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Featured Article

Suicidal ideation and behavior assessment in dementia studies: An Internet survey

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Abstract

Introduction: The AARR task force on suicidal ideation and behavior (SI/SB) in dementia conducted an online survey on the extent of SI/SB in individuals diagnosed with mild cognitive impairment (MCI) or dementia who were participating in clinical trials.

Methods: Investigators with experience in conducting SI/SB assessments in clinical trial subjects with MCI or dementia were invited to complete a global 19-item online survey.

Results: A total of 204 evaluable responses were collected with the majority from North America and Europe (83.4%) and the remainder from Asia, Latin America, and Mideast/Africa. The mean (SD) number of subjects personally assessed by the respondents in the past year with MCI, mild-moderate dementia, or severe dementia was 12.8 (26.2), 31.2 (39.6), and 10.1 (34.7), respectively. The mean number of subjects in each diagnostic group with suicidal ideation (SI), suicidal behavior (SB), or completed suicide (CS) was on average quite low (0.3 to 1.1 for SI, 0.1 to 0.2 for SB, and 0.0 to 0.2 for CS). Confidence in subject self-reports of SI/SB over different time periods declined with increasing severity of cognitive impairment and with increasing duration of the recall time period assessed. Of respondents, 56% and 75% had low confidence in self-ratings of SI/SB from subjects with severe dementia over the past 24 hours and the past week to 1 month, respectively. Ratings of the reliability of information collected on SI/SB also decreased with increasing severity of cognitive impairment. Approximately 70% of respondents rated the reliability of the information they obtained from all sources (patient, caregiver, and others) for subjects with MCI as high, but only about half (42.0% to 55.3%) and less than a quarter (17.4% to 24.3%) rated the reliability of information obtained for subjects with mild to moderate dementia or severe dementia as high, respectively.

Discussion: These results support the usefulness of prospective SI/SB assessments in MCI and mild dementia, raise questions about the reliability of assessments in moderate dementia, and confirm their lack of clinical utility in severe dementia. The results highlight the need for development of validated assessment instruments adapted to the stage of cognitive decline of the patients under study and may be the most effective in the earliest stages of the disease.

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Keywords: Prospective assessment of suicidal ideation and behavior in dementia; Suicidal ideation and behavior in dementia clinical trials; C-SSRS in dementia trials

1. Introduction

In August 2012, the Food and Drug administration (FDA) issued a revised draft guidance requiring the prospective assessment of suicidal ideation and suicidal behavior (SI/SB) in clinical studies of drugs being developed for CNS indications [1,2]. The guidance indicated that for CNS drug trials, prospective monitoring for SI/SB should be done in all patients in all studies with a few exceptions (such as studies in severe dementia). The guidance also recommended the use of the Columbia-Suicide Severity Rating Scale (C-SSRS) as the preferred instrument for prospective assessment of SI/SB, while noting that other instruments could be acceptable if shown to be valid and to reliably map potential suicide-related events to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) [3,4].

In practice, since the emergence of the guidance, the C-SSRS has been widely used for the assessment of SI/SB in clinical trials of patients with mild cognitive impairment (MCI)/pre-dementia, mild or moderate Alzheimer's disease (AD), and other dementias, despite the fact that neither it nor any other SI/SB assessment instrument has been demonstrated to be reliable and valid when used in patients with dementia.

After the issuance of the FDA guidance, the Alzheimer's Association Research Roundtable formed the Task Force on Suicidal Ideation and Behavior in Persons with Dementia Spectrum Conditions, comprised of representatives from industry, academia, advocacy organizations, and regulatory agencies. (AARR Task Force members: Larry Alphs (Chair–SIB Task Force), Janssen Alzheimer's Immunotherapy (JAI); Robert Brashear, JAI; Phillip Chappell, Pfizer; Yeates Conwell, University of Rochester; Sarah DuBrava, Pfizer; Dean Hartley, Alzheimer's Association; Ni Aye Khin, Food and Drug Administration (FDA); Nick Kozauer, FDA; David Miller, Bracket; Rachel Schindler, Pfizer (Chair of AARR); Eric Siemers, Eli Lilly & Co; Michelle Stewart, Pfizer; Kristine Yaffe, UCSF.) Key questions and issues considered by the task force include: the epidemiology of SI/SB in AD and other dementias; the cause of suicidal ideation in these conditions; the impact of stage and severity of cognitive impairment on the incidence of SI/SB; what assessment tools are available and what is their validity when used in dementia patients; how can new instruments more sensitive to the stage of illness be developed; how best to conduct SI/SB assessments in clinical trials of dementia patients to minimize bias and negative impact; and what is the preferred methodology and approach to the evaluation of signal detection of SI/SB in dementia clinical trials [5].

