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EDITORIAL

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# What the new US FDA guidance in assessing suicidal ideation and behavior in clinical trials means for trial design

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"The logic behind the expanded suicidal ideation and behavior assessment is difficult to dismiss, in essence, the additional burden of screening for SIB in clinical drug trials is minimal compared with the added safety benefit."

While antidepressants have been associated with an overall reduction in the rates of suicide in patients with depression [1], case reports of increased suicidal ideation and behavior (SIB) in patients taking antidepressant medications are in long standing [2–6]. However, it is not clear whether the increased SIB seen in patients taking antidepressants is part of the natural disease course of major depressive disorder, or whether antidepressants themselves, independent of the primary disease process, are responsible for the presence of SIB. Regardless of the causal relationship, the general consensus is that patients, especially those experiencing depression, should be carefully monitored for increased SIB when changes in psychotropic medication are made (i.e., stop, start or dosage titration). The US FDA Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials, expands the monitoring of SIB to be included in "*all clinical trials involving any drug being developed for any psychiatric indication, as well as for all antiepileptic drugs and other neurologic drugs with central nervous system (CNS) activity, both inpatient and outpatient, including multiple-dose Phase 1 trials involving healthy volunteers*" [101].

## New FDA guidance

Based upon the available evidence, the FDA undertook an evaluation of the relationship between antidepressant medication usage and increased SIB. The initial recommendations from the FDA in October 2004 [102] warned against increased SIB in children and adolescents prescribed antidepressants, specifically noting that during the "*initial few months*" of a course of antidepressant therapy, or at times of dose titration, "*patients should be observed for clinical worsening, suicidality or unusual changes in behavior.*" In June 2005 [103] this recommendation was expanded to include adults and noted the occurrence of an 'activation syndrome' [7–10], which should also be monitored for patient safety ("*anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia/psychomotor restlessness, hypomania, and mania…there is concern that such symptoms may represent precursors to emerging suicidality*"). While the initial recommendations were for selective serotonin-reuptake inhibitors, the warnings were quickly expanded to include all antidepressants, and over time are being included in clinical trials outside of psychiatry. Initially released in 2010 and then revised in 2012, the FDA Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials, outlines specific SIB monitoring requirements for clinical trials [101].

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## Impact on clinical trials

The impact on clinical trials of the FDA recommendations and requirements for SIB monitoring was immediate. The result was a small but important addition – prospective SIB monitoring was added to clinical trials protocols overseen by the FDA. The FDA Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials, reflects the results of extensive study of SIB in clinical drug trials, and reinforces updated reporting requirements that have been in place since shortly after the initial warnings. New and existing clinical trials protocols for any psychiatric indication are required to contain clinical monitoring for SIB. SIB is required to be classified using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) criteria [11]. The C-CASA criteria divides SIB into nine domains: completed suicide; suicide attempt; preparatory acts toward imminent suicidal behavior; suicidal ideation; self-injurious behavior intent unknown; fatal event (not enough information to classify as suicide); self-injurious behavior without suicidal intent; other injury with no intent for self harm (accident, psychiatric and medical); and, nonfatal event (not enough information to classify). While laborious in appearance the C-CASA system can be easily and effectively implemented using one of a number of the available clinician-rated and patient self-report assessments of SIB, with the Columbia Suicide-Severity Rating Scale (C-SSRS) being the 'gold standard', and other measures designed to meet FDA reporting requirements, such as the Concise Health Risk Tracking scale and the Concise Associated Symptoms Tracking scale that are currently being included in clinical trials to increase patient safety [12–14]. In general, the largest impact for clinical trials is the requirement to screen patients involved in the development of drugs for any psychiatric indications, for SIB at each clinic visit, and to classify all SIBs using the C-CASA criteria.

Essentially, the C-CASA coding system requires clinical staff to formally gather information on SIB. The information obtained for coding is consistent with that gathered during a standard SIB assessment screening, followed with a more in-depth interview as needed. The largest change in the design of clinical trials is the requirement to formally evaluate SIB and code the results within C-CASA domains at each clinical visit.

