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Developing Biomarkers in Mood Disorders Research Through the Use of Rapid-Acting Antidepressants

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Abstract

An impediment to progress in mood disorders research is the lack of analytically valid and qualified diagnostic and treatment biomarkers. Consistent with the National Institute of Mental Health (NIMH)'s Research Domain Criteria (RDoC) initiative, the lack of diagnostic biomarkers has precluded us from moving away from a purely subjective (symptom-based) towards a more objective diagnostic system. In addition, treatment response biomarkers in mood disorders would facilitate drug development and move beyond trial-and-error towards more personalized treatments. As such, biomarkers identified early in the pathophysiological process are proximal biomarkers (target engagement), while those occurring later in the disease process are distal (disease pathway components). One strategy to achieve this goal in biomarker development is to increase efforts at the initial phases of biomarker development (i.e., exploration and validation) at single sites with the capability of integrating multimodal approaches across a biological systems level. Subsequently, resultant putative biomarkers could then undergo characterization and surrogacy as these latter phases require multisite collaborative efforts. We have used multimodal approaches – genetics, proteomics/metabolomics, peripheral measures, multimodal neuroimaging, neuropsychopharmacological challenge paradigms and clinical predictors – to explore potential predictor and mediator/moderator biomarkers of the rapid-acting antidepressants ketamine and scopolamine. These exploratory biomarkers may then be used for *a priori* stratification in larger multisite controlled studies during the validation and characterization phases with the ultimate goal of surrogacy. In sum, the combination of target engagement and well-qualified disease-related measures are crucial to improve our pathophysiological understanding, personalize treatment selection and expand our armamentarium of novel therapeutics.

Keywords

biomarker; predictor; mediator; moderator; depression; major depressive disorder; bipolar disorder; bipolar depression; drug development; neuroimaging

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INTRODUCTION

Despite the United States Food and Drug Administration (FDA)'s 15-year high approval of 39 new drugs in 2012, only two (5.1%) were approved for central nervous system (CNS) indications.[1] In 2004, the FDA issued a "Critical Path Initiative" to improve the industry-wide efficiency of product development and safety. In 2005, the FDA then offered guidance for a voluntary submission path for exploratory pharmacogenomic data to increase biomarker-driven drug development. Of the 40 voluntary data submissions presented to the agency between 2004–7, depression was included as a major therapeutic area of interest.[2]

Collectively, CNS disorders (including unipolar depression and bipolar disorder) has a greater societal burden than cardiovascular disease or cancer and is currently the largest contributor to all-cause morbidity in the European Union. [3] There have been successes in biomarker-driven drug development in the medical subspecialties, but early phase II failures continue to plague drug development in mood disorders due to the following: high attrition rates, long lead-time development, disease heterogeneity and inadequate mechanistic understanding of a complex end-organ [4]. As a result, industry investment in CNS disorders has plummeted in recent years. The development of biological markers, or "biomarkers," will be critical to reinvigorate drug development for the treatment of neuropsychiatric disorders.

The Biomarkers Definitions Working Group [including members of the FDA, National Institutes of Health (NIH), extramural academia and the pharmaceutical industry] has defined a "biomarker" as "a characteristic that is objectively measured and evaluated as (an) indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention"[5] (Table 1). However, "biomarker"[a] is the most general overarching term (See Table 1 for key terms in biomarker research). A clinical endpoint quantifies a characteristic related to how an individual thinks, feels, functions or survives; in mood disorders, standard clinical endpoints include mood, psychic distress/anxiety, sleep, appetite and suicidal ideation. Surrogate endpoints are biomarkers that may substitute for these clinical endpoints to predict clinical benefit or harm. Moreover, biomarkers identified as presenting early in a pathophysiological process are regarded as proximal/target engagement biomarkers, *e.g.* increased serotonin 1A receptor occupancy[6], while more distal biomarkers often reflect common disease pathway components, *e.g.* improved anhedonia. To be clinically useful, a biomarker must have high sensitivity/specificity (construct validity), be reproducible and acceptable to the patient (face validity) [7].