In recognition of the lack of any published information on the use of SI/SB tools in dementia clinical trials, the task force developed and conducted an online survey of the assessment of SI/SB in participants enrolled in clinical trials of AD and other forms of dementia. The goal of the survey was to obtain information on the extent of SI/SB in cognitively impaired individuals participating in clinical trials and the challenges and hurdles encountered by investigators in conducting SI/SB assessments in this patient population.

2. Methods

2.1. Survey questionnaire development

A subcommittee of the AARR SI/SB Task Force identified potential challenges and issues in the conduct of SI/SB assessments in clinical studies of patients with cognitive impairment, based on anecdotal reports and discussion with key stakeholders. Based on this input, a total of 19 items were developed for inclusion in the survey.

To complete the survey, a person needed to have personally conducted SI/SB assessments during the course of clinical trials; otherwise, the survey was terminated.

Items assessed information related to the demographics, background, and clinical experience of respondents and operational aspects of SI/SB assessment; and asked respondents to rate their level of confidence in subject self-reports of SI/SB and the reliability of the information obtained. Respondents also rated the level of patient and caregiver acceptance of SI/SB assessments as well as how helpful prospective assessments of SI/SB were in identifying patients at risk. A final open-ended question invited respondents to provide any additional comments, they wished on the issue of prospective assessment of SI/SB in patients with MCI or dementia.

The survey was beta-tested by several experts in the field external to the working group before being finalized and implemented online.

2.2. Sample identification

Sites were invited to participate in the survey using lists of e-mail addresses provided by Bracket, Inc and the Alzheimer's Association. The e-mail list obtained from Bracket, Inc. was developed from a previous survey sponsored by the International Society for CNS Clinical Trials and Methodology, which identified sites that had participated in clinical studies of AD or other dementias (approximately 95% of sites had participated in AD trials) in the last 2 years [6]. The Alzheimer's Association email list consisted of physicians who are members of the International Society to Advance Alzheimer's Research and Treatment.

The survey was sent to 2160 e-mail addresses using the services of the software company Convio. A letter

accompanying the e-mail invitation summarized the goals of the survey and stated that the site should have only one person complete the survey and that the person completing the survey should be someone who had personally conducted SI/SB assessments during the course of clinical trials. The data were collected in March 2013 using an online survey instrument, Survey Gizmo.

2.3. Data analysis

All available data were included in the initial evaluation. In cases of multiple responses from the same IP address, only the last response was used in the final analysis. Continuous variables were summarized using descriptive summary statistics. Categorical variables were summarized using frequency and percent. Summaries were evaluated for potentially questionable extreme values, and if found, summarizations were repeated with and without potentially erroneous data. A qualitative review and categorization of open-ended text responses were performed.

A copy of the survey can be found in the Supplementary Material.

3. Results

3.1. Overall response rate

A total of 362 responses were collected over the 4-week period of the survey (for a response rate of 362 of 2160 or 16.8%). When duplicate responses from sites were eliminated (retaining only the last response from each IP address), there remained a total of 296 responses, each from a unique site. Respondents who had not personally conducted SI/SB assessments were excluded from further analysis, leaving a final evaluable sample of 204 responses.

3.2. Characteristics of respondents

By background training, most of the respondents were psychologists (26.0%), psychiatrists (21.2%), neurologists (19.6%), or nurses (16.2%). In terms of the role of the respondents at their site, raters comprised most of the respondents (37.3%), followed by principal investigators (26.5%), sub-investigators (14.7%), and site coordinators (13.7%). Most of the responses originated from North America (39.1%) and Western Europe (32.3%), with less representation from other regions (Eastern Europe = 12.0%, Asia = 10.4%, Latin America = 5.2%, and Mideast/Africa = 1.0%).

