Objective: The rapid emergence of translational developmental neuroscience as the key driver in understanding the onset of mental illness, the restructuring of academic health science centers on the NIH Roadmap, and dramatic shifts in drug, biological, device, and psychosocial intervention development all have important consequences for pediatric anxiety disorders as a field. Method: This article, which tracks the final presentation at a day-long symposium on pediatric anxiety disorders at the 2010 annual meeting of the Anxiety Disorders Association of America (ADAA), will try to outline where the field will head over the next decade as these forces combine to shape research and practice. Results: After 20 years of large comparative treatment trials that have defined the place of current generation treatments, the field is shifting toward interventions that will emerge from the revolution in translational developmental neuroscience and that herald the dawn of stratified and ultimately personalized medicine. With a much more efficient discovery to translational continuum, intervention development and dissemination will benefit from the concurrent transformation of the clinical and clinical research enterprise. Conclusion: Dramatic advances in science and changes in the structure of medicine will condition the future of clinical research across every therapeutic area in medicine. For the field of pediatric anxiety disorders to thrive it will be important to embrace and actively participate in this revolution so that anxious youth are viewed as a key target population and, consequently, preemptive, preventive, and curative interventions will be developed for children by first intent. Depression and Anxiety 28:88–98, 2011.

Key words: developmental neuroscience; healthcare policy; biomarkers; clinical trials; anxiety disorders

Over the past several years, the scientific context for thinking about pediatric anxiety disorders has shifted dramatically. Echoing longstanding data in youth showing that anxiety disorders begin early and predict disorder in adulthood, epidemiological data now confirms that the great majority of anxious ill adults were first mentally ill as children. At the same time, recent advances in translational developmental neuroscience have shown that mental illnesses of all types can be referenced directly to the developing central nervous system and its interactions with the environment. The simple fact that these are trajectory-based illnesses have enormous implications for the nature and organization of how we understand interventions for anxious youth. Despite the fact that the fundamental biology will be difficult to disentangle and...
where it does it may not initially be clear how to translate, say, a newly discovered genetic deficit in a gene that determines neuronal migration into a drugable target.\cite{7,8} Efforts to preempt, prevent, and cure pediatric anxiety disorders across the lifespan will have to begin in childhood using interventions that directly target key neurodevelopmental processes that drive trajectories of atypical as contrasted to typical development.\cite{9}

Responding in part to the recent National Advisory Mental Health Council (NAMHC) workgroup report (co-chaired by Drs. March and Pat Lewis) that called for a transformational approach to understanding neurodevelopmental disorders\cite{5} the NIMH not only “gets it” but is driving the shift from adult to pediatric studies. Tom Insel, the current NIMH Director, recently articulated a strategic plan for the NIMH that emphasizes interventions that emerge from the NIMH’s investment in trajectory-based discovery and translational neuroscience.\cite{6} ‘The driving vision is to explicate the underlying neurobiology, identify new treatment targets, develop drugs, biologics, devices, and refined psychosocial interventions for new targets, and do so in a lifespan context that emphasizes early developmental events.

In addition to advances in translational science, the NIH Roadmap also points the field toward changes in the structure of academic medicine\cite{10} that dovetail with public policy changes intended to encourage what the Institute of Medicine calls the learning and accountable health system.\cite{11} Focused on enhancing the knowledge and process environment in order to drive quality improvement,\cite{12} the Roadmap uses a network of Clinical Science Translation Awards (CTSA) to 60 academic health centers that will form the backbone of the NIH investment in discovery, translational, and clinical research. With an informatics infrastructure in place that allows context-based decision support,\cite{13} health systems can learn from patient care and areas of low performance can be improved.\cite{14}

