Electronic Assessment of Suicidal Ideation and Behavior for Meta-Analyses across Multiple Trials and Treatment Indications

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Abstract

Methodological Question: The 2012 FDA guidance regarding suicidal ideation and behavior (SIB) recommends prospective assessment of SIB at baseline and all planned follow-up visits when other clinical outcomes are to be collected in all drug development trials for psychiatric indications, as well as for antiepileptic or other drugs with CNS activity. A primary reason for this recommendation is to guarantee more complete SIB assessments concurrent with administered treatments and placebo, and signals indicative of increased risk would be easier to detect in individual trials. Aggregation of data across multiple trials for meta-analyses could more readily confirm true signals or provide counter-evidence of spurious, false-positive events, providing better sensitivity and specificity estimates. The FDA guidance states "The full assessment of suicidal ideation and behavior generally should involve a pooled analysis of all controlled trials, so that it will not be possible to conclude that a drug has no effect on suicidal ideation and behavior until a substantial database is available for this analysis."

Aims: Databases created from use of the C-SSRS (or other acceptable instruments, such as the electronic self-report eC-SSRS) that directly classify SIB into preferred categories can provide the basis for such analyses. Aggregation and analysis of the database described below was designed to meet the FDA recommendations and to provide clinical insight regarding differences in SIB prevalence rates among patients participating in clinical studies investigating treatments for different therapeutic areas and indications.

Methods: Data from 74,406 eC-SSRS assessments of SIB were extracted from 35 clinical trials. Patient-reported suicidal ideation and behavior were compared at baseline (lifetime) and prospectively during trial participation across multiple therapeutic areas and 17 treatment indications. Trials were categorized as Psychiatric (MDD, PTSD, opioid dependency, GAD), Neurologic (pain, epilepsy, insomnia, multiple sclerosis, Parkinson's disease, restless leg syndrome), or non-CNS studies (pulmonary, fibromyalgia, analgesia, anti-viral).

Results: The number and type of eC-SSRS assessments administered within each therapeutic category and the percentage of observations with each SIB are provided in Table 2.

Conclusions: Neurologic and non-CNS studies found similar prevalence rates of SIB using the eC-SSRS at baseline and prospectively during study participation. These rates were substantially less than the suicidal ideation and behavior rates self-reported by psychiatric patients. Although less frequent, positive findings were a substantial safety concern in these non-psychiatric trials.

Introduction

Following analyses showing that retrospective reports of suicidal ideation and behavior (SIB) were associated with certain medications[1,2], the U.S. Food and Drug Administration (FDA) determined a need for systematic prospective assessment of the possible suicide risk in some medications under development. Initial results were based on meta-analyses of randomized controlled trials (RCTs) and derived from adverse event case-reports of various kinds. The process was burdensome and handicapped by the retrospective and poor quality (e.g., missing data) of the source data, and such methodological limitations impaired the ability to draw causal conclusions. The FDA determined that prospective assessment would provide greater safety for subjects and better quality data for meta-analyses. FDA issued two draft guidance documents describing the desired prospective process for assessing SIB. [3,4]

The 2012 FDA draft guidance recommends prospective assessment of SIB at baseline and all planned follow-up visits when other clinical measures are to be collected in all drug development trials for psychiatric indications and for antiepileptic or other drugs with CNS activity.

FDA Guidance also identified the importance of discriminating SIB from Non-Suicidal Self Injurious Behavior (NSSIB) with no intent to die. Beyond protecting subjects, a primary reason for this recommendation was to guarantee timely and complete SIB assessments concurrent with administered treatments and placebo. Aggregation of data across multiple trials for meta-analyses could more readily establish true risk or lack thereof and provide counter-evidence of post-marketing spurious, false-positive events.

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In the FDA draft guidance, the required categories were adopted from the Columbia-Suicide Severity Rating Scale (C-SSRS). The guidance recommends use of the C-SSRS5 or other acceptable modes of administration, such as the electronic self-report eC-SSRS[6]. These instruments directly classify SIB into preferred categories identified in the guidance. Aggregation of data and analysis of the database described below was designed to meet the FDA recommendations.

These databases also provide an opportunity for gathering SIB prevalence rates across several therapeutic areas, many different indications and medications. A previous analysis of 35,224 eC-SSRS assessments[7] involved almost exclusively psychiatric disorders (99%) of depression (MDD) and post-traumatic stress disorder (PTSD). The results were limited in regards to their ability to provide meaningful data using the eC-SSRS in non-psychiatric disorders. This poster presents data addressing those limitations with a larger number of subjects participating in multiple non-psychiatric research studies in addition to subjects with psychiatric disorders

Methods

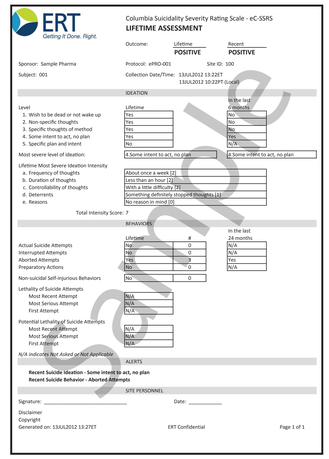
Data from 74,406 eC-SSRS assessments of SIB were extracted from 35 clinical trials. Patient-reported ideation and behavior were compared at baseline (lifetime assessment of the most severe ideation and all prior suicidal behaviors) and prospectively during trial participation across three broad therapeutic areas and 17 treatment indications. Trials were categorized as Psychiatric (Generalized Anxiety Disorder, Major Depressive Disorder, Opioid Dependency and Post Traumatic Stress Disorder), Neurologic (epilepsy, insomnia, multiple sclerosis, pain, Parkinson's disease, restless leg syndrome), or non-CNS studies (analgesia, Hepatitis C, fibromyalgia and pulmonary). Each assessment covered the same questions about suicidal ideation and behaviors defined in Table 1.

