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Focus Article

Measures That Identify Prescription Medication Misuse, Abuse, and Related Events in Clinical Trials: ACTTION Critique and Recommended Considerations

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Abstract: **Accurate assessment of inappropriate medication use events (ie, misuse, abuse, and related events) occurring in clinical trials is an important component in evaluating a medication's abuse potential. A meeting was convened to review all instruments measuring such events in clinical trials according to previously published standardized terminology and definitions. Only 2 approaches have been reported that are specifically designed to identify and classify misuse, abuse, and related events occurring in clinical trials, rather than to measure an individual's risk of using a medication inappropriately: the Self-Reported Misuse, Abuse, and Diversion (SR-MAD) instrument and the Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS). The conceptual basis, strengths, and limitations of these methods are discussed. To our knowledge, MADDERS is the only system available to comprehensively evaluate inappropriate medication use events prospectively to determine the underlying intent. MADDERS can also be applied retrospectively to completed trial data. SR-MAD can be used prospectively; additional development may be required to standardize its implementation and fully appraise the intent of inappropriate use events. Additional research is needed to further demonstrate the validity and utility of MADDERS as well as SR-MAD.**

Perspective: ***Identifying a medication's abuse potential requires assessing inappropriate medication use events in clinical trials on the basis of a standardized event classification system. The strengths and limitations of the 2 published methods designed to evaluate inappropriate medication use events are reviewed, with recommended considerations for further development and current implementation.***

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Key words: *Medication abuse, medication misuse, abuse potential.*

Weighing an analgesic medication's benefits against its risks of abuse to inform scheduling, labeling, and treatment guidelines[20,32] requires identifying abuse potential (ie, use for nonmedical psychoactive effects[32]) during drug development. This necessitates careful, thorough, and standardized assessment and classification of inappropriate medication use events (ie, misuse, abuse, and related events [MAREs][27]; see Table 1 for definitions; see also U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion[31]) occurring in clinical trials. At the current time, there are no standardized, commonly accepted methods to capture and categorize events related to misuse or abuse in clinical trials. A potential model for such an instrument, the Columbia-Suicide Severity Rating Scale, was developed to categorize suicidal ideation and behavior events occurring in antidepressant clinical trials.[18,19] The Columbia-Suicide Severity Rating Scale classifies events comprehensively, efficiently, and accurately retrospectively as well as prospectively while limiting the overidentification of suicidal ideation and behavior. The prospective version has been recommended for assessing suicidal ideation and behavior in trials submitted to the U.S. Food and Drug Administration.[33] A similar instrument is needed to evaluate abuse potential in analgesic clinical trials.

Recent Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (http://www.immpact.org) recommendations[16] and a review of instruments measuring aspects of inappropriate medication use[28] emphasize the importance of: 1) evaluating a medication's abuse potential in a manner that is distinct from assessing the risk that a participant might use medications inappropriately, and 2) determining the putative intent underlying potential inappropriate use events to distinguish abuse events from other events. To that end, identifying inappropriate medication use events in clinical trials is critical for understanding abuse potential. When such events occur, it is also necessary to capture additional characteristics (ie, tampering, withdrawal, addiction, diversion, and overdose[27]; Table 1) because these supplemental details may imply problematic treatment effects that can inform the assessment of abuse potential. Further, prospectively assessing inappropriate use events within the context of an ongoing clinical trial, with training for study staff to determine the putative intent of these events, is essential for accurate classification.[16] In general, although currently available instruments measuring inappropriate medication use have clinical utility to evaluate patient adherence to opioid therapy in clinical practice, a recent review indicated that they do not distinguish between types of events, consider intent, or evaluate a specific medication's abuse potential per se (see Table 2 for a summary).[28]

In light of the challenges in measuring inappropriate use events to identify medications with abuse potential, the Abuse Liability Evaluation for Research, Treatment, and Training (ALERTT) working group of the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION; http://www.acttion.org) public-private partnership met to examine the 2 approaches of which we are aware that have specifically been developed to assess these