Without a fundamental understanding of the biology of mental illness to inform intervention development very difficult problem—interventions will continue to fail at proof of concept or worse at Phase III. Consequently, there has been a dramatic change in the willingness of the pharmaceutical industry to invest in research and development in neurosciences medicine in general and in psychiatry in particular.\cite{15} While tools and technologies, such as the ability to define the patterns of gene expression and to manipulate the major pathways for signal transduction in brain subregions as they impact early development, now permit interrogation, the CNS in model organisms and human children, the translational payoff is years away.\cite{8,15,16} Hence, driven by high costs, an empty pipeline, success rates that are lower for neuroscience trials that in any other therapeutic area, competition with generics, and the need to satisfy not only the FDA but payers regarding a treatments incremental value,\cite{14} companies such as Glaxo-Smith-Kline and AstraZenica have pulled out of R&D for mood and anxiety disorders altogether.\cite{17} With some exceptions notably with biotech and small pharma, many others are downsizing preferring to wait until improvements in our understanding of fundamental biology generates new drugable targets that can be moved through the preclinical drug development process and eventually into early phase clinical trial programs.\cite{18} Co-chaired by Drs. March and David Lewis, the NAMHC recently completed a report, *From Discovery to Cure*, that lays out the near term future for NIMH-funded interventions research.\cite{19} Given its enormous investment in discovery and translational neuroscience, all targeted toward the search for personalized interventions, the Council report aligns the Institute with the turn toward early phase proof of concept studies seen in the industry.

Accordingly, the NIMH also is moving away from studying current generation treatments toward an emphasis on discovery and translational neuroscience and, where the science is ready; it results in early phase intervention development.\cite{19} The consequences for our field are clear: limited activity for mood and anxiety disorders in adults and, since pediatric drug development programs typically follow adult intervention development, not much will be happening on the psychopharmacology front\cite{17} while we wait for dramatic advances in science and changes in the structure of medicine to condition the future of clinical research across every therapeutic area in medicine. For the field of pediatric anxiety disorders it means working assiduously to build a knowledge environment in which anxious youth are viewed as a key target population and, consequently, preemptive, preventive, and curative interventions can be developed for children by first intent.

This article, which tracks the final presentation at a day-long symposium on pediatric anxiety disorders at the 2010 annual meeting of the Anxiety Disorders Association of America (ADAA), will try to outline where our field will head over the next decade as these forces combine to shape research and practice. To narrow the range of potential topics, it will focus (speculatively for a change) on five themes as they impact intervention development: (1) how 20 years of large comparative treatment trials define our starting point, (2) the revolution in translational developmental neuroscience and what it means for the future, (3) the transformation of the clinical and clinical research enterprise, (4) biomarkers on the road to stratified and ultimately personalized medicine, and (5) the future T1 “early phase” and of T2 “late phase” intervention development. Given easily available recent commentaries by the author on the future of psychotherapy\cite{20} specific barriers to developing pediatric psychopharmacology as a field,\cite{21} and the two Council Workgroup reports on translational developmental neuroscience\cite{5} and in interventions research,\cite{19} for heuristic purposes this
article focuses primarily on the development of small molecules and biologics, but the implications for psychosocial interventions and devices follow suit.

TWENTY YEARS OF COMPARATIVE TREATMENT TRIALS

Over the past 20 years, the field of pediatric psychiatry supported by funding from the National Institutes of Mental Health (NIMH) has conducted a series of groundbreaking comparative treatment trials including the Multimodal Treatment for Children with ADHD (MTA) study, the Pediatric OCD Treatment Study (POTS) and its successors POTSII and POTSjr; the Treatment of Adolescents with Depression Study (TADSx); and the Child/Adolescent Anxiety Multimodal Study (CAMS). These pivotal trials examined the relative benefits of medication, CBT, and their combination. Each was funded because it met the following criteria: proven monotherapies, reliable assessments, room for improvement with the monotherapies, public health need, and potential for the results to change practice in a positive way.

It is useful to consider the trials as a group, because they were based on the accumulated methodological wisdom of experienced clinical trialists many of whom participated in two or more of these studies. The beneficiary of all this cumulative experience, CAMS is usefully seen as a best of breed highly refined hybrid clinical trial that mixed pragmatic elements (primarily a large and heterogeneous sample, but notably without depressed subjects) with many explanatory elements (academic site-based research, tightly controlled assessment and treatment protocols, an assessment battery with many moderators and mediators representing multiple sub-questions). In essence, all four trials are hybrids that, despite a pragmatic intent to change practice, are much more like Phase III efficacy trials than true pragmatic trials, which use simple protocols conducted by practicing clinicians and with patients in community settings.