3.3. Clinical experience of respondent sites

Overall, sites reported substantial experience in the conduct of clinical trials in cognitively impaired subjects. The mean number of trials per site over the past 2 years was 1.8 trials in MCI (range, 0–40), 5.2 in mild-moderate dementia (range, 0–50), and 1.1 in severe dementia (range, 0–50); sites also reported conducting an average of 2.8 studies in other diagnoses over the same time period (range, 0–30). Estimates of the number of subjects studied were also substantial. The mean number of cognitively impaired subjects studied per site per diagnostic category was 17.5 (range, 0–400) in MCI, 34.6 (range, 0–325) in mild-moderate AD, and 7.9 (range, 0–300) in severe AD subjects.

Sites reporting the highest number of trials and subjects studied (>3 standard deviation [SD] from the mean) were distributed across most of the geographic regions included in the sample (North America, 8; Western Europe, 8; Asia, 4; Eastern Europe, 1). In some instances, the number of subjects appeared to be disproportionate to the number of clinical trials reported (e.g., a respondent from China reported having studied 300 subjects with severe AD while participating in only 1 clinical trial of severe AD). The largest numbers of studies (40 MCI, 50 mild to moderate AD, and 50 severe AD) were reported by respondents from sites in China and Korea, reflecting the experience of very large specialized clinics serving a large population of subjects with cognitive impairment.

Respondents were asked to provide estimates of the number of subjects they had personally assessed in the past year and how many of those subjects had reported SI or SB or had died by completed suicide (CS). SI was referred to in the survey as "suicidal thinking" but was not further defined so could have included both passive and active suicidal thoughts. SB was defined as including actual attempts, aborted, or interrupted attempts, and preparatory acts toward an imminent attempt [2]. Nonsuicidal self-injurious behaviors were excluded. The data are summarized in Table 1.

In patients personally assessed by the respondents in the past year, the mean (SD) number of patients with SI was 0.3 (1.1) in MCI, 1.1 (3.2) in mild-moderate dementia, and 0.5 (2.4) in severe dementia. The mean (SD) number of patients with SB was 0.1 (0.7) in MCI, 0.2 (0.6) in mild-moderate dementia, and 0.1 (0.8) in severe dementia. One CS was reported in a total of 2307 MCI patients, 3 CSs in a total of 5584 patients with mild-moderate dementia, and none in a total of 1780 patients with severe dementia.

3.4. Operational aspects of SI/SB interviews

Most of the respondents reported interviewing both the subject and the caregiver in performing the SI/SB assessment (68.7% of respondents in MCI, 89.0% in mild-moderate AD, and 75.0% in severe AD). In the case of MCI, 30.6% of respondents only interviewed the subject, whereas 18.1% of respondents only interviewed the subject in the case of subjects with severe AD.

Among respondents who interviewed both the subject and the caregiver (N = 101 to 136), the majority indicated that discrepancies between the subject and caregiver reports occurred never or only occasionally in subjects with MCI (69.3%) or mild to moderate AD (70.1%). About half of the respondents (47.2%) reported that subject and caregiver

Table 1
Summary statistics for subjects personally assessed by survey respondent in the past year*

	Statistic	Number assessed	Number with SI	Number with SB	Completed suicides
MCI	Mean (SD)	12.8 (26.2)	0.3 (1.1)	0.1 (0.7)	0.005 (0.1)
	Median	1	0	0	0
	25th, 75th percentiles	(0, 15)	(0, 0)	(0, 0)	(0, 0)
	Min–Max	0–200	0–10	0–4	0–1
	Total	2307	58	29	1
Mild/mod dementia†	Mean (SD)	31.2 (49.6)	1.1 (3.2)	0.2 (0.6)	0.02 (0.1)
	Median	18	0	0	0
	25th, 75th percentiles	(8, 35)	(0, 1)	(0, 0)	(0, 0)
	Min–Max	0–500	0–25	0–5	0–1
	Total	5584	203	27	3
Severe dementia	Mean (SD)	10.1 (34.7)	0.5 (2.4)	0.1 (0.8)	0
	Median	0	0	0	0
	25th, 75th percentiles	(0, 5)	(0, 0)	(0, 0)	(0, 0)
	Min–Max	0–300	0–20	0–10	0
	Total	1780	83	16	0

*Number of survey responses per item ranged from 177–182.
†Excludes as a probable reporting error, one respondent who reported six completed suicides in 30 assessed mild-moderate AD subjects.

reports never or only occasionally differ in subjects with severe dementia. Depending on the diagnostic group, discrepancies between subject and caregiver were reported as occurring often or always by about 8% to 13% of respondents. In addition, the proportion of respondents reporting that they were unable to assess if discrepancies existed ranged from 23.7% for MCI and 15.8% for mild/moderate dementia to 42.5% for severe dementia. These results highlight the need for better guidance for clinicians on how discrepant information should be incorporated into the SI/SB assessment.

