Received: 28 July 2021 | Revised: 4 December 2021 | Accepted: 8 December 2021

DOI: 10.1111/cts.13216

MINI-REVIEW

Target to treatment: A charge to develop biomarkers of response and tolerability in child and adolescent psychiatry

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Funding information
This work was supported, in part, by the NCATS Clinical and Translational Science Award pilot grant (S.L.S.), part of UL1TR002366. Additional support was provided by the Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD) through Grants R01HD098757 (J.R.S.) and R01HD099775 (J.R.S.) and by the Yung Family Foundation. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH or NCATS.

Abstract

The current pediatric mental health crisis is characterized by staggering rates of depression, anxiety, and suicide. Beyond this, first-line pharmacologic interventions for depressive and anxiety disorders in children and adolescents produce variable responses with two in five youths failing to respond. Given the heterogeneity of treatment response in pediatric depressive and anxiety disorders, pharmacodynamic biomarkers are necessary to develop precision therapeutics by identifying clear targets to guide treatment. This mini-review summarizes candidate biomarkers and their development in pediatric mental health conditions. A framework for how these biomarkers may relate to safety, efficacy (e.g., surrogates for clinical endpoints), tolerability or target engagement (i.e., drug action) in children and adolescents is also presented. Taken together, accumulating data suggest that, in children and adolescents with myriad psychiatric disorders, pharmacodynamic biomarkers could facilitate developing drugs with well-defined targets in specific populations, could inform treatment decisions, and hasten patients' recovery.

INTRODUCTION

The current pediatric mental health crisis is characterized by staggering rates of depression, anxiety, and suicide—now the second leading cause of death among children and young adults aged 10–24.[1] Whereas inadequate psychiatric resources, disparities in care, and limited evidence for many pharmacologic treatments for anxious and depressed youth fuel this crisis, the stress of a pandemic has further intensified this perilous situation.[2,3]

CURRENT APPROACHES TO DEVELOPING PSYCHOPHARACOLOGIC INTERVENTIONS FOR YOUTHS

The kindling for this crisis is a complicated pediatric clinical trials landscape which created a precarious imbalance between evidence-based treatments and mental health needs. Few psychotropic medications have US Food and Drug Administration (FDA)-approval for use in youths with depressive and anxiety disorders and off-label

prescribing is the norm.[4] Beyond this, antidepressants with FDA-approvals for depressive and anxiety disorders (e.g., fluoxetine, escitalopram, and sertraline) produce variable responses and two in five adolescents fail to respond.[5] Clinical trials in children and adolescents with depressive and anxiety disorders frequently rely on unidimensional measures of overall symptom severity as the primary outcome. These measures generally use a linear combination (i.e., average or sum) of measurement across multiple symptom dimensions, which can be misleading. Beyond this, and high placebo response rates,[6] improvement in some symptoms may be more important for overall improvement than other symptoms, and symptoms can interact in complex ways. A related concern is that in certain youths who have "depression" or "anxiety," experience symptoms driven by exogenous factors—life struggles, adversity, and chronic variable stress—that boost scores on some measures. Thus, core symptoms may not drive these symptom ratings; rather, they may be driven by impairment. Finally, traditional approaches to identifying effective treatments for children and adolescents with mental health conditions are often mired by joint significance concerns related to efficacy and tolerability.[7] Yet, response (i.e., efficacy) is inherently linked to tolerability and vice versa, but the joint model of both variables needed to account for their interaction are rare in clinical psychopharmacologic treatment trials in youths. These issues complicate the interpretation of these studies and lead us to abandon potentially effective interventions.

Children and adolescents who are lucky enough to respond to medication often enjoy functional recovery; however, response can take months. Delayed response—which is common for antidepressant medications in children and adolescents—relates, in part, to pharmacodynamic processes (e.g., activation of second messenger systems and gene expression). Children, adolescents, and their families deserve precision therapeutics in pediatric mental health—an approach that identifies who will respond to what medication, at what dose the first time.