Biomarker research and development in mood disorders mirrors medicine's paradigm shift towards personalization [8] by the use of surrogate endpoints (Table 1) to accelerate drug screening. This may be accomplished with more rapid efficacy measures – target engagement on a cellular and molecular level instead of nonspecific end-organ damage or subjective assessments – and thereby reduce the duration and costs associated with clinical trials [9] (Table 2). Unfortunately, the development of neurobiological markers has been hampered by a combination of several factors: CNS complexity (in both normal physiology and pathophysiology), restricted tissue access, and poor CNS permeability (via the "blood brain barrier") to drug and investigational neuroimaging ligands. Yet, exploratory biomarkers in major mood disorder research *have* emerged, with examples being found in

[a]Another term that may be encountered, especially in the psychiatric genetics literature, is "endophenotype," which typically refers to a heritable biomarker that is present in affected individuals and those at-risk for the disorder. In the schizophrenia literature, a classic endophenotype is impaired startle/prepulse inhibition in both patients and at-risk siblings, which has been shown to be associated with single nucleotide polymorphisms in several overrepresented genetic polymorphisms in both preclinical and clinical studies.

clinical and demographic factors, genetics, cellular and molecular biology, neurophysiology (quantitative electroencephalography and auditory-evoked potentials), and neuroimaging [10; 11]. Now, with high-throughput "multi-omics"[12] (genomics, epigenetics, proteomics, transcriptomics, metabolomics and lipidomics), a deeper pathophysiological understanding of complex neuropsychiatric disorders, and thus the identification of viable biomarkers, may be obtained.

VALIDATION AND QUALIFICATION

Method or analytical validation and qualification are critical initial steps to reduce the risk of type I (false-positive) and type II (false-negative) errors in subsequent clinical applications, *i.e.* early type I errors could subject patients to unnecessary testing and risk while type II errors could irrevocably lead researchers, clinicians, patients and the public astray to waste valuable limited resources [13]. Method validation appraises the performance of a potential biomarker, and, as a result, ensures high construct validity (reflects the entity that it is intended to measure)[14]. There are two critical concepts in method validation: 1) *exploratory validation*, which consists of assays of target engagement and other basic pharmacokinetic and pharmacodynamic investigations; and 2) *advanced validation*, which in drug development, consist of fit-for-purpose validation of diagnostic broadening, expanding the reference range and alternate routes/modalities of administration.

Biomarker qualification is an evidentiary correlation with patho/physiological processes and/or clinical endpoints [15]. As Wagner indicated in his excellent review on biomarkers in strategic drug development, biomarker qualification broadly consists of the following processes: exploration, demonstration, characterization, and surrogacy (Figure 1)[16]. As the process of biomarker qualification progresses through these phases, the stringency of evidence increases. To date, biomarker research in mood disorders has been circumscribed to the exploration and demonstration stages. However, the FDA has developed a Biomarkers Qualification Process (BQP) for regulatory review, drug development, and eventually, patient care for more qualified biomarkers.[17]. Since the strength of evidence increases as a putative biomarker advances through the stages of qualification, method validation in biomarker research may be an iterative process. For example, in an early phase I protocol, method validation of a given biomarker may be purely exploratory, but in subsequent phase I trials, a surrogate endpoint biomarker may be utilized for primary hypothesis testing or more advanced purposes, *e.g.* dose finding or indication expansion.

We will now turn our attention to a proposed biomarker schema in mood disorder research: diagnostic and treatment response (consisting of predictor and mediator/moderator) biomarkers.[18]

DIAGNOSTIC BIOMARKERS

Although neurovegetative symptoms of depression (i.e., insomnia, anergia, appetite, anhedonia or mood-congruent ruminative thoughts) and hypo/mania (i.e., decreased need for sleep, increased energy/goal-directed activity and racing thoughts) are classic diagnostic symptoms of mood disorders, they have unfortunately not proven to be useful biomarkers due to their subjectivity and overlap with other neuropsychiatric disorders. Additionally, symptomatology does not necessarily correlate with pathophysiology or treatment response. Therefore, the development of biologically-plausible, evidence-based diagnostic biomarkers is critically needed to advance our existing descriptive nosology. In order to develop such biomarkers, the field may need to utilize alternative conceptual frameworks, *e.g.* the clinical neuroscience framework of the National Institute of Mental Health's Research Domain Criteria (RDoC) [19] to move beyond our current descriptive diagnoses[b].