The consequence: it is safe to say that 20 years of research and upwards of fifty million dollars in direct cost dollars have led to important new knowledge, but not nearly enough of it and most of what has been learned has not reached the community. The MTA gave us long acting stimulants and, consequently, growth suppression, along with better ADHD control. Interestingly, anxiety in the MTA moderates ADHD outcomes: unlike their nonanxiety counterparts, more anxious subjects benefit from both combined treatment and intensive behavior therapy and not just medications. POTS made CBT the default treatment for OCD in the eyes of many experts and sufferers, but like CBT for other disorders it is hard to find in the community condemning the majority of sufferers to ineffective and often dangerous polypharmacy. Arguably the most informative and certainly the most productive trial in terms of papers published, TADS showed that unlike OCD, where CBT does the heavy lifting, medication is essential for rapid response; maximum medical benefit across multiple domains occurs months sooner with combined CBT and medication; longer treatment improves outcomes and decreases relapse dramatically; and, importantly, CBT may eliminate medication associated suicidal events. CAMS, replicating previous studies, showed that CBT and medication work equally well and that combined treatment offers the maximum medical benefit across multiple domains of outcomes.

Importantly, except for the dramatic impact that long-acting stimulants—a gift of the MTA Study—have had on ADHD, findings from these pivotal studies have not translated well into practice in part because these trials were done by researchers in research clinics with protocols and methods that don’t translate easily into practice settings, viz. the extensive quality control provisions for the MTA titration trial and the assessment and therapist adherence provisions in TADS. As discussed below, the burden associated with stringent quality control measures is fine in explanatory but unacceptable in pragmatic trials, where it forms a major deterrent to effective dissemination of new treatments. Accordingly, two decades of impressive research have left us with too few mostly acute studies that do not necessarily ask the questions that are of maximum interest to decision makers (e.g. poly pharmacy, staged treatment strategies), lack generalizability, have not paid sufficient attention to safety, are too small for personalization (moderators), are not structured properly for studying mechanisms of action (mediation), are very expensive and take a long time to complete, and were performed long after the drug treatments at least were in widespread clinical use.

Good but not nearly good enough.

TRANSFORMATIONAL DEVELOPMENTAL NEUROSCIENCE

At the same time that researchers were extracting information from studies of the two most effective interventions for anxious youth—CBT and SSRIs—it became apparent that anxiety, like other disorders, in psychiatry likely have their origins in the interaction between nervous system biology and experience early in life. As shown in Figure 1, the processes

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1Since the treatment of anxious patients will be “housed” within the broad field of neurosciences medicine, I use the term “psychiatry” to refer not to a particular professional discipline but to the conceptual umbrella under which scientific inquiry occurs and discoveries are translated from the laboratory to clinical practice globally.
that go awry in mental illness involve time-sensitive modulation in gene expression, cellular interactions, circuit formation and function, and behavior, all interacting alongside environmental experience to produce typical or atypical developmental trajectories.\cite{37,38} Central to this vision is the prominence of early development. For example, while there are arguably no “mouse models” for human disease,\cite{39} model mice lacking the gene encoding the serotonin1A receptor develop anxiety-like behaviors in adulthood that is unless the 1A receptor is briefly “turned on” in the early post-natal period.\cite{40} Allelic variation in the serotonin transporter produces vulnerability to depression in the presence of early life trauma in a dose-dependent fashion, showing that environmental events powerfully interact with genetic risk to determine who becomes mentally ill.\cite{41} Interestingly, environmental factors may block or boost gene expression for good or for harm via DNA methylation, histone modification, or RNA silencing.\cite{42,43} These examples highlight the fact that the processes that drive developmental trajectories unquestionably reflect complex interactions among genetic, epigenetic, and environmental risk and protective factors and that the onset of symptoms may not indicate the actual beginning of the illness, e.g., symptoms may appear long after the causal processes, leading to mental illness have begun. In turn, these processes inevitably will become the targets for interventions that aim to restore normal developmental process or to initiate compensatory processes that

return a patient to a functional neurodevelopmental trajectory.\cite{9,36,37,44,45}

Emphasizing the importance of developmental neuroscience to understanding the fundamental biology of mental illness, the 2008 NAMHC Workgroup report entitled *Transformative Neurodevelopmental Research In Mental Illness* recommended that the NIMH refocus its discovery and translational neuroscience portfolio on identifying and translating testable developmental targets into new preemption and treatment efforts.\cite{5} As shown by increased funding for both developmental cellular and molecular and cognitive and affective neuroscience, a brief review of the NIH portfolio, program announcements, and RFAs along with the strategic plan highlights the importance NIMH places on this undertaking. Since the NIH now funds the complete continuum for drug discovery through global health (for the NIMH view, see\cite{6,7,8}), including opportunities for collaboration between industry, academic, and the NIH,\cite{18} it is clear that the interventions community in pediatric anxiety and mood disorders needs to move beyond current generation treatments to embrace this new vision if it is to remain scientifically productive and, more importantly, to bring new and better treatments to patients.