THE POTENTIAL ROLE OF OBJECTIVE BIOMARKERS OF RESPONSE IN CHILD AND ADOLESCENT PSYCHIATRY

Objective biomarkers of response (i.e., pharmacodynamic biomarkers) are critical to developing precision therapeutics; they hold the potential to identify clear targets to guide treatment. These biomarkers may speak to safety, efficacy (e.g., surrogate for clinical end point or how a patient feels or functions), tolerability, or target engagement (i.e., drug action).[8] Pharmacodynamic biomarkers can be leveraged for both drug development and repurposing (Figure 1); they can be employed to demonstrate quantifiable response and facilitate successful trials through processes, such as sample stratification (e.g., enrichment with those who demonstrate evidence of target engagement or pathway modulation), exposure optimization, and dose finding. For psychotropic medications, pharmacodynamic biomarkers are urgently needed to identify subgroups that are more likely to respond (or not respond) and at what exposure early in drug development (e.g., exposure optimization). This could focus drug development efforts on a targeted group that is more likely to respond and, at the same time, identify patients that are less likely to respond at a given exposure (e.g., due to genetic variability leading to reduced receptor expression) who may benefit from alternative treatments or dosing schemes or who may have a distinct disease phenotype. Pharmacodynamic biomarkers that predict clinical outcomes can be used to target treatment and may function similarly to predictive or prognostic biomarkers.[8]

Given the heterogeneity of depressive and anxiety disorders and the common use of self-reported symptom monitoring, which is complicated by recall bias, pharmacodynamic biomarkers are necessary to advance mental health therapeutics for children and adolescents. This mini-review describes how we might qualify pharmacodynamic biomarkers in child and adolescent psychiatry to (1) aid in drug development and repurposing and (2) to improve the therapeutic landscape.

DEVELOPING PHARMACODYNAMIC BIOMARKERS OF RESPONSE IN CHILD AND ADOLESCENT PSYCHIATRY

The development of pharmacodynamic biomarkers must be rigorous to ensure the quality and strength of evidence supports the context of use. Below, we pose four questions that must be answered as we develop pharmacodynamic biomarkers in child and adolescent psychiatry. Examples from pediatric pharmacodynamic biomarker studies are used preferentially, when available, to illustrate our points. However, due to the dearth of pediatric data, examples from adults are also included.

How do you plan to use pharmacodynamic biomarkers?

First, we must identify the objective of pharmacodynamic biomarker development. Is the pharmacodynamic biomarker intended to support drug approval