TREATMENT RESPONSE BIOMARKERS AND SURROGATE ENDPOINTS

Distal in the pathophysiological cascade, treatment response biomarkers are intrinsically "disease-related." For sake of convenience, treatment response biomarkers may be further subdivided into the following categories: predictor, mediator/moderator and surrogate endpoint biomarkers. Predictor biomarkers are factors that *a priori* discriminate potential response to an evidence-based intervention; as a result, they increase or decrease the likelihood of subsequent clinical response. Mediator and moderator biomarkers are factors that correlate with a particular outcome, whether the outcome is desirable (*i.e.* the anti-manic effects of lithium) or undesirable (*i.e.* completed suicide in a bipolar manic patient).

Surrogate endpoint biomarkers are well-established, objective and quantitative measures that correlate with pathophysiological processes and can be altered by evidence-based treatment; they must have a strong evidence base and compelling context for utilization, especially when intended for regulatory purposes [15](Figure 2). For example, hemoglobin A1C in diabetes meets all of the requisite criteria for a surrogate endpoint biomarker –an objective, quantitative measure that reflects an underlying pathophysiological process (excessive serum glucose promoting the glycosylation of hemoglobin in peripheral erythrocytes), that correlates not only with long-term glucose control but also correlates with adverse clinical outcome risk (retinopathy, nephropathy and cardiovascular disease) and can be altered by oral antihyperglycemic medications and exogenous insulin. There are analytically valid and qualified surrogate endpoints in alcohol use disorders, *i.e.* laboratory assessments for chronic alcoholism: elevated gamma-glutamyl transpeptidase and other liver function tests, carbohydrate-deficit transferrin and mean corpuscular volume, There have also been successful biomarker research towards surrogacy in Alzheimer disease, *i.e.* β-amyloid positron emission tomography imaging[20] and peripheral measures (in serum and cerebrospinal fluid)[21]. Even though surrogate endpoint biomarkers have been elusive in mood disorders, the above examples provide hope for the future.

One method for the identification of predictive biomarkers is a "systems biology"-based approach via the collection and integration of several intersecting but hierarchical levels (Figure 3).[22] In escalating levels of organization, this includes genetic polymorphisms, cellular and molecular biology, structural and functional neuroimaging, and demographic and clinical features, which is in contrast to the more traditional reductionist approach. For example, both glial dysfunction and synaptic deficiencies have been identified in depressive disorders; [23] however neither is likely to be causal in isolation. Instead, the dynamic interplay between neuronal and non-neuronal components on the genetic, molecular and cellular levels creates the substrate for dysfunctional neural circuitry and physiology that manifests as neurovegetative symptoms of depression.[24] In psychiatry, this "systems biology" approach will require dedicated interdisciplinary efforts for data gathering and analysis, and potentially computational neuroscience modeling, to reach its full potential [25; 26].

Once a predictor biomarker or surrogate endpoint is identified, *a priori* subject stratification may provide the conceptual framework for subsequent treatment studies. Such "efficacy-

[b]Some of the proposed RDoC domains that may have diagnostic relevance in the major mood disorders are the following: *negative valence systems* – loss, frustrative non-reward; *positive valence systems* – reward valuation, effort valuation/willingness to work, expectancy/reward prediction error, action selection/preference-based decision-making, initial responsiveness to reward, sustained responsiveness to reward, reward learning, habit; *cognitive systems- cognitive (effortful) control* – goal selection, updating, representation and maintenance, response selection, inhibition or suppression, performance monitoring; *cognitive systems: working memory* – active maintenance, flexible updating, limited capacity, interference control; *social processes: affiliation attachment* – attachment formation and maintenance; *social processes: social communication* – reception of facial communication, production of facial communication; *arousal and regulatory systems* – arousal, circadian rhythms, and sleep and wakefulness.

stratifying biomarkers"[27], *e.g.* a family history of alcohol use disorders in a first-degree relative in both treatment-resistant MDD[28] and bipolar depression,[29] can proactively leverage patient data early to increase power and, hence, reduce the need for excessively large samples to overcome diagnostic heterogeneity. *A priori* subject stratification may also exclude subjects at high-risk of little-to-no response to a given intervention [30]. Early patient stratification is already in use in other fields such as oncology, *e.g.* HER2 monoclonal antibody trastuzumab therapy for over-expressing tumors in breast cancer, cetuximab use in epidermal growth factor receptor-overexpressing KRAS wild-type metastatic colorectal cancer, [31; 32] and in autoimmune diseases. [33; 34] *A priori* subject stratification has also been successfully used in alcohol use disorder research – the *OPRM1A118G* single nucleotide polymorphism predicts a positive response to naltrexone [35].

