

FDA Briefing Document

**Psychopharmacologic Drugs Advisory Committee
(PDAC) Meeting**

February 3, 2016

Topic: Cognitive Dysfunction in Major Depressive Disorder

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the topic of cognitive dysfunction in major depressive disorder (MDD) to the advisory committee in order to gain the Committee's insights and opinions and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Table of Contents

1	DIVISION DIRECTOR MEMORANDUM.....	4
2	HISTORICAL PERSPECTIVE	6
2.1	Pseudospecificity	6
2.2	Evolution of the Division’s Position.....	7
2.3	Roadmap: Cognitive Impairment Associated with Schizophrenia	8
3	CLINICAL PRESENTATION	8
4	COLLABORATION WITH NIMH.....	8
5	CONSIDERATIONS FOR STUDY DESIGNS.....	9
5.1	Domains of Cognitive Function	9
5.2	Adjunctive Treatment vs. Monotherapy.....	9
6	SUMMARY	10
7	REFERENCE LIST	12
8	ATTACHMENT - NIMH MEMO	14

1. Division Director Memorandum/Division Memorandum



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medication Error Prevention and Risk
Management
M E M O R A N D U M**

DATE: January 4, 2016

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TO: Members of the Psychopharmacologic Drugs Advisory Committee
(PDAC)

SUBJECT: February 3, 2016, Meeting of the PDAC

Introduction:

This half-day PDAC meeting will focus on issues critical to the Center for Drug Evaluation and Research (CDER) assessment of whether cognitive impairment of major depressive disorder (MDD) is a suitable target for drug development, and if so, how it could be convincingly studied.

The Division of Psychiatry Products (DPP) has taken the position in the past that cognitive dysfunction in MDD was a pseudo-specific drug target—meaning that this claim would be considered artificially narrow and related to the overall disorder of MDD. Current research supports the concept and subject matter experts have begun to agree that cognitive dysfunction in MDD is a disabling part of MDD which can be considered a distinct problem that to date has not been evaluated in drug trials. While the field is progressing toward consensus on this issue, the purpose of this PDAC meeting is to have the discussion, with experts, in public.

After presentation by experts gathered for discussion, the focus of the meeting will be to decide if cognitive dysfunction in MDD is distinct enough to warrant drug development programs to treat this aspect of the disease specifically (worthy of a drug target claim). We will then focus on how best to measure change in cognitive function of MDD in a clinical trial, and what type and how much change is clinically meaningful to patients and clinicians. We are specifically interested in the Committee's thoughts on acceptable

primary efficacy endpoints that can demonstrate clinical relevance for a claim for the treatment of cognitive dysfunction in MDD and the trial design to assess change in these endpoints

Background

As stated above, the Agency is seeking input from the Committee on issues related to cognitive dysfunction in MDD as an appropriate drug development target, acceptable primary efficacy endpoints for a claim for the treatment of cognitive dysfunction in MDD, as well as potential study designs that could be used to investigate cognitive dysfunction in MDD.

The following draft, non-voting, points to consider will be discussed by the Committee members:

1. Is the cognitive dysfunction in MDD (Major Depressive Disorder) an appropriate drug development target? If so, which cognitive domains are mainly affected by the cognitive dysfunction in MDD and what is the best method to assess these affected domains?
2. What are the acceptable primary efficacy endpoints for a claim of the treatment of cognitive dysfunction in MDD?
3. Is a functional assessment necessary as a co-primary endpoint?

2. Historical Perspective

Until very recently, the Division of Psychiatry Products (DPP) viewed the construct of cognitive dysfunction as a pseudospecific treatment target in the context of Major Depressive Disorder (MDD). The Division's stance on the topic was that, because impaired cognition is one of the core symptoms of MDD, cognitive symptoms would be expected to improve along with mood symptoms; the cognitive symptoms were seen as part of the overall condition of MDD rather than as an independent entity or comorbidity. Although the Division acknowledged that available antidepressants did not always address cognitive symptoms, we concluded that adequate data to support this new indication as an entity distinct from overall improvement in depression were lacking. Specifically, DPP determined that the construct of cognitive dysfunction as it pertains to MDD had not yet been fully characterized, that the clinical meaningfulness of changes on measures of cognitive functioning had not been established, and that the optimal study design for assessing a drug's effect on cognition had not been defined.