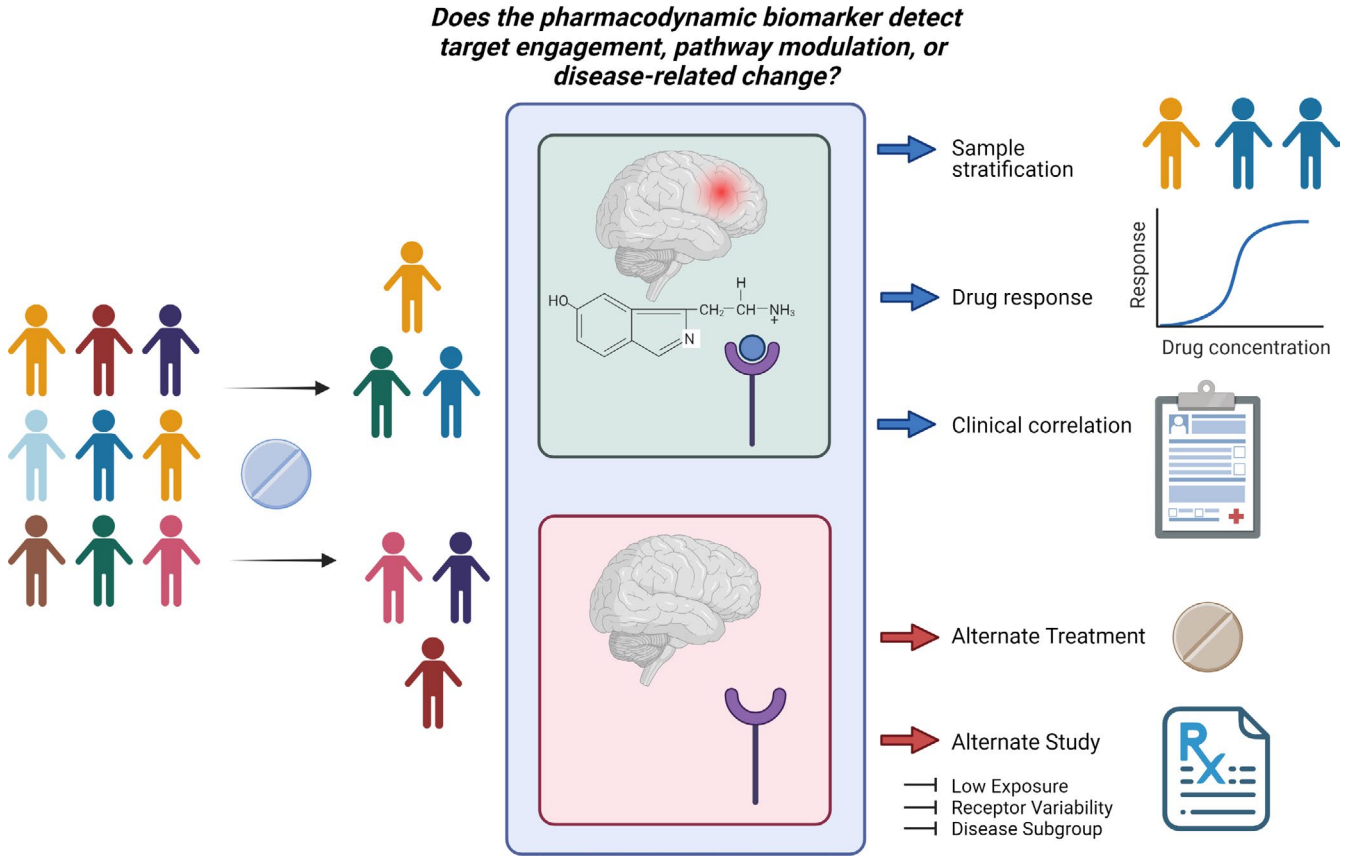

FIGURE 1 The potential of pharmacodynamic biomarkers to aid in drug development, repurposing, and precision therapeutics in children and adolescents

or labelling decisions? Will it serve as the primary end point or surrogate end point (i.e., intended to substitute for a clinical outcome)? If intended to support regulatory decisions, formal qualification of the pharmacodynamic biomarker should be considered. Biomarker qualification is a formal, complex and iterative process which requires input from multiple stakeholders (e.g., sponsors and regulatory agencies). The FDA has provided guidance for biomarker qualification[9] and various groups have reviews describing the process of integrating regulatory guidance (e.g., the FDA and European Medicines Agency [EMA]) into biomarker development.[10]

The qualification process may be initiated by an individual, a sponsor, or consortia who then bears the burden of risk. An investigator may study a pharmacodynamic biomarker for a single compound, find the data to be promising, and then generate interest within a consortium for further development with related compounds. Biomarker qualification leads to a spectrum of outcomes, from integration in the drug development process to involvement in approval decisions and inclusion in labeling. Unfortunately, there is yet to be a qualified pharmacodynamic biomarker for mental health treatment.

The use of lactate infusion to probe benzodiazepine response in CO_2-sensitive panic disorder serves as an example of a potential pharmacodynamic biomarker that stopped short of formal qualification. Table 1 lists this and other potential pharmacodynamic biomarkers that require additional study.

If formal qualification is not desired or cannot be achieved due to limited evidence, an investigator may seek guidance from the FDA to gain insight or garner support that a promising biomarker warrants continued study from a regulatory perspective.