IMPORTANCE OF TECHNOLOGICAL ADVANCES IN BIOMARKER RESEARCH AND DEVELOPMENT

Improvements in technology and biomedical research often go hand-in-hand. Many of the major advances in neuroscience biomarker development have stemmed from advances in neuroimaging technology, including structural (magnetic resonance imaging, diffusion tensor imaging), functional (functional magnetic resonance imaging, positron emission tomography/single-photon emission computed tomography), biochemical (magnetic resonance spectroscopy) and neurophysiological (electroencephalography and magnetoencephalography) methodologies. Sensitive and specific assays for serum, urine and cerebrospinal fluid have informed us regarding mediators and pathways involved in the pathogenesis and treatment of major mood disorders, *e.g.* neurotrophins, inflammation and oxidative stress. High-throughput sequencing at ever-decreasing costs [from a candidate gene approach in small populations, to genome-wide association studies (GWAS) in hundreds-to-thousands of patients] have accelerated our understanding of major mood disorder genetics. Not only can individual genes be identified, but the elucidation of entire molecular pathways may be possible via GWAS, which facilitates moving beyond simple allelic differences to copy number variations, epigenetics, transcriptional and microRNA profiling. Finally, as in other disorders with complex/non-Mendelian genetics, the true power of psychiatric genetics will likely be combinatorial – as in imaging genetics [36] and multi-assay, serum-based testing [37] – to create both diagnostic and treatment biomarker *panels*. Thus, future technological advances may lead to breakthroughs in biomarker research and development in neuropsychiatric illnesses.

EXPERIMENTAL MEDICINE MODELS IN BIOMARKER RESEARCH

Provocative challenges in healthy volunteers have greatly improved our understanding of the pathophysiology and treatment of psychiatric disorders, *e.g.* tryptophan depletion and subanesthetic ketamine infusion to mimic the symptoms of major depression and schizophrenia, respectively [38; 39]. Non-medication provocation paradigms have also been used in healthy volunteers to induce anxiety/fear, *e.g.* social stress (simulated public speaking)[40] and fear-potentiated startle[41]. Experimental medicine models may also facilitate biomarker research by providing a greater catchment of potential research subjects and the ability to dynamically capture symptom onset and improvement/recovery in a controlled milieu, which, for the latter, has historically occurred more slowly in neuropsychiatric disorders but is now also possible in patients due to the identification of rapid-acting antidepressants.

BIOMARKERS OF RAPID-ACTING ANTIDEPRESSANTS

The efficacy of traditional monoaminergic antidepressants may take weeks-to-months, and during this initial treatment phase, patients continue to suffer with attendant risks, *e.g.*, increased suicidal behavior [42–44]. Severe depressive episodes with suicidal thinking and intent should be regarded as equivalent to emergent medical conditions, where rapidly effective treatments with evidence-based surrogate endpoints have been demonstrated to reduce morbidity and mortality[45; 46]. Several medications, including ketamine [47]and scopolamine [48], have been identified to have rapid-acting antidepressant effects. Proof-of-concept studies [27] have utilized phenotypic data, neurophysiologic measures, and neuroimaging to elucidate underlying neural correlates of treatment response, which has led to the identification of several possible exploratory predictor and mediator/moderator biomarkers (Table 3). The next steps are the biomarker demonstration and characterization phases (Figure 3). A tremendous advantage associated with agents that produce rapid antidepressant effects are that these phases can occur on a compressed time scale and thus move more quickly than with traditional monoaminergic antidepressants.

