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Letter to the Editor

Making pharmacotherapy trials for substance use disorder more efficient: Leveraging real-world data capture to maximize power and expedite the medication development pipeline

A National Institutes of Health priority is to develop novel pharmacotherapies for substance use disorder (SUD), but medication trials require considerable resources (Tompkins et al., 2015). Thus, randomized controlled trials (RCTs) must be cost-effective, timely, and reflective of medications' true efficacy. An often-overlooked means of accomplishing these goals is to assess substance use more reliably. Increasing reliability increases power (Beckstead, 2013), reducing the required participant sample and increasing confidence in results.

The gold standard of use assessment is biomarker-confirmed self-report. Biomarkers provide abstinence data, but limited quantity-frequency information. Conversely, self-report (e.g., Timeline Follow-back [TLFB]; Sobell and Sobell, 1992) provides quantity-frequency, but suffers from estimation and recall errors. These errors can be minimized via real-world data capture, in which participants report their use at least daily in their natural environment and only need to remember use over brief periods. Previous work suggests real-world data capture provides advantages over TLFB (e.g., Kaplan and Koffarnus, 2019). Yet, while many researchers are aware of the benefits, few SUD RCTs utilize real-world data capture. Perceived difficulty or cost may be barriers to implementation.

Daily diaries (DD) are a cost-effective, easy-to-implement, and low-burden means of accurately assessing use, even over extended time periods. Unlike older paper-and-pencil approaches, modern technology facilitates DD with temporal precision and compliance (Vachon et al., 2019). More intensive options (e.g., ecological momentary assessment) also exist. To illustrate, 21 smokers in a two-week pilot study reported cigarettes per day (CPD) via DD, provided expired breath carbon monoxide (CO) at 0, 7, and 15 days, and completed an end-of-study 15-day TLFB (Tomko et al., 2019). For this illustration, CO levels represent an objective smoking measure. TLFB-CPD explained 40 % and DD-CPD explained 49 % of the variance in CO. Used as preliminary data in a power analysis for an RCT targeting a 0.55 Cohen's D at 80 % power, this means 216 participants would be required if DD-CPD was the outcome vs. 260 for TLFB-CPD, a 16.9 % difference (Beckstead, 2013). We also examined DD-CPD supplementing TLFB-CPD for missing DD data (DD compliance was 85 %). Supplemented DD-CPD explained 48 % of the variance, essentially unchanged.

This reduction would yield significant savings through reduced recruitment, administration, treatment, laboratory, and compensation costs. The smaller sample size could also be collected more quickly, reducing trial completion time and speeding dissemination. In comparison, while DD costs vary, inexpensive options exist, including low-cost options via smartphone application or text message, and most Americans own smartphones. Technology costs in Tomko et al. (2019) were $3000 in the first year and $1000 in subsequent years. As an example based upon our past RCTs, assuming enrollment of 4 participants/month, $14/week in DD compensation per participant ($2/DD), and $9000 in technology costs for 5 years of data collection, DD would cost $45,288 for a 216-person, 12-week RCT. In contrast, for recruitment alone, which can exceed $2600 per completer, estimated savings could total $114,400 (Tompkins et al., 2015). Further, 44 fewer participants would allow the RCT to finish 11 months earlier.

Real-world data capture has limitations. Work is needed comparing it to TLFB for substances besides alcohol and cigarettes, different patterns of use (e.g., heavy vs. light), and binary outcomes (e.g., abstinence) standard for SUD RCTs. DD also cannot address other self-report limitations, including intentional misreporting. Ambulatory devices (e.g., CO monitors, transdermal alcohol sensors) are emerging and may provide increased validity over self-report, albeit at higher costs. However, existing devices do not always demonstrate clear superiority over self-report (e.g., Kaplan and Koffarnus, 2019).

Real-world data capture offers the means to make RCTs more efficient through increasing power, reducing expenses, and expediting findings. Other benefits include assessing phenotypes (e.g., craving, subjective effects) with ecological validity. Researchers should consider using real-world data capture in SUD RCTs to improve the medication development pipeline.

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Contributors

RC wrote the initial draft. EM, KG, and RT contributed to the design and execution of the pilot study. RC, LS, and RT conducted statistical and financial analysis. All authors contributed to the writing of the letter. All authors have reviewed and approved the final letter.

Declaration of Competing Interest

Ryan W. Carpenter, Lindsay M. Squeglia, Noah N. Emery, Erin A. McClure, Robert Miranda Jr., and Rachel L. Tomko declare that they have no conflicts of interest. Kevin M. Gray has provided consultation to Pfizer, Inc. for work unrelated to the content of this manuscript.

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