2.1 Pseudospecificity

A pseudospecific claim is, essentially, one that is artificially narrow. The majority of products under DPP's regulatory purview are indicated to treat a particular syndrome or condition described in the Diagnostic and Statistical Manual for Mental Disorders (DSM)—schizophrenia, MDD, Generalized Anxiety Disorder, and so on. These syndromes are defined by committees of medical experts that review the biological and epidemiological data on a periodic basis. When deviating from that general rule, the Division evaluates the available evidence to determine whether or not there is reasonable certainty that the particular component or set of symptoms is distinct from the overall disorder. For example, rather than granting indications for the treatment of bipolar disorder, products are indicated for the treatment of manic episodes or depressive episodes associated with bipolar I disorder; this is because of the considerable evidence that these mood states are distinct, and that treatment for each could be expected to be different.

In the present case there is more than the usual level of doubt that cognitive dysfunction is necessarily well-assessed or captured by the usual metrics for measuring drug effect in the depressive disorder. Only the psychomotor retardation item on the Hamilton Depression Rating Scale (slowness of thought and speech; impaired ability to concentrate; decreased motor activity) is related to cognitive function. Impairment in cognitive function is an important source of depression-related disability and there is some evidence that it may not resolve with the resolution of the acute episode of depression; therefore, it seems a good candidate for special attention as a drug target.

Moreover, in a more general sense, for many HAMD items, it seems wholly possible that different drugs could have different effects (e.g., insomnia, agitation, anxiety, gastrointestinal symptoms, weight loss, obsessional and compulsive symptoms), or even adverse effects, so that interest in the components of an overall scale does not appear unreasonable. Assessing the components would, of course, call for evaluation of the

individual components, or perhaps more targeted additional evaluations. Overall, however, interest in the distinct elements of the depressive state is not unreasonable, and is not really “pseudospecific” unless the elements of the HAMD essentially always move together, which they plainly do not.

From both a marketing perspective and a health perspective, it makes sense to try to identify a specific group of patients or set of symptoms for which a drug product is particularly effective, thus allowing for individualization of treatment and, of course, a potential promotional advantage over similar products. If that claim attempts to link some aspect of an illness to the drug’s therapeutic effect when that link is, in fact, irrelevant to that effect, such a claim could be considered pseudospecific. A classic example of this is “treatment of depression in women.” Unless a drug improved symptoms of depression only in women and not in men, a claim for treatment of depression specifically in women would be artificially narrow and, thus, pseudospecific. On the other hand, current regulations call for analysis of drug effects by gender and race, so that an analysis by subgroup and inclusion in labeling is not just acceptable, but desired, so long as there is no claimed advantage.

Until the pathophysiologic basis of psychiatric diagnoses can be further delineated, this approach necessarily entails a degree of subjectivity. In the absence of a blood test or brain scan that can replace the DSM, one cannot say with certainty that a particular aspect of a disease state is a distinct target for drug action; one can only evaluate the available evidence and make a judgment call. For this reason, it is important to periodically re-examine the state of the evidence as it applies to claims thought to be pseudospecific.

2.2 Evolution of the Division’s Position

In June of 2014, the Division began to reevaluate its view of cognitive dysfunction associated with MDD. At that time, Dr. Farchione (now the Division’s Deputy Director) was invited to participate as a discussant during a workshop on cognitive dysfunction at the American Society for Clinical Psychopharmacology (ASCP) Annual Meeting [1]. During the session, the speakers described features of cognitive dysfunction in MDD, including the domains of cognitive functioning that are typically affected by depression. The speakers also described evidence supporting the idea that cognitive deficits that remain despite treatment of core mood symptoms are more likely to be residual symptoms than to be side effects of treatment. Finally, the speakers presented results of clinical trials examining changes in cognition during treatment. The data presented in this workshop suggested that, perhaps, it was time for the Division to re-examine the available evidence related to cognition and MDD and reconsider whether or not it should still be deemed pseudospecific.

Two additional meetings focused specifically on cognitive dysfunction in MDD occurred in 2014 and 2015—a half-day program through the Massachusetts General Hospital Psychiatry Academy [2], and a full-day program sponsored by the Institute of Medicine [3]. Each of these meetings expanded on the information presented at the ASCP workshop, including additional data from clinical trials, neuroimaging studies, and assessment; thus, providing further impetus for the Division to take a closer look.

2.3 Roadmap: Cognitive Impairment Associated with Schizophrenia

In 2004, representatives from FDA, the National Institute of Mental Health (NIMH), Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) investigators, and experts from academia and industry participated in a joint meeting to develop guidelines for assessing cognitive impairment associated with schizophrenia [4]. During this meeting, experts discussed the kind of trial design that would be considered adequate from a regulatory perspective—inclusion and exclusion criteria, need for a co-primary functional endpoint, statistical approaches, etc.—and published consensus recommendations. These recommendations have served as *de facto* guidance for FDA purposes since that time. However, during informal discussions, many of these same stakeholders expressed concern that a similar approach toward cognitive impairment associated MDD could result in overly prescriptive recommendations.