Additionally, clarifying similarities and differences in response to ketamine and scopolamine may potentially be useful for biomarker validation and qualification. Although they both share rapidly acting antidepressant qualities, their mechanisms of action differ as ketamine acts as an N-methyl-D-aspartate (NMDA) receptor antagonist and scopolamine as a non-selective muscarinic cholinergic antagonist. Interestingly, evidence from preclinical models indicates that activation of mammalian target of rapamycin (mTOR)([49; 50]; Figure 3) is critical for the rapid antidepressant-like effects associated with both agents (mTOR phosphorylation in the rat prefrontal cortex occurred following low-dose ketamine and scopolamine in rodent models).[51] Similarly in humans, increased mTOR phosphorylation has been observed in peripheral mononuclear cell protein extracts after ketamine treatment. [52] As such, peripheral measures of mTOR activity, *e.g.* S6 kinase 1 inhibition [53], may facilitate novel compounds screens for rapid antidepressant properties.

At present, no target engagement biomarker for either ketamine or scopolamine has been identified in the brain. Nevertheless, disease-related exploratory biomarkers have been identified for both ketamine and scopolamine (Table 3). For instance, increased pretreatment/baseline anterior cingulate cortical (ACC) function in a fearful face paradigm predicted treatment response to ketamine,[54] which is congruent with baseline ACC metabolism differentiating treatment responders to standard antidepressants.[55] Additionally, increased baseline blood-oxygen-level dependent (BOLD) signal in the bilateral occipital cortex during the stimulus-processing component of an emotional working memory task predicted treatment response to scopolamine [56]. Although exciting, these results remain exploratory due to the small sample sizes and lack of replication.

CONCLUSIONS AND FUTURE DIRECTIONS

Despite the great promise of biomarkers across all fields of medicine, fewer than 100 of the 150,000 papers (0.06%) citing biomarkers have been validated and qualified in routine clinical practice.[57] The lack of standardization of specimen collection/storage, inadequate matching of control and disease samples, underpowered sample sizes, and replication hurdles may continue to hamper translation.[57] Future progress in neuroscience may require close consultation with mathematical, statistical, and computational specialists. Data sharing and community standards for capturing neuroimaging data will also be instrumental, and grass-roots initiatives, *e.g.* International Neuroinformatics Coordinating Facility (INCF), and standardized computing platforms for neuroimaging, *e.g.* the NeuroDebian project and Analysis of Functional Neuroimages (AFNI) software, may improve data sharing and

collaboration between intramural, extramural, and industry sectors.[58] To this end, collaborative networks have been established in lieu of the isolative, private investigator-driven approach.[57]

In conclusion, psychiatry is lagging behind other fields of medicine; biomarker research and development, however, have revealed several exciting predictor and moderator/mediator biomarkers with rapid-acting antidepressants. We believe that continued research and development through the four phases of biomarker research and development – exploration, demonstration, characterization and surrogacy – may result in major advances in mood disorder diagnosis and treatment that improve the quality of life of our patients and their loved ones suffering from these devastating illnesses (Figure 4).

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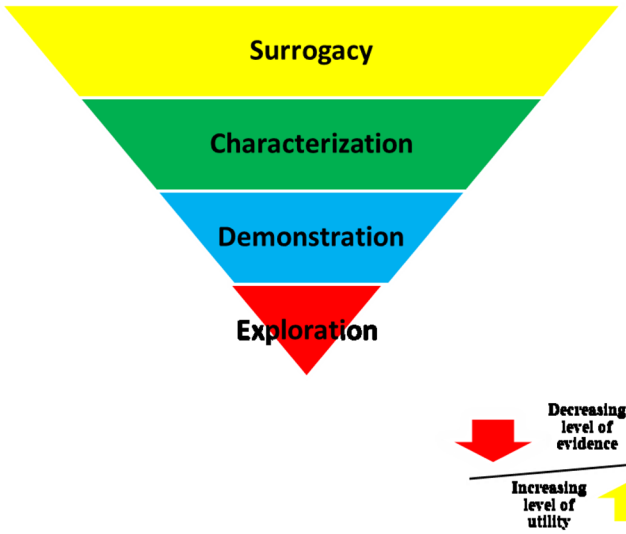
Key Points

