Alzheimer's & Dementia: Translational Research & Clinical Interventions 2 (2016) 60-68

Featured Article

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

Phillip Chappell[a,*], Sarah Dubrava[a], Michelle Stewart[a], Dean M. Hartley[b,**], Larry Alphs[c], H. Robert Brashear[d], Yeates Conwell[e], David Miller[f], Rachel J. Schindler[g], Eric R. Siemers[h], Kristine Yaffe[i]

[a]*Pfizer, Groton, CT, USA*
[b]*Alzheimer's Association, Chicago, IL, USA*
[c]*Janssen Scientific Affairs, LLC, Titusville, NJ, USA*
[d]*Janssen Alzheimer Immunotherapy & Research & Development, LLC, South San Francisco, CA, USA*
[e]*University of Rochester, New York, USA*
[f]*Bracket, Inc., Wayne, PA, USA*
[g]*Pfizer, New York, NY, USA*
[h]*Eli Lilly and Company, Inc., Indianapolis, IN, USA*
[i]*University of California, San Francisco, CA, USA*

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.

*Corresponding author. Tel.: +1-860-271-9947; Fax: +1-860-715-7527.
**Corresponding author. Tel.: +1-312-355-5000; Fax: +1-866-741-3716.
E-mail address: Phillip.b.chappell@pfizer.com (P.C.), dhartley@alz.org (D.M.H.)

http://dx.doi.org/10.1016/j.trci.2016.02.002

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