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Table 1. Definitions of MAREs and Supplemental Designations[27]

	Definition
Event	
Misuse-event indicator	Any intentional therapeutic use of a drug product in an inappropriate way. Misuse specifically excludes those events that meet the definition of an abuse-event indicator
Abuse-event indicator	Any intentional, nontherapeutic use of a drug product or substance, even once, for the purpose of achieving a desirable psychological or physiological effect
Suicide-related event	A self-injurious or potentially self-injurious behavior associated with at least some intent to die or that resulted in death. Evidence that the individual intended to kill him/herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. A suicide attempt may or may not result in actual injury (adapted from Posner et al, 2007[19])
Therapeutic error	A mistake in a therapeutic regimen
None of the above	Sufficient information exists to determine that none of the previous categories apply
Unknown	Insufficient information exists to determine which category applies
Supplemental designation	
Tampering	The inappropriate manipulation of a drug product
Withdrawal	Symptoms or signs due to the decline in blood concentration of a drug substance (eg, after dose reduction, at the end of a dosing interval, after discontinuing treatment) or due to the administration of an antagonist
Addiction-related indicator	Behavioral, cognitive, and physiological phenomena that may develop after exposure to a substance (typically on a repeated basis), which may include a strong desire to take the drug, difficulties in controlling drug use, persistent drug use despite harmful consequences, intractable and distracting thoughts about the drug, or placing a higher priority on drug use than other activities and obligations
Diversion	Any intentional act that results in transferring a drug product from lawful to unlawful distribution or possession. Diversion can occur in all categories except therapeutic error
Overdose	Any act that results in drug exposure exceeding that which is generally recommended or medically accepted

NOTE. Inappropriate use events occurring in clinical trials receive 1 "event" classification, as well as any relevant "supplemental designation" classifications.

events as defined by a standardized classification and definition system.[27] The current article presents a critical analysis of these approaches to evaluating and classifying MAREs in clinical trials of analgesic medications, as well as any medications with abuse potential.

Methods

In June, 2013, ACTTION convened a meeting of the ALERTT working group (ie, academic, industry, clinical, public health, and regulatory experts in pain and addiction) to discuss methods to assess MAREs occurring in clinical trials of analgesic medications. The key criterion for an assessment method to be reviewed in this meeting was adherence to a standardized classification and definition system of inappropriate use event categories (ie, abuse events, misuse events, suicide-related events, and therapeutic errors) and supplemental designations (ie, tampering, withdrawal, addiction-related indicator, diversion, and overdose[27]; Table 1). Other measures of inappropriate medication use that were briefly considered during the meeting, but that were not well suited to evaluating and classifying inappropriate medication use events, have been reviewed previously (see Table 2 for a summary).[28] Only 2 recently developed approaches (ie, Self-Reported Misuse, Abuse, and Diversion [SR-MAD] instrument for prescription opioids[25]; Misuse, Abuse, and Diversion Drug Event Reporting System [MADDERS[29]]) that were created specifically to address the gaps in procedures for identifying and adjudicating inappropriate use events occurring in clinical trials were examined in depth. The ALERTT group focused on details presented during the meeting and in articles that have been published since the meeting[25,29] regarding each tool's ease of implementation, ability to retrospectively and prospectively identify behaviors suggestive of MAREs, standardization of event adjudication, and ability to gather comprehensive and exhaustive information when behaviors suggestive of inappropriate use events arise in prospective trials. Subsequent to the meeting, a Web of Science search (http://webofknowledge.com; February 20, 2017) for articles citing the standardized MAREs classification and definition system[27] was conducted and did not identify any additional assessment methods. In addition, Web of Science searches (February 20, 2017) did not identify any publications citing SR-MAD[25] or MADDERS[29] that provided additional information regarding the use of these tools to capture inappropriate medication use events in a clinical trial. In this article, we briefly describe each tool, followed by examples of how each might be applied, as well as an evaluation of the strengths, limitations, and available data regarding each tool's measurement properties. On the basis of this review, we suggest recommended considerations for measuring MAREs in clinical trials prospectively as well as retrospectively.