The time required to complete prospective SI/SB assessments did not appear to vary with level of cognitive impairment. About half of the respondents (51.0%–59.9%) indicated that the prospective assessment of SI/SB could be done in $\leq$15 minutes regardless of the level of impairment, whereas about a third (25.9% in MCI, 34.6% in mild to moderate AD, and 31.7% in severe AD) indicated that the interviews required between 15 and 30 minutes to conduct.

Other sources of data used by respondents included medical or psychiatric records (77.3%), information provided by the referring physician (59.6%), or information from assisted living or nursing home staff (50.4%). About 13% of respondents indicated that they did not use any source of information other than the subject and the caregiver.

A total of 37 respondents indicated their site used self-report questionnaires to evaluate SI/SB in clinical trials of subjects with MCI or dementia. The most common "self-report" instrument was the C-SSRS, suggesting the online self-rated version of the C-SSRS (the "eC-SSRS") [7] or perhaps that the respondents did not understand the question. Other self-report instruments included the Geriatric Depression Scale [8], the Beck Depression Scale [9], the Beck Suicide Intent Scale [10], the Neuropsychiatric Inventory [11], and the Sheehan-Suicide Tracking Scale [12].

3.5. Qualitative ratings of the level of confidence in and reliability of SI/SB data from subjects with dementia

In general, the level of confidence respondents had in the data attained from prospective SI/SB assessments, and their judgment of the reliability of the data was very similar for both SI and SB; therefore, results for suicidal ideation and behavior are discussed together.

Respondents' level of confidence declined almost monotonically with increasing severity of cognitive impairment and with increasing duration of the time period over which subjects were asked to provide information (Figs. 1 and 2). For example, about 70% of respondents had a high level of confidence in the accuracy of reports of SI/SB from subjects with MCI over the past 24 hours. However, less than half of respondents (22%–38%) had high confidence

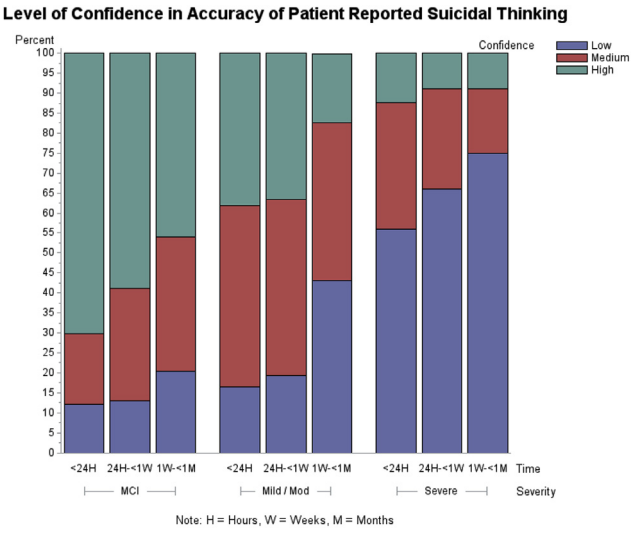

Fig. 1. Level of confidence in accuracy of patient self-reports of suicidal ideation.

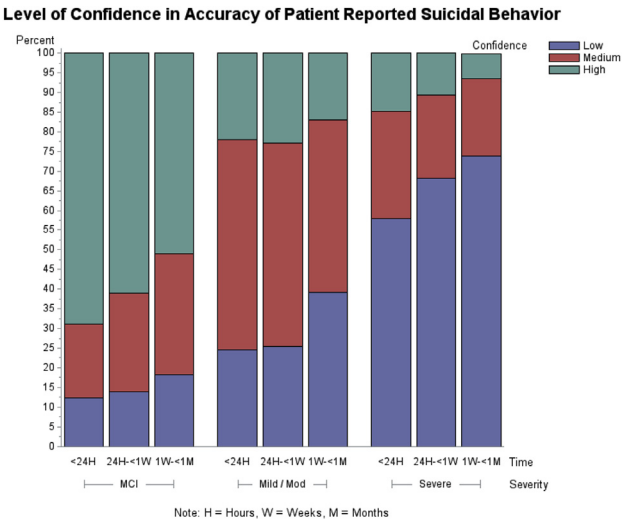

Fig. 2. Level of confidence in accuracy of patient self-reports of suicidal behavior. *Includes actual attempts, aborted or interrupted attempts, and preparatory acts toward making an attempt (such as acquiring the means of committing suicide); does not include nonsuicidal self-injurious behaviors.