1. Biomarkers are measurable characteristics that reflect normal physiological processes, severity or presence of some disease state or pharmacologic response to a given agent.
2. If a biomarker is involved in a pathophysiological process, it may occur either early or late. If the biomarker reflects events that occur early (proximal), it often reflects target engagement. If the biomarker occurs late (distal) in a pathophysiological cascade, it is by definition a disease-related/common pathway biomarker.
3. Biomarker validation and qualification are necessary processes. Method/analytical validation consists of initial exploratory and more advanced validation. In increasing level of evidence, biomarker qualification consists of exploration (research and development tool), demonstration (probable or emerging biomarker), characterization (known or established biomarker) and surrogacy (biomarker as clinical endpoint substitutes).
4. There are two major biomarker classifications that have exploratory evidence in mood disorder research: diagnostic and treatment (predictor, mediator/moderator and surrogate endpoint) biomarkers.
5. Technological advances have been critical to biomarker research and development. Some examples relevant to major mood disorders include genetics, cell and molecular biology, peripheral assays and neuroimaging. Further technological advances will likely advance our pathophysiological understanding and improve our treatment options for mood disorders.
6. Validation and qualification of exploratory biomarkers of the rapid-acting antidepressants ketamine and scopolamine is currently underway. Potential predictor and mediator/moderator treatment biomarkers via genetics, peripheral assays and neuroimaging have been identified.
7. Public and private sector collaborations as exemplified by the NIH-sponsored Biomarker Consortium is an exemplar of open-source biomarker data sharing. Due to the complexity and heterogeneity of psychiatric disorders, composite and multi-modal biomarker panels may ultimately be more successful for both diagnostic and treatment purpose.



Surrogacy	Holistic evaluation of the available data, demonstrating biomarker can substitute for a clinical endpoint	Biomarker can substitute as a clinical endpoint
Characterization	Associated with adequate preclinical sensitivity and specificity and linked with clinical outcomes in >1 prospective human study	Known or established biomarker
Demonstration	Associated with adequate preclinical sensitivity and specificity and linked with clinical outcomes but have not been reproducibly demonstrated in clinical studies	Probable or emerging biomarker
Exploration	Accompanied by *in vitro* and/or preclinical evidence but with no consistent relationship clinical outcomes in clinical studies	Research and development tool

Figure 1.
Pyramid of Biomarker Qualification
Adapted with permission from Figure 2 in Wagner, J. A. (2008) “Strategic approach to fit-for-purpose biomarkers in drug development.” *Ann Rev Pharmacol Toxicol* **48**: 631–651.

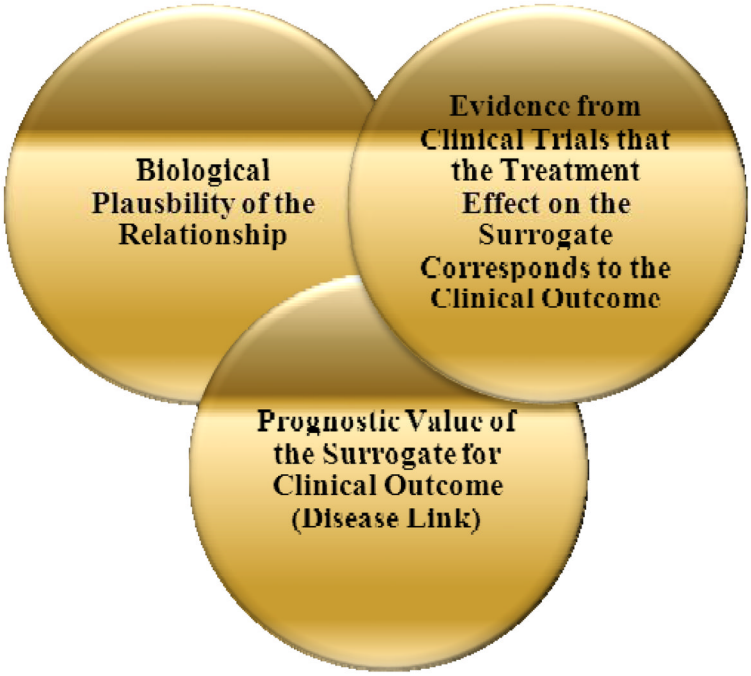


Figure 2.
International Conference on Harmonization E9 “Statistical Principles for Clinical Trials” – Three Criteria for Surrogacy