Measures Assessing MAREs

SR-MAD Instrument for Prescription Opioids

The SR-MAD instrument was developed to evaluate the occurrence of misuse, abuse, diversion, and tampering across individuals with acute and chronic pain exposed to prescription opioids, as well as to assess these behaviors in response to specific opioids.[21,22,25]

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Table 2. Challenges in Using Available Instruments to Evaluate Current Inappropriate Medication Use Events in Clinical Trials

Instrument	Challenges in Evaluating Inappropriate Use Events
Aberrant Drug Behavior Index[4]/Drug Misuse Index[34]	Includes items not directly evaluating inappropriate use events No time frame specified for evaluating inappropriate use No determination of intent underlying each event No determination of route of administration
Abuse Index Algorithm[1]	Includes items not directly evaluating inappropriate use events No time frame specified for evaluating inappropriate use No determination of intent underlying each event No determination of route of administration
Addiction Behaviors Checklist[35]	Includes items not directly evaluating inappropriate use events No determination of intent underlying each event No determination of route of administration
Addiction Severity Index fifth edition[14]	Does not differentiate between therapeutic use of prescription medications and inappropriate medication use Some items focus on lifetime history of inappropriate use No determination of intent underlying each event No determination of route of administration
Current Opioid Misuse Measure[3]	Includes items not directly evaluating inappropriate use events No determination of underlying intent No determination of route of administration
Drug Abuse Screening Tool[26]	Focus on lifetime history of inappropriate use, rather than current No determination of intent underlying each event No determination of route of administration
Hansen's aberrant behaviors list[9]	Assessment of past 90 days may not adequately reflect "current" inappropriate use No determination of intent underlying each event No determination of route of administration
Jeevanjee's opioid analgesic misuse checklist[10]	Assessment of past 90 days may not adequately reflect "current" inappropriate use No determination of intent underlying each event No determination of route of administration
Manchikanti's screening evaluation tool[12]	No time frame specified for evaluating inappropriate use No determination of intent underlying each event No determination of route of administration
Pain Assessment and Documentation Tool[17]	Includes items not directly evaluating inappropriate use events No time frame specified for evaluating inappropriate use No determination of intent underlying each event No determination of route of administration
Prescription Drug Use Questionnaire[7]	Includes items not directly evaluating inappropriate use events No time frame specified for evaluating inappropriate use No determination of intent underlying each event No determination of route of administration
Prescription Opioid Abuse Checklist[6]	No time frame specified for evaluating inappropriate use No determination of intent underlying each event No determination of route of administration
Prescribed Opioid Difficulty Scale-Concern Scale[2]	Assessment of past year may not adequately reflect "current" inappropriate use No determination of intent underlying each event No determination of route of administration
Prescription Opioid Misuse Index[11]	No time frame specified for evaluating inappropriate use No determination of intent underlying each event No determination of route of administration
Prescription Opioid Therapy Questionnaire[15]	No time frame specified for evaluating inappropriate use No determination of intent underlying each event No determination of route of administration

NOTE: Adapted from Smith et al.[28]

This instrument consists of 18 self-report items designed to assess inappropriate use of prescription opioids and the putative intent using multiple-choice response options, as well as evaluating concerns about opioid use using a 0 to 10 numeric rating scale.[25] Study participants are informed that their answers will remain anonymous to the extent permitted by applicable local and national regulations, a feature implemented in an attempt to elicit honest responding.[25] The initial version of the instrument asked individuals to report on their lifetime opioid usage in a clinic setting, and an alternate version has been developed for clinical trial administration that assesses investigational drug usage over the past 30 days.[21] An online version has been developed, as

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well.[21] The SR-MAD has been recently adapted to the Prescription Opioid Misuse and Abuse Questionnaire, which is undergoing validation in support of a longitudinal study of long-acting opioids (B. Setnik, personal communication, June 29, 2015; see also https://clinicaltrials.gov/ct2/results?term=pomaq&Search).