After each assessment, a report was sent to the site. Figure 1 illustrates a positive report.

Table 1. Suicidal Ideations and Behavior (SIB) assessed by the eC-SSRS

Suicidal Ideation	Definitions
0	No Lifetime Suicidal Ideation
1	Passive ideation
2	Active Ideation: Nonspecific (No method, intent, or plan)
3	Active Ideation: Method, but no intent or plan
4	Active Ideation: Method and intent, but no plan
5	Active Ideation: Method, intent, and plan
Suicidal Behavior	**Definitions**
Preparatory	Any suicidal behavior that stops short of an actual, interrupted, or aborted attempt
Aborted	Suicidal behavior toward making an attempt, but stopping self before making an actual attempt
Interrupted	Behavior toward a suicide attempt, but interrupted by someone before actually making the attempt
Actual	Potentially self-injurious behavior with some degree of intent to die as a result of the act

Figure 1 - A Sample Positive Report



Results

Call completion time in minutes (SD):

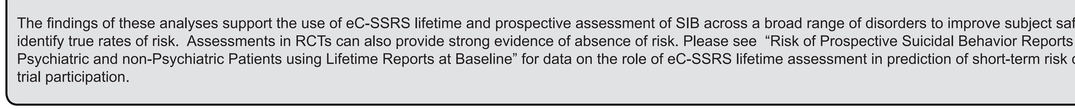


Table 2. The number and type of eC-SSRS assessments administered within each therapeutic category and the percent of observations with each SIB

Therapeutic Category	eC-SSRS Assessments	Patient-reported Most Severe Suicidal Ideation (%) 0	1	2	3	4	5	Patient-reported Suicidal Behavior (%) Prepar Behav	Aborted	Interrupt	Actual	Positive Reports % Ideation 4 or 5 or any Behavior	NSSIB (%)
Psychiatric	Baseline = 10,233	46.40	19.83	8.66	10.64	8.34	6.14	6.54	15.46	12.12	17.56	27.96	4.41
(16 studies)	*Since Last Call = 51,819*	*87.55*	*8.87*	*1.60*	*1.29*	*0.60*	*0.07*	*0.19*	*0.73*	*0.53*	*0.21*	*1.54*	*0.13*
Neurologic	Baseline = 1,912	82.01	8.37	2.98	2.98	2.30	1.36	1.62	3.92	2.82	3.29	7.27	0.89
(13 studies)	*Since Last Call = 4,352*	*99.24*	*0.44*	*0.23*	*0.05*	*0.05*	--	--	*0.05*	*0.07*	*0.02*	*0.11*	*0.05*
Non-CNS	Baseline = 1,991	82.97	7.73	4.22	2.31	2.06	0.70	1.00	3.82	2.96	3.16	6.18	1.66
(6 studies)	*Since Last Call = 4,099*	*98.88*	*0.93*	*0.02*	*0.10*	*0.05*	*0.02*	*0.07*	*0.10*	*0.10*	*0.10*	*0.29*	*0.07*

Conclusions

eC-SSRS completion times were comparable to those found in an earlier analysis of 35,224 eC-SSRS assessments where more than 90% of the population had psychiatric disorders[6]. The short completion times indicate low time burden for patients and staff with use of a fully structured self-report SIB assessment.

Consistent with clinical expectation, overall SIB rates for Neurologic and non-CNS disorders were substantially lower than reported by psychiatric patients. Although less frequent in non-psychiatric disorders, positive findings remain concerns for subject safety during trials and possible risk associated with medications being studied. Lifetime and prospective assessments address these concerns across all disorders.

NSSIB prevalence, both lifetime and prospectively reported, follows the same patterns as SIB. NSSIB is more frequent in psychiatric (4.41% lifetime and .13% prospectively reported) than non-psychiatric disorders (2.55% lifetime and .06% prospectively reported) while less frequent than SIB in both groups. The importance of distinguishing NSSIB from SIB in ruling out treatment emergence of SIB is supported by finding substantial NSSIB prevalence.

The findings of these analyses support the use of eC-SSRS lifetime and prospective assessment of SIB across a broad range of disorders to improve subject safety and to identify true rates of risk. Assessments in RCTs can also provide strong evidence of absence of risk. Please see "Risk of Prospective Suicidal Behavior Reports among Psychiatric and non-Psychiatric Patients using Lifetime Reports at Baseline" for data on the role of eC-SSRS lifetime assessment in prediction of short-term risk during remaining trial participation.

Study Limitations

- Lifetime reports of SIB, in the present baseline assessments, do not consider the recency of reported SIB in estimating the risk of prospective reports of suicidal behavior during study participation.
- All data included in these analyses were collected using the same instrument, the eC-SSRS, and a common IVRS interface to obtain the self-reported responses.
- The analyses of eC-SSRS assessments do not address the extent to which participant reports of SIB were, or were not, confirmed by clinician follow-up.

Disclosures: All authors have a financial interest in the eC-SSRS. ERT provides electronic patient reported outcome services to industry-sponsored clinical trials, including eC-SSRS assessments. Licensing fees are provided to the Research Foundation for Mental Hygiene and Healthcare Technology Systems for delivery of eC-SSRS™ assessments. Dr. Mundt is a consultant to ERT and has minor stock holdings in Healthcare Technology Systems. Dr. Posner is Director of the Center for Suicide Risk Assessment at the Research Foundation for Mental Hygiene. Dr. Greist is a principal stock shareholder of Healthcare Technology Systems. Mr. Federico is Vice President of ePRO Solutions for ERT.

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