in reports from subjects with mild to moderate dementia over the same time period, and only 12%–15%, in reports from subjects with severe dementia. The proportion of respondents with high confidence in the accuracy of subjects' reports of SI/SB also decreased with increasing duration of the recall period, for example, falling to 46%–51%, 17%, and 6%–9%, for reports covering the past period ranging from >1 week to ≤1 month for subjects with MCI, mild-moderate dementia, and severe dementia, respectively. It is interesting to note that respondents' confidence in the accuracy of patient self-reports of SI and SB was very similar, suggesting investigators do not perceive any difference in patients' ability to recollect and report on past objective behaviors versus past subjective states.

Conversely, the proportion of respondents reporting low confidence in subject's reports of past SI/SB increased with increasing severity of cognitive impairment and increasing duration of the recall period. In the case of self-reports from subjects with severe dementia covering the past week to 1 month period, three-fourths of respondents indicated that they had a low level of confidence in the accuracy of the reports, either for SI or SB.

Respondent ratings of the reliability (low, medium, high, not sure) of information on SI/SB obtained from subjects, caregivers, and others in conducting prospective assessment of subjects with MCI or dementia also decreased with increasing severity of cognitive impairment (Table 2). Approximately 70% of respondents rated the reliability of the information they obtained from all sources for subjects with MCI as high, but only about half (42.0% to 55.3%) rated the reliability of information obtained for subjects with mild to moderate dementia as high, and less than a quarter (17.4% to 24.3%) rated the reliability of the information obtained on subjects with severe dementia as high. Conversely, 32.6% and 24.3% of respondents rated the information obtained from all sources on suicidal ideation (SI) and suicidal behavior (SB), respectively, in subjects with severe dementia as having low reliability, and about a quarter of respondents (22.9% for SI and 23.6% for SB) indicated that were not sure how reliable information on this subject group was.

As shown in Table 2, the proportion of high ratings for the reliability of information on past suicidal behavior was somewhat greater than the proportion of high ratings for reliability of information on past suicidal ideation.

3.6. Assessment of understanding of the concept of intention

As shown in Table 3, more than 90% of respondents felt that subjects with MCI or mild to moderate dementia would understand the question "Have you had some intention of acting on your thoughts to kill yourself?" either very much or to some degree, compared with 36.8% of respondents for subjects with severe dementia. The proportion of very much ratings drops off precipitously with increasing severity of dementia, whereas the proportion of not at all or not sure ratings is markedly increased in severe dementia.

3.7. Subject/caregiver acceptance and clinical usefulness of prospective assessments of SI/SB

Most respondents rated the level of subject and/or caregiver acceptance of prospective assessments of SI/SB in clinical trials as either high or medium (86.9% in MCI, 85.4% in mild to moderate dementia, and 75% in severe

Table 2
Respondent ratings of the reliability of information on SI/SB obtained from all sources used in prospective assessments

	MCI (N = 146)		Mild/moderate dementia (N = 150)		Severe dementia (N = 144)	
	SI	SB	SI	SB	SI	SB
Low	6 (4.1%)	8 (5.5%)	12 (8.0%)	12 (8.0%)	47 (32.6%)	34 (24.3%)
Medium	32 (21.9%)	24 (16.4%)	68 (45.3%)	48 (32.0%)	39 (27.1%)	41 (28.5%)
High	100 (68.5%)	104 (71.2%)	63 (42.0%)	83 (55.3%)	25 (17.4%)	35 (24.3%)
Not sure	8 (5.5%)	10 (6.9%)	7 (4.7%)	7 (4.7%)	33 (22.9%)	34 (23.6%)

Abbreviations: SI, suicidal ideation; SB, suicidal behavior.