MADDERS

MADDERS was developed with the goal of identifying and distinguishing between MAREs and identifying diversion events. This assessment system can be used retrospectively and prospectively to evaluate triggering adverse events (AEs; eg, overdose, convulsion, agitation) and drug accountability discrepancies (eg, missing doses, evidence of tampering) occurring in clinical trials that potentially reflect MAREs.[29] Using MADDERS to identify MAREs and the putative intent involves: 1) trained adjudicators evaluating triggering AEs and drug accountability discrepancies that occurred during a completed clinical trial (ie, retrospective assessment), or 2) trained study staff implementing standardized forms to probe triggering AEs and drug accountability discrepancies that are then classified by trained site investigators into the MARE categories during an ongoing clinical trial (ie, prospective assessment).

Recommended Considerations

Critical Review of SR-MAD

The greatest advantage of the SR-MAD instrument is its ease of use to identify behaviors related to misuse, abuse, and diversion of opioid medications. It can be administered to participants in prospective randomized clinical trials (RCTs) to evaluate whether inappropriate medication use is occurring. Classification of events as misuse or abuse depends upon the intent the participant ascribes to the events. For example, if a participant reports having taken more medication than was prescribed and indicates that the purpose was to "treat my pain better," that response would be identified as "misuse." If the excess medication use was reportedly undertaken "to feel pleasant or high," that would be identified as "abuse." If a participant indicates that the intent underlying their inappropriate medication use was therapeutic as well as nontherapeutic in nature (eg, "to treat pain" and "to feel high"), their usage would then be classified as both event types.

The development of the SR-MAD instrument involved several steps including cognitive interviews with individuals with chronic pain, which led to wording changes to improve comprehension of the instrument items, as well as helping to support the instrument's content validity.[21,23] To date, the version of this instrument that assesses inappropriate medication use across the lifespan has been tested in individuals who are at low and high risk of inappropriate medication use.[24,25] Additional testing is needed of the version that assesses current inappropriate medication use (ie, over the past 30 days), as well as within the context of an RCT with medications with differing abuse potential. Further information regarding the instrument's measurement properties is also needed.

Although implementing SR-MAD in a clinical trial would be relatively straightforward, the consensus perspective was that sole reliance upon self-report to determine an event's intent may lead to underreporting of inappropriate medication use events despite efforts to maintain anonymity. Participants may provide misleading information or fail to provide contextual details necessary for event classification (eg, taking excess medication "to feel less depressed or nervous" may be insufficient to determine whether this is misuse or abuse, and no follow-up is possible because of participant anonymity). Other notable limitations of SR-MAD are that a standardized training system regarding classification of misuse or abuse events does not currently exist, nor can it be used for retrospective analysis of completed RCTs. The SR-MAD does not distinguish between other MAREs identified by the ALERTT working group (ie, suicide-related event, therapeutic error[27]), although this does not detract from classification of misuse and abuse events.

Critical Review of MADDERS

The primary strengths of the MADDERS system are its assessment of MAREs retrospectively as well as prospectively, and use of standardized training for the adjudicators who classify events (in the retrospective and prospective assessments) and the study staff who collect information on triggering AEs and drug accountability discrepancies (in the prospective assessment). MADDERS also seeks out additional information regarding triggering AEs and drug accountability discrepancies.[29] For example, if retrospective assessment of a clinical trial identified a participant who had a triggering AE of "feeling drunk," then the entire AE narrative including any available trial data relevant to the event, information about the occurrence of any drug accountability discrepancies, and any additional information requested by adjudicators would be extracted from the patient-level data and provided to adjudicators who would classify the event into the MARE categories.

When using the prospective version of MADDERS during an ongoing clinical trial, triggering AEs or drug accountability discrepancies prompt further assessment by site staff to obtain additional detail about the event, contextual factors, and putative intent.[29] For example, if a participant was missing some of his/her medication at a study visit, the site staff would follow up with specific questions to determine the reason for the discrepancy, and if the investigator judged that the event was therapeutic in nature, it would be classified as "misuse." A notable advantage of prospective assessment is that additional information obtained throughout the trial can be used to revise previously classified events. If the participant continues to have drug accountability discrepancies and a urine drug screen shows there is no evidence of the medication in the participant's system, the study staff would discuss this event further with the participant. If the participant admits to selling the

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drug, the events initially classified as "misuse" can then be revised to "none of the above" with the supplemental designation of "diversion."

