Applying Evidence From Clinical Trials: Need for Pediatric Learning Health System Research

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Nationally, the lifetime and 12-month prevalences of adolescent major depressive disorder (MDD) have been reported to be 11.7% and 8.2%, respectively.[1,2] Recent data have also shown increases in prevalence from 2004 to 2015.[3] These trends, coupled with a limited availability of pediatric and adolescent mental health specialists, have resulted in an increased demand for frontline pediatric providers to manage depression. Clinical management involves the use of pharmacological and psychotherapy interventions. Decisions on the most appropriate treatment course for a specific patient are typically based on the biomedical knowledge base composed of research studies as well as the judicious application of clinical experience and wisdom.

Findings from randomized controlled trials (RCTs) that were rigorously performed and transparently reported in peer-reviewed medical journals are the most influential type of evidence, affecting both clinical decision-making and guideline development. The RCT has the reputation of being the gold standard for evidence generation because of its capacity to balance confounders (both measured and unmeasured) between groups, thereby strengthening the validity of treatment effect estimation. However, even this powerful study design has limitations of which practicing clinicians should be aware.[4,5] Ideally, eligibility criteria for clinical trials should be narrow to ensure that observed effects can be attributed to the treatment (internal validity) yet broad enough so that results can be generalized to as many patients as possible (external validity). For practicing clinicians, it is not enough to know whether a treatment works; it is also important to know for whom the treatment works and for whom it does not. Although this tension is not new in either adult or pediatric clinical research, it continues to be of critical clinical and scientific importance and should always be considered when applying clinical research studies to patients.

These trade-offs between internal and external validity are clearly illustrated by the findings of Blanco et al[6] in the current issue. Using data from the National Comorbidity Survey Replication Adolescent Supplement, the authors implemented common eligibility criteria to estimate the proportions of all adolescents affected by MDD who would be included in a typical RCT. They found that 60% of affected youth would be excluded from pharmacological trials and 40% would be excluded from psychotherapy trials if common eligibility criteria were applied. These exclusions were often a consequence of co-occurring morbidities.[6] However, practicing clinicians provide care in real-world settings in which the co-occurrence of mental and other health conditions is common, rendering much of the pediatric evidence base for MDD not applicable to a large share of the patients who need treatment.

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To fill the many gaps in the understanding of MDD management (and more generally, the pediatric knowledge base), a new approach for augmenting the conventional RCT is needed. We believe that the emerging field of learning health system research addresses this need. As defined by the National Academy of Medicine, a learning health system is any type of health care delivery system that combines research, data science, and quality improvement to yield knowledge as a byproduct of the patient-clinician interaction in real-world settings.[7] A recently commissioned study by the Agency for Healthcare Research and Quality characterized the unique features of learning health system research and the competencies that investigators will need when conducting this type of scientific inquiry.[8] The characteristics include research that is conducted in real-world settings, in which the researcher is embedded in the health system in which the work is being done and both patients and clinicians are engaged in the design and conduct of the study. RCTs in learning health systems typically have few patient selection criteria to produce results that are valid for a large majority of affected patients seen by practicing clinicians. This type of research has been called pragmatic because it produces practical information that can directly inform clinical decision-making.

Additionally, in 2014, the Patient-Centered Outcomes Research (PCOR) Institute launched PCORnet, which is aimed at creating a sustainable national infrastructure that would support pragmatic observational research and clinical trials.[9] PEDSnet, a PCORnet network with data on >5.4 million children and youth, serves as a model pediatric learning health system that purposefully integrates research and improvement as part of 1 system of care.[10] The learning health system model does more than just leverage big data for large clinical trials; it also engages a distributed network of stakeholders in working collaboratively to generate meaningful research questions and the evidence needed to rapidly learn what works for each patient.

As Blanco et al[6] remind us, the need to fill the gaps in the pediatric knowledge base has become increasingly acute. The applicability of findings to routine clinical care remains an important and vital goal as the development of new, evidence-based treatments continues. New learning health system models serve as emerging solutions in which patients, clinicians, researchers, and health systems collaborate to conduct pragmatic research in real-world settings. Although learning health systems provide a path forward for producing data that can support decision-making on the frontlines of care, access to high-quality mental health services for children and youth must also continue to be a national priority.

ABBREVIATIONS

MDD: major depressive disorder
PCOR: Patient-Centered Outcomes Research
RCT: randomized controlled trial

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