What do you expect the biomarker to tell you?

Answering this question requires determining the "context of use," which defines what will be detected in the clinical population of interest and will dictate the type of studies required to provide adequate evidence. The context of use should be grounded in a biological rationale that is shared between the mechanism of action of the drug and pharmacodynamic biomarker. As an example, Javitt et al. recently evaluated functional magnetic

TABLE 1 Potential PD biomarkers in pediatric and adolescent psychotropic drug development

Potential biomarker	Potential context of use	Potential pharmacologic probe	PD	Pred[a]	Author (year)
Lactate-induced panic attack	Detect anxiolytic drug effect in CO_2-sensitive panic disorder	Lactate	•		Vollmer et al. (2015)[14]
Platelet serotonin transporter kinetics	Determine treatment-related effects on serotonin transporter inhibition in platelets as a proxy for brain serotonin transporter inhibition	Sertraline (children and adolescents), Fluvoxamine (adults), Fluoxetine (adults)	•		Sallee et al. (1998),[15] Rausch et al. (2001),[16] Rausch et al. (2002),[17] Rausch et al. (2005),[18]
Serotonin receptor binding detected by PET	Quantify initial and steady state treatment-related effects on serotonin receptor binding	Nefazodone (adults), Paroxetine (adults), Olanzapine (adults)	•	•	Kapur et al. (1997),[19] Kapur et al. (1998),[20] Meyer et al. (1999),[21] Meyer et al. (2001)[22]
dMCC %BOLDΔ detected by fMRI with ketamine infusion	Detect glutaminergic pathway modulation in psychotic disorders to aid in drug development	Ketamine vs. placebo	•		Javitt et al. (2018)[23]
Cortico-limbic %BOLDΔ detected by fMRI during passive-food view	Detect drug response in adult women with binge eating disorder	Lisdexamfetamine vs. placebo	•	•	Fleck et al. (2019)[24]
Task-based qEEG	Detect stimulant response in pediatric ADHD	Methylphenidate, dextroamphetamine	•	•	Chabot et al. (1999),[25] Song et al. (2005),[26] Isiten et al. (2017),[27] Ogrim and Kropotov (2019)[28]
Amygdala-based whole brain FC during resting state fMRI	Detect early response to escitalopram in adolescents with generalized anxiety disorder	Escitalopram vs. placebo	•		Lu et al. (2021)[29]
Cortico-limbic FC during task-based fMRI	Detect cortico-limbic pathway modulation in high-risk depressed youth	Omega−3 polyunsaturated fatty acids (n−3 PUFA)	•	•	Li et al. (2021),[30] McNamara et al. (2021)[31]
Cortical inhibition and excitation during TMS	Detect GABAergic (SICI) and Glutaminergic (ICF) pathway modulation in adolescents with major depressive disorder		•		Croarkin et al. (2013),[32] Lewis et al. (2016),[33] Doruk Camsari et al. (2019)[34]

TABLE 1 (Continued)

Potential biomarker	Potential context of use	Potential pharmacologic probe	PD	Pred[a]	Author (year)
Short-interval intracortical inhibition during TMS	Detect GABAergic pathway modulation in Autism Spectrum		•		Masuda et al. (2019)[35]
40 Hz ASSR detected by EEG/MEG	Detect NMDA/glutaminergic modulation in Schizophrenia (potential use in depression, suicidality)	NMDA antagonist AV−101 (adults)	•		Murphy et al. (2021)[36]
NeuroCart (drug-sensitive CNS test battery)	Detect blood-brain barrier penetration and neurophysiologic modulation by candidate CNS compounds		•		Groeneveld et al. (2016),[37] Sverdlov et al. (2021)[38]
Baseline glutamate, Glutamate + glutamine concentrations in ACC, vlPFC detected by ^{1}H MRS	Determine initial change in neurotransmitter dynamics in adolescents with bipolar I disorder	Divalproex	•	•	Strawn et al. (2012)[39]
Prefrontal NAA concentrations detected by ^{1}H MRS	Quantify initial neurotransmitter dynamics in bipolar I disorder	Quetiapine (adults), Olanzapine (adolescents)	•	•	Adler et al. (2013),[40] DelBello et al. (2006)[41]
Prefrontal-amygdala FC during resting state fMRI	Detect treatment-related connectivity effects in youth with bipolar disorder	Lithium, Quetiapine	•	•	Lippard et al. (2021)[42]
Cortical %BOLDΔ detected by fMRI during attention task	Detect treatment-related functional cortical activity in children	DHA vs. placebo	•		McNamara et al. (2010)[43]