Initial data on the MADDERS retrospective assessment indicated that it can differentiate between drugs with and without abuse potential, providing preliminary evidence of construct validity.[29] Additionally, a high level of agreement was observed between experts adjudicating mock narratives into the event classifications begins to establish the system's reliability.[29] Implementation of MADDERS into prospective RCTs of medications with differing abuse potentials is needed.

The challenges of implementing MADDERS are that it relies in large part upon participant self-reports of AEs and requires more resources than a self-report assessment (eg, trained staff following up on triggering AEs and drug accountability discrepancies). The consensus perspective, however, was that because study staff use the information obtained from the standardized MADDERS assessment alongside their clinical judgment and any additional information (eg, urine drug testing) to inform event categorization, the added trial burden was likely to result in more accurate event categorization.

Discussion

Identifying a medication with abuse potential requires, in part, information on the medication's pharmacology, pharmacokinetics, and pharmacodynamics, as well as data from human abuse potential studies involving recreational drug users, and inappropriate use events in clinical trials of drugs affecting the central nervous system and analgesic clinical studies.[8,30,32] To obtain accurate information about inappropriate use events in clinical trials evaluating analgesic medications, as well as other medications that affect the central nervous system, a classification tool is needed that sensitively and specifically detects behaviors indicative of abuse, misuse, or other related events and classifies them into the appropriate category.

Currently, only MADDERS[29] and SR-MAD[25] are designed to identify and classify misuse and abuse events occurring in clinical trials. Both systems use self-report to identify inappropriate medication use events, and it could be argued that because individuals who use their medication inappropriately attempt to conceal and deny this behavior, these instruments will have low sensitivity in identifying abuse events (eg, missing abuse events or incorrectly classifying them as misuse events). SR-MAD offers participants anonymity to manage this concern,[25] albeit with the limitation that follow-up to gather sufficient data for classification is not feasible. MADDERS triangulates inappropriate medication use events and their putative intent by supplementing the information gathered from participant interviews with additional available data (ie, any relevant patient-level information for retrospective assessment, follow-up discussions, drug accountability discrepancies, test results, and clinical judgment for prospective assessment) that could provide context for events.[5]

Of the currently available assessments, the MADDERS system[29] is best suited to documenting and classifying inappropriate medication use events into the 6 MAREs categories (Table 1)[27] in trials of analgesic drugs.[13,20] We are aware of no assessment other than MADDERS that gathers as much information about inappropriate medication use events in an attempt to discern the putative intent underlying the event. In fact, the value of this system lies in its focus on sufficiently documenting triggering events that occur in trials, rather than on evaluating the characteristics of individuals in the trial. At this time, research is limited regarding its measurement properties (eg, inter-rater reliability, sensitivity, specificity), and data describing its performance in prospective clinical trials are needed. Despite this, we propose consideration of this system to assess MAREs in clinical trials. Other systems could also be acceptable if they directly classify events of interest into the MAREs categories and supplemental designations in a standardized way.[27] SR-MAD[25] is a promising approach to capturing misuse- and abuse-related events in prospective studies. The ability to obtain greater detail regarding participants' intent, as well as development of a standardized scoring system to distinguish between misuse and abuse events, are needed before using the SR-MAD instrument to evaluate a medication's abuse potential.

Conclusions

Clinical trials have long been designed to evaluate whether a treatment is efficacious, but it is equally critical to assess a treatment's negative effects. Specifically, greater effort is needed to identify inappropriate use events occurring in clinical trials and categorize these events on the basis of the underlying intent. In doing so, the field of medicine will be better able to evaluate a treatment's abuse potential, allowing regulators, policy makers, clinicians, and patients to weigh therapeutic benefit against abuse risk.

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