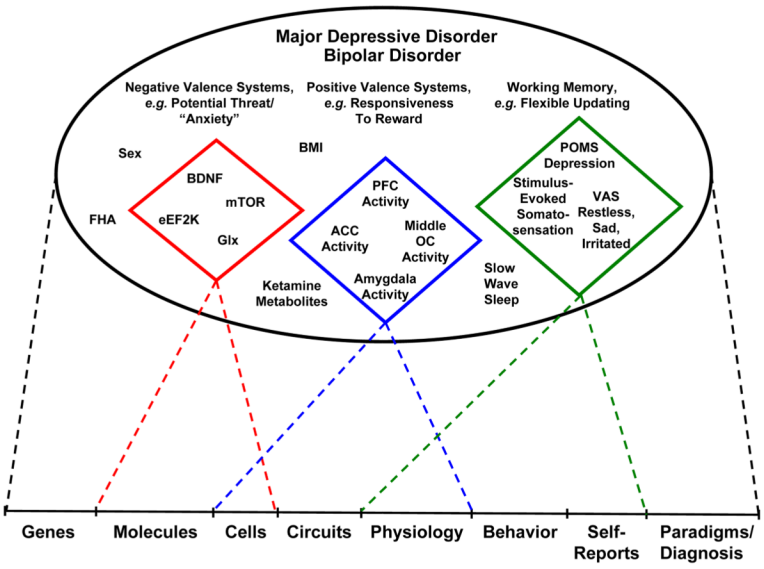


Figure 3.

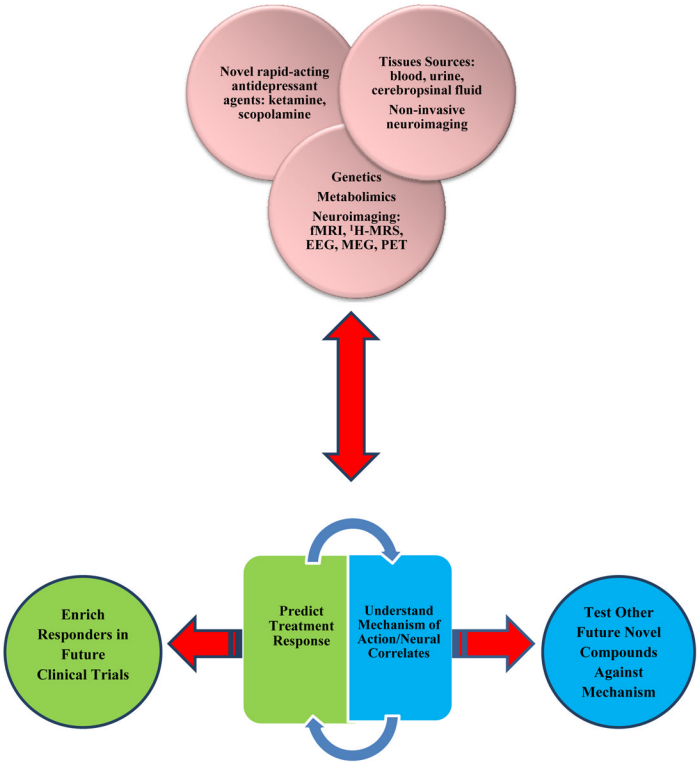


Figure 4.
Conceptual Approach to Biomarker Research and Development in Major Mood Disorders

Table 1

Important Biomarker Definitions

Biomarker	A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic response(s) to a therapeutic intervention
Clinical Endpoint	A characteristic or variable that reflects how a patient feels, functions, or survives
Surrogate Endpoint	A biomarker that is intended to substitute for a clinical endpoint and is expected to predict clinical benefit (or harm, or lack thereof) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence
Target Engagement Biomarker	A biomarker that occurs early in a pathophysiologic cascade and provides molecular and pharmacokinetic/psychodynamic information
Validation	The fit-for-purpose process of assessing the assay and its measurement performance characteristics, and determining the range of conditions under which the assay will give reproducible and accurate data
Qualification	The fit-for-purpose evidentiary process of linking a biomarker with biological processes and clinical endpoints

Adapted with permission from Table 1 in Wagner, J. A. (2008). “Strategic approach to fit-for-purpose biomarkers in drug development.” *Ann Rev Pharmacol Toxicol*. **48**: 631–651.