**THE TRANSFORMATION OF THE CLINICAL AND CLINICAL RESEARCH ENTERPRISE**

In *The Learning Health Care System*, the Institute of Medicine (IOM) defines evidence-based medicine (EBM) thus: “The decisions that shape the health and health care of Americans should be grounded on a reliable evidence base, will account appropriately for individual variation in patient needs, and will support the generation of new insights on clinical effectiveness.”\cite{11} According to the IOM, the failure to do so is related to a structural inability of evidence generation to keep pace with the need for better information to guide clinical decision-making.\cite{11} As a field, we are entering a period where high-through molecular, imaging, and clinical data will allow us to define the molecular basis of disease, which in turn will allow the possibility of shifting from caring for acute and chronic diseases to preemption or prevention. For mental illness, this transition is made explicit in the NIMH strategic plan, which commits the NIMH to “(1) define the pathophysiology of disorders from genes to behavior, (2) map the trajectory of illness to determine when, where, and how to intervene to preempt disability, (3) develop new interventions based on a personalized approach to the diverse needs and circumstances of people with mental illnesses.”\cite{6}

For NIH as a whole, the National Institutes of Health Roadmap for Medical Research is intended to address gaps in the continuum from discovery through translation in part by (1) putting place initiatives, such
as the Blueprint for Neuroscience Research and the Therapeutics for Rare and Neglected Diseases (TRND) programs, which provide support for pre-clinical drug development from medicinal chemistry to animal toxicology and into Phase I human studies, and (2) the Clinical and Translational Science Awards (CTSA), which, while not aligned with any specific therapeutic area, are intended to eliminate barriers between clinical and basic research, provide standardized easily accessible research infrastructure, and in so doing to create an academic home for clinical and translational science. In addition to providing research infrastructure and promoting standardization, the CTSA have also helped to accelerate the trend toward regionalization of care such that academic medical centers no longer occupy an ivory tower but as a consortia cover much of the population in the United States. One consequence of this effort will be the generation of linked (using CTSA-derived tools such as i2b2) data repositories that contain patient health, -omics, and imaging data from clinical and research platforms, including vast networked electronic health/medical records. With proper bioinformatics and biostatistical support, it should be possible to use these data from tens of millions of patients redefine trajectory-based disorders in ways that produce a nosology for trajectory-based mental disorders that is analogous to the movement from breast cancer to biomarker stratified cancers of the breast. To date there has been little neuroscience representation in the national CTSA, but that is changing with initiatives from, among others, the American College of Neuropharmacology (ACNP), and it will be very useful for researchers in pediatric anxiety disorders to be aware of and participate in the CTSA if possible.

BIOMARKERS ON THE ROAD TO STRATIFIED AND PERSONALIZED MEDICINE

As defined in a recent IOM report, biomarkers are quantitative measurements from cell tissue, blood or that provide information about biological processes, a disease state, or about response to treatment. A biosignature is a collection of biomarkers optimized for predictive validity. Biomarkers are often thought to be limited to one of the -omics platforms. -Omic refers to the study of the contribution of genes, proteins, and metabolic pathways to human physiology and to the fact that variations along -omics pathways are thought to lead to disease vulnerability. Specific -omics technologies include genetics/genomics, epigenetics, transcriptomics, proteomics, and metabolomics. Genetics refers to single polymorphism studies; genomics refers to multigene studies, including the extension to systems biology. In contrast to single -omics approaches, systems biology examines the interactions between the -omics aspects of biological systems as they give rise to organismal behaviors in health and in diseases. While neuroimaging profiles are also important, the shift from establishing biological plausibility to a diagnostic or other test likely will not happen until intermediate phenotypes based in cognitive neuroscience replace the DSM as the phenotypic target and we understand more about how to combine neuroimaging with -omics data.

