ideation/behavior at baseline (*n*)	572	827	586	788
No category change	508 (88.8)	747 (90.3)	545 (93.0)	742 (94.2)
Worsened to suicidal ideation	59 (10.3)	78 (9.4)	36 (6.1)	35 (4.4)
Worsened to suicidal behavior	5 (0.9)	2 (0.2)	5 (0.9)	11 (1.4)
Suicidal ideation at baseline (*n*)	164	187	24	38
No category change	107 (65.2)	116 (62.0)	15 (62.5)	19 (50.0)
Worsened to suicidal behavior	3 (1.8)	2 (1.1)	2 (8.3)	2 (5.3)
Improved to no ideation	54 (32.9)	69 (36.9)	7 (29.2)	17 (44.7)

Categories were defined as follows: no suicidal ideation/behavior (C-SSRS ideation score = 0); suicidal ideation (endorsement of any C-SSRS ideation question); suicidal behavior (endorsement of any C-SSRS behavior question). Category shifts were based on each patient's maximum C-SSRS score during double-blind treatment.
C-SSRS, Columbia-Suicide Severity Rating Scale; GAD, generalized anxiety disorder; MDD, major depressive disorder.
[a]Analyzed in patients from the pooled safety populations who had an available baseline and ≥ 1 available postbaseline C-SSRS assessment.

depression and anxiety were not allowed in any of the studies, which may have had an effect on the current post-hoc analyses. As shown previously in studies with MDD (Trivedi *et al.*, 2013) and GAD (Bomyea *et al.*, 2013), patients who have both disorders are at an increased risk for suicidality. Given the exclusion criteria of the individual studies, the results of this post-hoc analysis may not be generalizable to a broader adult patient population. Another potential limitation is that in addition to the analyses carried out in younger patients, no adjustments were made for sociodemographic and clinical factors that have been associated with suicidal ideation, such as lower education level, sex (male), unemployment, previous suicide attempt, greater depression symptom severity, and number of depressive episodes (Trivedi *et al.*, 2013). More studies are needed to explore the effects of these factors on suicide-related outcomes in patients treated with antidepressants.

Conclusion

Little or no evidence of treatment-emergent suicidal ideation or behavior was found in patients with MDD or GAD who received vilazodone in double-blind, placebo-controlled trials. Among patients who entered these studies with no recent suicidal ideation or behavior at baseline, more than 85% continued to have no suicidality during treatment. During the double-blind treatment, the incidences of suicide-related events, whether

assessed on the basis of patient-reported adverse events or regular C-SSRS monitoring, were similar or lower with vilazodone than with placebo. In a 52-week, open-label study of vilazodone in MDD patients, the incidence of suicidal ideation decreased over time, with serious suicidal ideation (C-SSRS = 4 or 5) occurring in 0 to less than 1% of patients at all study visits. The potential risk for treatment-emergent suicidality was low with vilazodone, irrespective of age or psychiatric diagnosis. However, as is the case with all antidepressants, continued monitoring of suicidal thoughts and behaviors is recommended in all patients who receive this treatment.

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Conflicts of interest

M.E. Thase declares a potential conflict of interest in his role as advisor or consultant for the following companies: Alkermes Inc.; Allergan; AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Cerecor Inc.; Fabre-Kramer Pharmaceuticals Inc.; Forest Laboratories Inc. (an Allergan affiliate); Gerson Lehrman Group; GlaxoSmithKline; Guidepoint Global LLC; Eli Lilly and Company; H. Lundbeck A/S; MedAvante (an Allergan affiliate); Merck & Co. Inc.; Moksha8 Pharmaceuticals Inc.; Naurex Inc.; Neuronetics; Novartis Pharmaceuticals Corporation; Ortho-McNeil-Janssen Pharmaceuticals Inc.; Otsuka Pharmaceutical Co. Ltd; Pamlab Inc.; Pfizer Inc.; Shire; Sunovion Pharmaceuticals Inc.; Trius Therapeutics; and Takeda Pharmaceuticals North America Inc. Dr Thase has received grants for clinical research from: Alkermes Inc.; AssureRx Health Inc.; Avanir Pharmaceuticals; Forest Laboratories Inc.; Janssen Pharmaceuticals Inc.; Otsuka Pharmaceutical Co. Ltd. He owns stock, stock options, or bonds in MedAvante. J. Edwards, S. Durgam, C. Chen, C.-T. Chang, and C.P. Gommoll acknowledge a potential conflict of interest as full-time employees of Allergan. M. Mathews was a full-time employee of Forest Research Institute, an Allergan affiliate, at the time of the studies.

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