Abbreviations: ACC, anterior cingulate cortex; ADHD, attention deficit hyperactivity disorder; ASSR, auditory steady state response; BOLD, blood-oxygen level dependent response; CNS, central nervous system; dMCC, dorsal mid cingulate cortex; EEG, electroencephalogram; FC, functional connectivity; fMRI, functional magnetic resonance imaging; ^{1}H MRS, proton magnetic resonance spectroscopy; ICF, intracortical facilitation; MEG, magnetoencephalogram; NMDA, N-methyl-D-aspartate; PD, pharmacodynamics; PET, positron emission tomography; Pred, Predictive; qEEG, quantitative electroencephalogram; SICI, short-interval cortical inhibition; TMS, transcranial magnetic stimulation; vlPFC, ventral lateral prefrontal cortex.

[a]Potential pharmacodynamic biomarkers that may also serve as predictive biomarkers based on the purpose of the primary study.

resonance imaging (fMRI) as a pharmacodynamic biomarker of glutaminergic "functional target engagement" for early phase drug trials (Table 1). Blood oxygen level-dependent response, thought to be partially dependent on glutamate release, was detected after ketamine (i.e., glutaminergic MOA) and placebo in a prespecified region (i.e., midcingulate cortex) thus detecting functional target engagement or, perhaps more precisely, glutaminergic pathway modulation.

Another example is the use of fMRI to detect reward response in eating disorders. Frank et al. quantified predictive error reward response in prespecified regions of interest and demonstrated exaggerated reward response (i.e., positive predictive error) in restrictive eating disorders and diminished reward response (i.e., negative predictive error) in those with binge-based eating disorder. Whether this biomarker could detect pharmacodynamic response is yet to be investigated. It is plausible

that reward system modulation by opioid antagonism would be detected given both the drug and predictive error detected by fMRI interface with an opioid reward mechanism.[11]

Quantitative electroencephalogram (qEEG) has been explored as a pharmacodynamic biomarker in pediatric attention deficit hyperactivity disorder (ADHD) treatment and appears responsive to stimulant medication (Table 1). However, controlled studies with a clear and consistent context of use are lacking. Future studies should identify the optimal qEEG measure (e.g., theta/beta ratio), connect the biological rationale of the measure with the medication mechanism of action, and determine a relevant outcome (e.g., identifying methylphenidate vs. amphetamine responder).

What steps need to be taken to ensure analytical validity?

In other words, what evidence is needed to ensure the pharmacodynamic biomarker measures what its intended to measure? The extent of validation will depend, in part, on the answers to the above questions, particularly the context of use. Mirroring the analytical method validation process for drugs, elements such as sensitivity, specificity, reproducibility, and reliability should be considered and intentionally tested. Sources of biological variability (e.g., genetic, metabolomic) should also be defined and explained, if possible. As an example of reproducibility and reliability, the study design utilized by Javitt et al. to develop a pharmacodynamic biomarker of glutaminergic target engagement included a multisite neuroimaging feasibility evaluation. This is important given multisite trials are inherent in many drug-development programs and evidence of biomarker consistency across sites, particularly for neuroimaging, is necessary.