For C-CASA coding, an evaluation of suicidal ideation (domain 4) must be made to identify the presence and severity of passive or active ideation. Examples of passive suicidal ideation are: the wish not to be alive; or the desire to go to sleep and not wake-up. Active suicidal ideation must be further classified as: non-specific thoughts (e.g., thoughts of killing oneself with no thought of how; no method, intent or plan); thoughts of a method of suicide, but no intent or plan; thoughts of a method of suicide, with intent to perform a suicidal act, but no plan; thoughts of a method of suicide, with the intent to perform a suicidal act, and the presence of a specific suicide plan.

> "...the largest impact for clinical trials is the requirement to screen patients involved in the development of drugs for any psychiatric indications, for suicidal ideation and behavior at each clinic visit, and to classify all suicidal ideation and behavior using the Columbia Classification Algorithm of Suicide Assessment criteria."

In addition, suicidal behaviors will need to be assessed in order to complete C-CASA coding. An evaluation will need to be made to determine if actions of purposeful self-harm were committed or if any non-suicidal self-injurious behaviors occurred for the event or time interval being coded (domain 8 – other injury with no intent for self-harm). If there was purposeful self-harm a determination of suicidal intent must be made (an understanding and an expectation that the behavior could lead to death; domains: 2 – suicide attempt, and 7 – self-injurious behavior without suicidal intent). Also, an evaluation to identify the presence of preparatory actions toward imminent suicidal behavior (domain 3) must be made. Specifically, clinicians will need to determine if there were any interrupted or aborted suicide attempts, or if any preparations for suicide have been made. In instances of mortality, a postmortem forensic evaluation of SIB is required, the purpose of which being to determine if the death was the result of a self-injurious behavior and if there was some intent to die associated with the behavior (domains: 1 – completed suicide, and 6 – fatal event without adequate information to code as suicide). In instances when specific information about the behavior is not available and intent cannot be determined or reasonably inferred, the behavior will be coded in one of the C-CASA 'not enough information' domains (domain: 5 – self-injurious behaviour, intent unknown, or 9 – nonfatal event with not enough information to classify).

While the assessment of SIB using the C-CASA criteria appears a bit laborious at first glance, closer examination will reveal that the information required for coding can be obtained quickly and easily. The C-CASA-based assessments require some brief training, but can be administered by a wide variety of providers, caregivers and clinical raters. Some of the current systems involve a self-report screening device and/or a brief interview (as few as three or four questions) that take only a few minutes to complete and interpret depending upon the patients symptom presentation. C-CASA systems have

quickly and effectively been integrated into clinical trials because they not only help recognize patients who are at increased risk, but also because they require little additional time and effort on the part of clinical staff and patients. Antidepressant clinical trials now include a longitudinal SIB assessment component. The systematic assessment of SIB is beginning to become a component of pharmacotherapy treatment protocols beyond psychiatry.

"Antidepressant clinical trials now include a longitudinal suicidal ideation and behavior assessment component. The systematic assessment of suicidal ideation and behavior is beginning to become a component of pharmacotherapy treatment protocols beyond psychiatry."

## Translating research to clinical practice

The research techniques developed for evaluating SIB in clinical trials [15,16] have translated well to clinical practice in a variety of general medical and psychiatric specialty care settings [17]. Treatment guidelines for the use of antidepressants now include the assessment of SIB, regardless of clinical setting. The American Psychiatric Association Treatment Guidelines (2010) recommend the longitudinal tracking of treatment response (symptom severity, tolerability and safety) when treating patients with antidepressants. The safety assessment would include an evaluation of SIB. Some of the networks involved in clinical trials, such as the National Network of Depression Centers, Clinical Trials Network and Depression Trial Network, included SIB assessment, in addition to medication compliance, depressive symptom severity and antidepressant tolerability, as part of all clinical visits.

While the possibility of increased risk of SIB associated with psychotropic compounds with pronounced CNS effects is the topic of continuing debate, to err on the side of safety, participants need to be monitored for SIB patients throughout all phases of the drug development and approval process for "*any drug being developed for any psychiatric indication, as well as for all antiepileptic drugs and other neurologic drugs with central nervous system (CNS) activity.*" The logic behind the expanded SIB assessment is difficult to dismiss, in essence, the additional burden of screening for SIB in clinical drug trials is minimal compared with the added safety benefit.

## Financial & competing interests disclosure

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