A biomarker or biosignature conveys important information about one of two classes of biomarkers: diagnostic, which can refer stratifying patients on disease state for either diagnosis or prognosis, and intervention, which can be preemptive, preventive, or curative and can determine choice of treatment, tailor the dose of treatment, or provide a surrogate endpoint to facilitate the study of intervention efficacy. A brief comment on terminology. According to the Institute of Medicine, “indicated” preventive interventions target high-risk individuals that have not crossed the threshold into clinical disorder, “selective” interventions target nonsymptomatic but increased-risk populations usually by addressing risk factors, and “universal” interventions are aimed at total populations. The terms predictive, preventive, and preemptive are frequently attached to selective and indicated prevention, specifically suggesting that prediction based on biomarker status can lead to the avoidance of illness or its preemption entirely. Tom Insel, the current NIMH director, has popularized the term, “preemptive psychiatry,” pointing out that the ultimate goal of personalized medicine is to prevent disease preferably via selective but if not indicated prevention.

Independent of terminology, the ultimate goal of biomarker science is to employ molecular and imaging profiling that enables tailoring treatment to the needs of an individual patient. Stratified medicine, which is almost certain to precede personalized medicine, means using molecular diagnostic testing to tailor health care to a group of patients with similar characteristics. In conventional biostatistical terminology, stratified medicine refers to using predictor or moderator variables to assign patients into subgroups relative to a particular study endpoint. In our field, the shift to stratified medicine implies switching from phenotypic markers to predictors/moderators that are closer to the biology of the organism.

Physicians in other areas of medicine routinely use biomarkers to guide treatment, e.g. the serum biomarker hemoglobin A1c for diabetes management or cardiac enzymes for myocardial infarction, but in neurosciences medicine (apart from substance abuse) intervention biomarkers are largely absent for the simple reason that biomarker science is in its infancy. Understanding the fundamental biology of the illnesses we treat is clearly the key to developing new more effective treatments. On the other hand, the identification and validation of biomarkers and/or...
biosignatures that reflect this underlying biology is a key component of interventions research since running a biomarker stratified trial (selected by using a companion diagnostic) is not only the best way to match a drug to a patient population that needs it but the best way to insure a positive clinical development program. To illustrate the point, biomarkers are routinely used in other therapeutic areas during intervention development. For example, in non-small cell lung cancer (NSCLC), gefitinib, a biologic (an antibody as contrasted to a small molecule) which antagonizes epidermal growth factor receptor (EGFR)-tyrosine kinase, is a potent treatment, but only in those patients with a particular genetic form of EGFR. In another example, the Foundation for the NIH is sponsoring biomarker stratified adaptive RCTs in advanced breast cancer, the Investigation of Serial Studies to Predict Your Therapeutic Response (I-SPY) studies, that use the patient’s own tumor tissue and a commercially available gene chip, the MammaChip, to improve treatment outcomes by using a companion diagnostic to identify the best treatment strategy at each point in disease progression, e.g. to apply stratified medical strategies to personalize care.

While the FDA has released guidance documents on validating biomarker/biosignatures, there is still confusion in the field over what is required to identify, validate, and apply a companion diagnostic for diagnosis/prognosis or for interventions purposes. For the most part, the knowledge required to develop diagnostic tests and companion diagnostics has been more widely applied in other areas of medicine in large part because of the lack of knowledge regarding illness pathology, viz. early work on genetic and metabolomic biomarkers. On the other hand, Alzheimer’s disease provides an example of a trajectory-based approach to integrating biomarkers into drug development in a public–private partnership context. For example, individuals with the APOE epsilon4 allele that confers a higher risk for later onset of Alzheimer’s disease already show entorhinal cortical thickening at teenagers. From a treatment perspective, intervening late (analogous to the third myocardial infarction) may be suboptimal relative to early intervention (analogous to statins or preventive angioplasty) not only with respect to clinical impact but also with respect to maximizing signal detection for disease modifying therapies. Furthermore, the Alzheimer’s Disease Neuroimaging Initiative (ADNI) provides a very nice example of a public–private partnership specifically oriented toward identifying disease and intervention biomarkers that inform the development of disease modifying (inextricably trajectory based) therapies. Without question, mood and anxiety disorders are on a course to follow suit, but for this to happen the field must move beyond demonstrating mere biological plausibility to follow the regulatory pathway for developing diagnostics and companion diagnostics in general and for neurosciences specifically. Knowledge of biomarker science is much more widely available in industry than in the NIMH extramural community. For our field to develop preemptive treatments for anxiety disorders, including broader competence in biomarker science, it will be important to align the interests of industry and academia and to emphasize public–private partnership opportunities for biomarker identification and validation in the context of a therapeutic area-specific drug development program.