Table 2

Potential Benefits of Biomarker Research and Development

Utility of Biomarkers
Acceleration and increased efficiency of drug development
Ability to reduce costs and save time in treatment
Aid in refining mechanism of actions
Help assess target engagement for new or existing therapeutics

Table 3

Exploratory Biomarker with the Rapidly-Acting Antidepressants Ketamine and Scopolamine in Major Depression

Type	Biomarker	Medication	Finding
Predictor	First-Degree Relative with a Family History of Alcohol Use Disorder (AUD)	Ketamine	TRD patients with a positive FHA in a first-degree relative had significantly higher response rate than negative family alcohol history in both unipolar and bipolar depression
Predictor	Brain Derived Neurotrophic Factor (BDNF) val66met (rs6265) genotype	Ketamine	rs6265 single nucleotide polymorphism (val haplotype) predicts improved antidepressant response to ketamine
Predictor	Magnetoencephalography (MEG) and facial task Paradigms	Ketamine	Pretreatment ACC activity positively correlated with subsequent antidepressant response in TRD; exploratory analyses revealed negative correlation between pretreatment right amygdala activity and antidepressant response
Predictor	MEG and working memory (WM) task	Ketamine	Patients who showed least engagement of the pgACC in response to increased WM load showed the greatest symptomatic improvement; pretreatment functional connectivity between pgACC and left amygdala was negatively correlated with antidepressant and anxiolytic effects
Predictor	Proton Magnetic Resonance Spectroscopy (^{1}H-MRS)	Ketamine	Pretreatment Glx/glutamate ratio in the DM/DAPFC was negatively correlated with clinical improvement to ketamine; Glutamate levels in the ventromedial voxel revealed a significant association with reduction in anxiety symptoms 230 min after ketamine administration.*
Predictor	Baseline Vitamin B12	Ketamine	Higher baseline vitamin B12 levels predicted an improved antidepressant response to ketamine in bipolar depression (no association was observed with baseline folic acid, homocysteine and clinical factors)
Mediator/moderator	MEG and tactile stimulation	Ketamine	Stimulus-evoked somatosensory responses increased (relative to pre- infusion MEG) in responders vs. non-responders at 6.5 hours post- infusion
Mediator/moderator	Sleep electroencephalogram (EEG)/ polysomnography (PSG)	Ketamine	Increased peripheral BDNF and slow wave sleep correlated with improvement in ketamine responders; delta slow wave sleep (NREM1/NREM2) ratio on the night of infusion correlates with differential antidepressant response
Mediator/Moderator	Ketamine metabolites	Ketamine	Presence of specific ketamine metabolites in the post-infusion period predicts differential antidepressant response in unipolar vs. bipolar depression and correlates with psychotomimetic side effects
Predictor	Sex	Scopolamine	Female patients have an improved antidepressant response than male patients
Predictor	Baseline mood state measures	Scopolamine	Profile of Mood States (POMS) depression subscale and Visual Analogue Scale (VAS) restlessness, sad, and irritated scales significantly correlated with antidepressant response; also classified responders from non- responders with high specificity (85%)
Predictor	Functional Magnetic Resonance Imaging (fMRI) Blood-Oxygen Level Dependent (BOLD) + face-emotion WM task	Scopolamine	Increased baseline BOLD signal in the bilateral middle occipital cortex on the face-emotion working memory task predicted an improved antidepressant response
Mediator/moderator	Functional Magnetic Resonance Imaging (fMRI) Blood-Oxygen Level Dependent (BOLD) + face-emotion WM task	Scopolamine	Greater change in BOLD response in the bilateral middle occipital cortex on the face-emotion working memory task correlated with better antidepressant response

*albeit another ^{1}H-MRS study by an independent group reported no correlation between ketamine's antidepressant efficacy and changes in amino acid neurotransmitter (GABA, glutamate and glutamine) levels in the occipital cortex at both 3 hours and 48 hours post-infusion