Table 3
In your experience, how well can subjects with dementia or Mild Cognitive Impairment understand what is meant by the statement "Have you had some intention of acting on your thoughts to kill yourself?"

Level of understanding	MCI (N = 146)	Mild/moderate dementia (N = 150)	Severe dementia (N = 144)
Not at all	4 (2.7%)	6 (4.0%)	71 (49.3%)
To some degree	17 (11.6%)	85 (56.7%)	46 (31.9%)
Very much	118 (80.8%)	54 (36.0%)	7 (4.9%)
Not sure	7 (4.8%)	5 (3.3%)	20 (14.0%)

dementia), although the proportion of low acceptance responses increased with increasing severity of cognitive impairment (13% in MCI, 14.7% in mild to moderate dementia, and 23.6% in severe dementia).

Most of the respondents indicated that prospective assessment of SI/SB was very or moderately helpful in identifying subjects at risk with MCI (71.8%) or mild to moderate dementia (64.1%), but less than half of respondents (39.4%) found them equally helpful in subjects with severe dementia. The proportion of respondents indicating that prospective assessments were only a little bit or not at all helpful increased with increasing severity of cognitive impairment, from 21.8% in MCI, to 29.6% in mild to moderate dementia and to 45.8% in severe dementia. The proportion of respondents rating prospective assessments as not at all helpful rose from 3.5% in MCI and 4.2% in mild to severe dementia to 19.7% in severe dementia; and 14.8% of respondents indicated that they had no opinion of the helpfulness of assessments in patients with severe dementia.

3.8. Responses to open-ended question

The final question allowed respondents to write any additional comments they had. Major topics included comments on the usefulness of SI/SB assessments in patients with cognitive impairment, the limitations of specific scales (e.g., the C-SSRS), the benefits of doing SI/SB assessments, the importance of obtaining input from both caregivers and patients, and the low incidence of SI/SB in patients with dementia (Table 4).

4. Discussion

The results of this survey provide preliminary evidence that SI/SB does occur in patients participating in clinical trials of dementia spectrum disorders; yet, the overall incidence of SI/SB in clinical studies of patients with dementia appears likely to be quite low. However, the accuracy and reliability of SI/SB assessments in this patient population appear to be directly impacted by the level of cognitive impairment, such that meaningful assessment of suicidal risk and intent over even a recent period of time may not be practicable in patients with more severe cognitive impairment. Nonetheless, consistent with one of the chief aims of the draft FDA guidance—to ensure patient safety [1,2]—most of the survey respondents found prospective SI/SB assessments helpful in identifying patients at risk who had MCI or mild to moderate dementia, although not patients with severe dementia. These data, taken with the lack of validated assessment instruments adapted to the stage of cognitive decline,

Table 4
Thematic categorization of responses to open-ended question

Category	N	Example
Not necessary or useful	5	In my opinion and experience, the risk of suicide is very low in this patient population. It is not necessary to check this kind of behavioral (sic). I have treated for many years Alzheimer disease and mild cognitive impaired patients, and I have never had a case.
Negative comment about C-SSRS	4	In my professional opinion, C-SSRS is not an appropriate measuring tool for most of our patient population.
Important to assess/valuable	4	I think it is very important and does not require too much time to evaluate suicidal risk in dementia, and it can help us to detect some problems not always identified by caregivers and patients as important
Important to use caregiver and patient input	3	Best judged by clinician with interview of both and independent assessment.
Have had reports of suicidal ideation/behavior	2	Of my >3000 cognitively impaired patients in my practice, there were exactly two who have ever screened + for SI, and they were women who had a Hx: SI/SA much earlier in their lives.
Language/translation problems	1	It is a problem to present this survey in English to, for example, German native speaker as I am. I personally would not rely on information based on surveys like this in foreign languages although I fell [sic] my English is not that bad!
Conduct at every visit	1	We use sponsor-provided suicidality assessment forms for the assessor to complete at each visit.
High-functioning patients are offended	1	Some higher functioning patients are very offended when asking questions about suicidal thoughts, actions, and so forth
Assessment at every visit is too frequent	1	Despite limitations, inclusion of the assessment at least allows the topic to be discussed openly. I do have a problem with the frequency of the assessment, especially is [sic] subjects who at the site on a regular basis (i.e., monthly) and have adequate opportunity
Patients deny SI/SB/never had positive report	1	All the subjects that I have evaluated in my site recount not to have ideas anticipatorias [anticipatory] of suicide.
Other (unable to classify above)	3	

highlight the difficulties of obtaining accurate estimates of SI/SB in dementia patients.