THE FUTURE T1 “EARLY PHASE” AND T2 “LATE PHASE” INTERVENTION DEVELOPMENT OVERVIEW

Randomized trials are routinely categorized as either having a pragmatic or explanatory aim. Pragmatic clinical trials seek to answer the question: “does this intervention work under usual conditions?,” whereas explanatory trials are focused on the question: “can this intervention work under ideal conditions?” Trials with an explanatory aim can be defined as clinical trials in which the hypothesis and study design are developed specifically to evaluate the efficacy of an intervention (maximizing signal detection) and by a desire to understand the mechanism by which the intervention is associated with benefits or harms. In practice, explanatory trials focus on translating laboratory findings to clinical practice, and are usually labeled as T1 translation. Conversely, trials with a pragmatic aim (frequently called effectiveness trials in psychiatry) can be defined as clinical trials in which the hypothesis and study design are developed specifically to answer a question faced by decision makers at one or more levels of the health-care system, from patients and doctors to public policy makers. The second area of translation, to the community and back, is frequently called T2 translation and requires that clinical trials be moved from the research clinic into the community. Most clinical trialists outside of psychiatry believe that it is critical that explanatory and pragmatic aims (and T1 and T2 clinical trials) be kept clear and distinct as the experimental designs differ in many respects. As noted earlier, trials in pediatric anxiety disorders have tended to be hybrids of explanatory and pragmatic elements to the benefit of neither. For a review highlighting why the distinction is important aimed at practicing clinical trialists, see Treweek and Zwarenstein to readily distinguish explanatory from pragmatic trials along a continuum see the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) tool.

FUTURE OF RESEARCH AT T1

At the moment, T1 research is ascendant. After twenty plus years of focus on the current generation treatments, including many excellent comparative treatment trials and a few large pragmatic trials, both the industry and the NIMH are moving away from current generation treatments toward new interventions that realize the promise of the enormous investment in discovery and translational neuroscience. It widely acknowledged that the industry “blockbuster” model (where one highly profitable drug supports the development costs of up to nine others that do not recoup their costs) is now bankrupt (for an excellent solution-oriented review, see Paul). The number of new chemical entities approved each year has fallen dramatically over the past decade, and there are no drugs analogous to the SSRIs to take their place as industries’ CNS pipelines are empty with psychiatry worse off than neurology. Some large companies—Glaxo-Smith-Kline, Astra-Zenica, and Sanofi-Aventis—have pulled out altogether, while others such as Pfizer and Lilly have reduced their investment to focus only on selected high probability of success programs. While a detailed discussion of this trend is beyond the scope of this paper (for a review, see the above-mentioned article by Steve Paul), the impact will be to force the growth of small pharma and biotech where innovation has in any case traditionally taken place in large part because the connections to academia are much closer. As mechanisms of illness are understood, molecular targets will be identified, assays will be developed to identify drugs to hit those targets, compounds will be optimized for clinical delivery and walked through preclinical development into Phases I (pharmacokinetics/pharmacodynamics) and II (proof of concept) and on to Phase III efficacy trials. For this strategy to be successful, T1 clinical trials need to be optimized. An excellent example of where the industry is well ahead of academia in optimizing clinical trials design is in the use of adaptive designs for early phase clinical trials; conversely, academia is ahead of the industry in another kind of adaptive design, once used in late-stage trials to conduct pragmatic trials to study novel treatments including many excellent comparative effectiveness research), the ultimate goal of a PCT is to reveal which treatment or treatment strategy is best for an individual patient (e.g., personalized medicine). As Garber and Tunis point out in a recent New England Journal of Medicine editorial, the two methods are not at odds. Because of the self-evident need to be able to conduct clinical studies better, faster, and cheaper, CER will only happen if the field rapidly transitions to conducting pragmatic trials on the use of the electronic medical record (EMR) as the electronic data capture (EDC) tool. In so-called single-source trials the case record form (CRF) and the medical record (source document) are the same, which significantly reduces errors, inefficiencies, and costs by eliminating double and sometimes triple data entry, data justification, and much of the need for site monitoring. In general, single-source savings are estimated at 20–30% for any given clinical trial. Paying sites only for the cost of research above the cost of clinical care produces additional savings in the order of 30–50%. Thus, unlike large pragmatic trials that cost tens of million dollars—see, for example, the large practical trials recently conducted by the NIMH—pragmatic trials in the future largely be conducted by real doctors with real patients using the EMR as the research platform.

