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Critical Review

Instruments to Identify Prescription Medication Misuse, Abuse, and Related Events in Clinical Trials: An ACTTION Systematic Review

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Abstract: Measurement of inappropriate medication use events (eg, abuse or misuse) in clinical trials is important in characterizing a medication's abuse potential. However, no gold standard assessment of inappropriate use events in clinical trials has been identified. In this systematic review, we examine the measurement properties (ie, content validity, cross-sectional reliability and construct validity, longitudinal construct validity, ability to detect change, and responder definitions) of instruments assessing inappropriate use of opioid and nonopioid prescription medications to identify any that meet U.S. and European regulatory agencies' rigorous standards for outcome measures in clinical trials. Sixteen published instruments were identified, most of which were not designed for the selected concept of interest and context of use. For this reason, many instruments were found to lack adequate content validity (or documentation of content validity) to evaluate current inappropriate medication use events; for example, evaluating inappropriate use across the life span rather than current use, including items that did not directly assess inappropriate use (eg, questions about anger), or failing to capture information pertinent to inappropriate use events (eg, intention and route of administration). In addition, the psychometric data across all instruments were generally

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limited in scope. A further limitation is the heterogeneous, nonstandardized use of inappropriate medication use terminology. These observations suggest that available instruments are not well suited for assessing current inappropriate medication use within the specific context of clinical trials. Further effort is needed to develop reliable and valid instruments to measure current inappropriate medication use events in clinical trials.

***Perspective:** This systematic review evaluates the measurement properties of inappropriate medication use (eg, abuse or misuse) instruments to determine whether any meet regulatory standards for clinical trial outcome measures to assess abuse potential.*

***Key words:** Abuse potential, misuse, clinical trial, measurement properties.*

Research on prescription opioid analgesics suggests wide-ranging rates of abuse and addiction,[24,29] from less than 1% in a non-peer-reviewed letter to the editor focusing on postoperative pain medication abuse[49] to upward of 45% in a study of 20 patients with pain and a history of substance abuse.[19] Such heterogeneous estimates of abuse and addiction complicate the determination of the actual abuse risks associated with opioid analgesics. It is incumbent upon researchers to evaluate both analgesic benefit and the prevalence of distinct categories of *current inappropriate analgesic use events* (ie, abuse events, misuse events, suicide-related events, and therapeutic errors)[54] in randomized clinical trials (RCTs) validly and reliably in order to accurately identify a treatment's abuse potential (ie, use for nonmedical psychoactive effects).[59] Capturing distinct inappropriate use events (ie, behaviors indicating abuse, misuse, and other inappropriate medication use) in RCTs assists in evaluating a property of the drug (ie, its abuse potential), rather than identifying clinical conditions in the users (eg, drug use disorder). The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) emphasize collecting data on the occurrence of abuse, misuse, and diversion in phase 3 clinical trials of centrally acting drugs[59] and analgesic clinical studies.[22] Information on these events is then evaluated in combination with other relevant data (eg, pharmacokinetics/pharmacodynamics and human abuse potential studies in recreational drug users) to determine a treatment's abuse potential.[59] Currently, neither the FDA nor the EMA recommends any instruments to assess inappropriate medication use as an outcome in clinical trials requiring regulatory review, although available FDA guidances and EMA reflection papers present recommendations for developing patient-reported outcome instruments and qualifying drug development tools.[21,58,60]

Unlike prior reviews,[5,14,46,47] we explore whether available inappropriate use instruments fulfill regulatory standards by providing evidence of content validity (ie, "Evidence that the instrument measures the concept of interest including evidence from qualitative studies that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use"[58(p11)]) for assessing a selected concept of interest (ie, "the *thing* being measured"[58(p2)]) within a specific context of use (ie, "the intended application in terms of population, condition, and other aspects of the measurement context for which the instrument was developed"[58(p20)]). For the purposes of this review, the concept of interest and the context of use are current inappropriate use event categories (ie, abuse events, misuse events, suicide-related events, and therapeutic errors occurring in clinical trials [ie, phases 2 and 3], as defined by the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks [ACTTION] public-private partnership[54]). Further, we examine whether the instruments provide sufficient data regarding cross-sectional reliability and construct validity, longitudinal construct validity (ie, hypothesized relationships between concepts over time),[58] ability to detect change, and responder definitions to meet regulatory standards for assessing benefits and risks in clinical trials.[21,58,60] We do not review measures for abuse liability assessment in early-phase studies with substance abusers[16] or those designed to predict the development of inappropriate medication use.[14,57] It is important to acknowledge that most instruments reviewed were developed for other purposes (eg, diagnosis of substance use disorders), rather than identifying current inappropriate medication use events occurring in clinical trials. These instruments, many of which might appear suitable to measure inappropriate medication use, were included in this review to evaluate their applicability to the specific concept of interest and context of use, a necessary first step in developing an instrument that is valid for the selected concept and context. Our comments on the appropriateness of each instrument for the specified concept and context should not be taken to refer to each instrument's appropriateness for evaluating other concepts (eg, patient risk of developing a drug use disorder) in different contexts (eg, clinical practice).

Methods

Literature Search

We conducted an initial systematic search (search 1) of the U.S. National Library of Medicine database (ie, PubMed; http://www.ncbi.nlm.nih.gov/pubmed) using