The survey respondents reported substantial experience in conducting clinical trials and prospective assessment of SI/SB in cognitively impaired subjects. Nonetheless, the number of subjects personally assessed by the respondents in the past year who had SI, SB, or CS was on average quite low (Table 1). The apparent low levels of SB and CS reported in patients with more severe dementia seem consistent with the expectation that increasing cognitive impairment along with increased overall disability and dependency is likely to lead to reduced opportunity and capacity to plan for and execute self-harmful behaviors. On the other hand, the apparent higher rate of SI reported in severe dementia relative to mild-moderate dementia and MCI seems counter to respondents' reports of the increased difficulty of obtaining accurate and reliable self-reports of SI in patients with severe dementia and the increased reliance on caregiver input for assessment of more severely impaired patients (which may be confounded by bias or projection). In patients with more severe impairment, where assessments of subjective states may often be based on inferences from caregivers rather than observed behaviors, confounding of passive SI with active SI also may occur more commonly. Although of interest, these results should be regarded with caution given the limitations of the survey methodology which relies on unverified self-report vulnerable to recollection bias and which did not take into account such factors as the frequency of SIB assessments and the duration of clinical trials, which could impact the rate of detection and reporting of SI/SB. None the less, future studies, using more rigorous methodologies, should be conducted to determine if there is a relationship between severity of cognitive impairment and the risk of SI/SB.

As might be expected, respondents' confidence in subject self-reports of SI/SB over different time periods declined markedly with increasing severity of cognitive impairment and with increasing duration of the time period over which subjects were asked to provide information. In addition, respondents' ratings of the reliability of the information on SI/SB collected from all sources (patient, caregiver, and others) also decreased with increasing severity of cognitive impairment. The lowest levels of confidence and reliability were assigned to SI/SB patients with severe dementia. However, a substantial minority of respondents (16% to 43% depending on the past time period) also had low confidence in self-reports of SI/SB obtained from patients with mild to moderate dementia and rated the reliability of assessments in this patient group as low or medium (53.3% for SI, 40.0% for SB). Interestingly, 30% to 50% of respondents also had low or moderate confidence in self reports of SI/SB from patients with MCI. Given the mild degree of cognitive impairment in patients with MCI, this lack of confidence may also reflect the difficulty many patients may have in speaking about their suicidal ideas and impulses [8].

These results raise questions about the validity and reliability of SI/SB assessments in patients with mild to moderate as well as severe cognitive impairment and highlight the need for rigorous studies of the psychometric performance of the scales being used in this patient population. Further study of SI/SB assessment tools in this population is needed to identify existing tools or develop new ones capable of more robust SI/SB detection [5]. Given the results of this survey, taken with the variability in individual rates of cognitive decline [13], the threshold of cognitive impairment beyond which reliable assessments of SI/SB is no longer possible may be more a gray zone rather than a sharp line separating mild-moderate and severe dementia.

Operational challenges did not appear to be a major concern for the survey respondents. The majority reported that patients and caregivers are generally accepting of SI/SB assessments and that most assessments could be completed within 15 minutes, regardless of the severity level of the patient's dementia. The most notable challenges reported by the respondents related to assessment of patients with severe dementia. Among respondents who routinely interview both the patient and caregiver, nearly half indicated they could not assess whether there were discrepancies between the subject and caregiver reports they obtained, and about a quarter of respondents indicated they were not sure how reliable information on SI/SB obtained from all sources for patients with severe dementia was. These results indicate such discrepancies are not uncommon and, although the survey did not ask how these were resolved, may highlight the need for instruments to provide better guidance for clinicians on how discrepant information should be incorporated into the SI/SB assessment.

Some of the open-ended comments were positive in nature, highlighting the benefits to patient safety. Other respondents commented that they had seldom or never encountered SI/SB in their clinical practice with dementia patients and questioned the necessity or usefulness of doing SI/SB assessments in clinical trials of patients with dementia. Additionally, several respondents raised concerns about the appropriateness of using the C-SSRS in patients with dementia.