A major aim of CER is the improvement of health-care quality through the reduction in treatment variation, focusing clinicians on those treatments for which the evidence is strongest. Variations in treatment, especially those along geographical or socioeconomic lines, may indicate cases in which particular treatments are differentially over- or underutilized, reducing health-care quality. Knowledge in evidence-based medicine (EBM) is typically encapsulated into...
Clinical Practice Guidelines (CPGs) for distribution. If CPGs are put together in accord with the best available evidence, clinicians should be more likely to practice in accord with the best evidence by following guidelines.[105–107] Unfortunately, this has not been the case perhaps because CPGs are difficult to incorporate into a practice workflow, are not easily updated, do not reflect clinical practice, and/or are not sufficiently granular to personalize care for a specific patient. In order to improve care we must develop tools that more effectively provide decision support.[108] To this end, guidelines have been incorporated into computerized clinical decision systems[109,110] with the presumption that increased adherence to guidelines will help with better decisions and so help deliver superior outcomes. In the future, the EMR will go far beyond standard CPGs to implement text and graphics-based decision support that is personalized to a specific patient based on outcome trajectories for similar patients whose data reside in the large data sets mentioned earlier. This then is the future of medicine. With the advent of innovative informatics coupled to electronic health records and the ability to do sophisticated -omics sampling in community practice settings, it will eventually be possible to compile research databases with tens of millions of patients, thereby enabling datamining, prospective cohort, and randomized trials that will lead directly to stratified medicine.

CONCLUSION

By focusing on developments that are already accelerating across medicine as a whole but that as yet have not really impacted pediatric mood and anxiety disorders, this review has attempted to identify and discuss areas of research that will shape our future. As illustrated in Figure 2 and described beautifully in a recent article by the NIMH Director, Tom Insel, on transforming psychiatry as a clinical discipline,[111] the age of symptomatic diagnosis and current generation treatments is passing; the age of interventions that emerge from the revolution in translational developmental neuroscience has begun. Because these newer interventions will emerge from an improved understanding of the fundamental biology of the illnesses, they will be more effective in patients who are ill and, excitingly, will eventually become preventive if not preemptive, e.g. they will be delivered to very young children who are at risk but not yet showing early signs of affective instability. As a result, the field of pediatric anxiety disorders will increasingly become the front end (the most important end) of a lifespan developmental model for mental illnesses that involve aberrant fear processing and emotion regulation. For a while, studies in adults will still lead studies in youth: developing interventions in anxious youth will emerge once the fundamental biology catches up such that science drives innovation and innovation drives application in the form of interventions. All this will play out in the midst of a revolutionary transformation of the clinical and clinical research enterprise that optimizes the learning and accountable health system for both research and clinical care, including linking EMR-based records with biospecimen repositories to enable the switch from phenotypic to a molecular neuroscience medicine. As part of this process, biomarkers on the road to stratified and ultimately personalized medicine will be a key development—finally, the age of molecular diagnosis and the dawn of the age of companion diagnostics to optimize treatment for psychiatry illness. Both the NIMH and the industry working collaboratively at least some of the time will focus on T1 “early phase” research as an inevitable part of capitalizing on the enormous investment in discovery and translational neuroscience. In the meantime, T2 “late phase” intervention development will focus not so much on clinical trials but on developing an optimized infrastructure for conducting data mining exercises, registries, cohort studies, and RCTs within the electronic medical record. By accelerating the translation of discovery and translational neuroscience into clinical application by supporting a smooth continuum of intervention development from preclinical studies to first-in-man and proof-of-concept research in humans and eventually into pragmatic trials, maximally effective for anxiety disorders across the lifespan will come about. For the field of pediatric anxiety disorders to thrive it will be important to embrace and actively participate in this revolution so that anxious youth are viewed as a key target population and, consequently, truly preemptive, preventive, and curative interventions will be developed for children by first intent.

Clinical and Translational Neuroscience Trends

Figure 2. The future of mood and anxiety disorders. Figure illustrates three interlocking trends: the movement from episodic care to personalized medicine; the movement from paper records through electronic medical records to context-based decision support; did the movement form phenotypic to biomarker stratified and ultimately personalized molecular diagnosis.
Acknowledgments. The cited research meets all applicable Duke University and Federal guidelines for research.

REFERENCES


Depression and Anxiety
60. Insel TR. From animal models to model animals. Biol Psychiatry 2007;62:1337–1339.
75. Insel TR. From animal models to model animals. Biol Psychiatry 2007;62:1337–1339.