Additional considerations for qEEG as a pharmacodynamic biomarker include the development and study of consistent protocols that control conditions such as eye position (i.e., open or closed), sleep deprivation, number of electrodes, and task versus resting state.

What are considerations for clinical validity?

Pharmacodynamic biomarkers may or may not correspond with a clinical outcome based on the available evidence or proposed context of use. At a minimum, pharmacodynamic biomarkers should detect target engagement, pathway modulation, or a disease-related change involving the drug mechanism of action. A recent randomized controlled trial of escitalopram in adolescents with generalized anxiety disorder utilized functional connectivity detected by resting state MRI to show that early functional connectivity changes (e.g., 2 weeks post-treatment) predicted clinical improvement in anxiety symptoms at 8 weeks (Table 1). If replicated, this biomarker, serving both pharmacodynamic and predictive purposes, could shave weeks off the response time for many patients that results from delays in switching medication later in treatment. This is particularly important given that randomized controlled trials of adolescents with depression reveal that early response and early changes in interventions are associated with greater improvement compared to delayed changes in treatments.[12]

Taking the above eating disorder example from Frank et al. a step further, longitudinal studies may be designed to understand how well fMRI-determined reward response upon acute treatment with reward modulating medications (e.g., opioid antagonists) predicts remission or symptom burden.[11] Clearly, this work may take years to establish and better therapeutics are urgently needed.

In the interim, the pharmacodynamic biomarker could potentially serve as a reasonably likely surrogate end point for a clinical outcome, meaning it detects an effect that is expected, but not established to have clinical benefit.[8] One example of work in progress is the identification of synaptic alterations by positron emission tomography (PET). Evidence suggests that reduced synaptic density throughout the brain may be seen in individuals with major depressive disorder.[13] Synaptic alterations may represent a surrogate for functional deficits and symptoms, but further work is needed to establish the connection. The glutaminergic agent, ketamine, increases synaptogenesis in a murine model. Whether ketamine produces the same effect in humans is yet to be determined; however, the development of PET as a biomarker of synaptic alterations may elucidate mechanisms of action for ketamine's antidepressive effects and provide a tool for facilitate novel therapeutic approaches.

For pediatric mental health disorders, identifying the "gold standard" clinical outcome for which to establish clinical validity requires multidisciplinary discourse, particularly given our understanding of the limitations of self-report clinical assessment tools.

CONCLUSION

To combat the pediatric mental health crisis and reduce rates of death and disability that result from ineffective treatment, we must develop better therapeutics and use existing therapeutics with more precision.

Pharmacodynamic biomarkers could allow us to reimagine the therapeutic landscape. These biomarkers could hasten the development of drugs with well-defined targets in specific populations, inform treatment decisions, and potentially restore functioning and decrease distress more quickly. However, developing these pharmacodynamic biomarkers requires analytic validity and a process that is mechanistically and clinically informed and carefully considers the context of use. We have briefly reviewed potential pharmacodynamic biomarkers and specific considerations to foster thought, facilitate identifying clear targets, and furthering the development of promising options in child and adolescent psychiatry. The time to act is now.

CONFLICT OF INTEREST

Dr. Strawn has received research support from AbbVie, PCORI, and the National Institutes of Health. He has provided consultation to Intracellular Therapeutics and the FDA. He receives royalties from Springer Publishing and UpToDate and received material support from Myriad. He has also received honoraria from CMEology, Genomind, Neuroscience Education Institute, the American Academy of Pediatrics, and the American Academy of Child and Adolescent Psychiatry. All other authors declared no competing interests for this work.

DISCLOSURE

As an Editor-in-Training for *Clinical and Translational Science*, Stephani Stancil was not involved in the review or decision process for this paper.

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How to cite this article: Stancil SL, Tumberger J, Strawn JR. Target to treatment: A charge to develop biomarkers of response and tolerability in child and adolescent psychiatry. *Clin Transl Sci*. 2022;15:816-823. doi:10.1111/cts.13216