5. Limitations of the study

Limitations of this study include the low response rate and the reliance on unverified self-report that is inherent to the survey methodology. There is evidence that the response rates of clinicians to surveys of all types, including electronic surveys, are diminishing [14]. Hence, low response rates are a common liability of Internet surveys and may lead to nonresponse bias that may limit the generalizability of the findings.

An additional limitation of the study is the lack of items inquiring about specific SI/SB rating scales. Other than one item asking about the use of patient self-report measures, there were no questions about site experience with specific SI/SB assessment instruments. However, it is a

reasonable assumption that most sites are using the C-SSRS, as recommended in the FDA guidance.

The survey also did not inquire about the presence and potential contribution of comorbid psychiatric conditions. Depression, in particular, is a well-established risk factor for suicide, which is very prevalent among elderly patients with cognitive impairment [5,15–17] and which can confound attempts to elucidate the unique contribution of underlying dementia to the risk of suicide [18,19]. Although the objective of the survey, as presented to the respondents and as reflected in the survey title, was to inquire about site experiences in prospective assessment of SI/SB in clinical trials of patients with dementia or MCI, it is possible that past (pre-trial) SI/SB may have been confounded with new onset SI/SB, occurring during the clinical study.

The survey also does not address whether respondent reports differed based on differences in methodology used to assess SI/SB (i.e., some respondents only interviewed the subject, whereas others interviewed both the subject and the caregiver, interviews varied in length) or on differences in the training and educational background of the respondents (i.e., 45% of respondents were physicians, 44% psychologists, nurses, or social workers, and 11% study coordinators and raters without professional degrees).

Finally, although most respondents reported that SI/SB assessments were helpful in identifying subjects at risk (i.e., 71.8% in MCI, 64.1% in mild-moderate dementia, and 39.4% in severe dementia), the survey did not explore whether detecting SI/SB actually improved patient outcomes. Given the significant effort now mandated by the FDA to conduct prospective assessments of SI/SB in clinical trials of patients with MCI and dementia, this is an important question that needs to be addressed in future studies.

6. Conclusions

Despite the limitations of this survey, these data indicate that suicidal ideation and behavior do occur in clinical trials of patients with MCI or dementia. However, the reported occurrence of SB and CS appears to be lower than SI and may decline further with increasing severity of dementia. The occurrence of SI/SB in clinical trials of dementia should not be surprising given reports on the background incidence of SI/SB in elderly and dementia patients [12,20–24]. Studies of the prevalence of SI/SB in patients with dementia in settings other than clinical trials have shown highly variable results (ranging from 1% to >42%) due to methodologic differences, the failure to use standardized terminology, and the lack of well-validated tools for assessment of SI/SB in this patient population (reviewed in [5]). As far as the authors are aware, there are no published data on the incidence of SI/SB in patients in clinical trials of dementia.

The survey results support the usefulness of prospective assessment of SI/SB in clinical trials involving MCI and milder forms of dementia, raise important questions about the validity and reliability of SI/SB assessments in moderately severe dementia, and confirm that assessment of SI/SB in severe dementia is not likely to be clinically useful. More than anything, the data highlight the need for rigorous studies of the psychometric properties of the currently available assessment tools across the full range of cognitively impaired patients and the need for development of validated assessment instruments and methods of assessment adapted to the stage of cognitive decline of the patients under study. As suggested by this survey, improvements in the field will require addressing a host of issues which we have discussed in more detail in a companion review on assessing SI/SB in adults with cognitive decline and dementia [5].

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.trci.2016.02.002.

RESEARCH IN CONTEXT

1. Systematic review: In recognition of the lack of any published information on the use of suicide ideation and suicide behavior (SI/SB) tools in mild-cognitive impairment and dementia clinical trials, the Alzheimer's Association convened a task force to assess these issues and conducted an online survey on the extent of SI/SB in dementia patients participating in clinical trials. The goal of the survey was to obtain information which has not been previously assessed on the extent of SI/SB in cognitively impaired individuals participating in clinical trials.
2. Interpretation: The novel data presented here support the usefulness of prospective SI/SB assessments in MCI and mild dementia in clinical trials, raise questions about the reliability of assessments in moderate dementia, and confirm their lack of clinical utility in severe dementia.
3. Future directions: The results highlight the need for development of validated assessment instruments adapted to the stage of cognitive decline of the patients under study.

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