3. Clinical Presentation

MDD is a debilitating and chronic illness. According to the World Health Organization (WHO) [5], depression is “the leading cause of disability worldwide, and is a major contributor to the overall global burden of disease.” This disease is characterized by low mood, anhedonia, feelings of guilt and worthlessness, low energy, and other emotional and physical symptoms. Cognitive dysfunction is not prominent in the diagnostic criteria for MDD; only one symptom—diminished ability to concentrate or indecisiveness—describes impairment in cognition [6].

Both MDD itself and the cognitive dysfunction associated with it are highly heterogeneous. That said, cognitive dysfunction is common both during acute depressive episodes and as a residual symptom after treatment [7-9]. These deficits can be both subjective and objective, though objectively measured deficits and patient reports of impairment may be discordant [10, 11], adding to the complexity of interpreting clinical trial data in this area. Cognitive dysfunction contributes to poor psychosocial and occupational functioning [12-14]; however, the functional impairment associated with cognitive dysfunction in MDD is not as severe as that observed in schizophrenia.

4. Collaboration with NIMH

Following the aforementioned IOM meeting, FDA began collaboration with NIMH in an attempt to better understand the current state of knowledge regarding cognitive dysfunction in MDD. NIMH conducted a review of the literature, summarizing the domains of cognition affected in MDD and providing examples of tests used to assess these domains. The review document also describes some general factors pertinent to cognitive assessment and challenges specific to the MDD population. Finally, the document outlines some considerations related to research and study design. The working draft of this document is included in the Attachment, below.

Ultimately, the goal of this collaboration is to develop a framework for assessment of cognitive dysfunction in MDD. Rather than explicitly defining a regulatory pathway with specific acceptable endpoints and trial designs, a framework that identifies cognitive domains of interest and describes the type of functional impairment associated with cognitive dysfunction in MDD allows for greater flexibility. Sponsors can refer to the framework to understand FDA's view on areas of impairment that are important to address, but will be free to choose whatever instrument or test battery they believe best measures those constructs. A framework can also provide sponsors with some insight into how FDA may evaluate the chosen instrument, and they can justify their choice accordingly. This framework has not yet been drafted, but the discussion points raised during this Advisory Committee meeting will likely help to shape the final document.

5. Considerations for Study Designs

DPP has not yet determined the optimal study design for assessing a particular drug product's ability to treat cognitive dysfunction associated with MDD. Some potential review issues are outlined below. The Division acknowledges that this is not an exhaustive description of relevant issues; this is intentional. We hope this will encourage a broad discussion during the Advisory Committee meeting.

5.1 Domains of Cognitive Function

Although a number of cognitive domains may be impacted by MDD, the most frequently implicated areas of dysfunction include memory, attention, and executive function [15-17]. Clinically relevant improvement in any one of these domains would likely support a labeling claim; however, the Division has not yet defined "clinically relevant" in this context, and has not yet determined if improvement in a single domain could result in a claim for treatment of "cognitive dysfunction" more broadly. The exact labeling language would depend on the primary endpoint selected. Given the overlapping nature of cognitive domains, no neuropsychological instruments purely assess a single domain. A sponsor would need to justify any proposed indication based on the properties of the instrument selected. If a sponsor chooses an instrument that primarily assesses a domain other than memory, attention, or executive function, additional justification would be required describing the relevance of that domain to MDD.

5.2 Adjunctive Treatment vs. Monotherapy

Adjunctive and monotherapy study designs evaluate very different concepts; these differences have implications for potential labeling claims. Regardless of approach, some general trial design considerations include:

- How would we distinguish between general improvement in depression (with accompanying improvement in cognition) from a specific effect of the drug (note that either could be of interest, i.e., either a drug-specific effect on cognition or a better understanding of how cognition is influenced by improvement of depression).

- How would one determine that a patient's level of cognitive function is related to his or her MDD rather than a baseline deficit?
- What is the appropriate length for such a trial?
- How would one demonstrate the clinical relevance of improvement in cognitive measures? Would both subjective and objective endpoints be required? Or is a functional co-primary endpoint necessary?

An adjunctive treatment design is more suitable for assessing a product's effect on "residual" cognitive symptoms. In this design, all patients would receive treatment with an antidepressant for a defined period of time and only those patients with persistent cognitive dysfunction despite improvement in other mood symptoms would be randomized to adjunctive treatment with a study drug or placebo. All patients would continue to receive the antidepressant on which their mood symptoms initially improved; therefore, if improvement in cognition simply lags behind improvement in mood, the adjunctive placebo group would show improvement during the randomized phase of the trial, and there would be no difference between treatment groups. However, if standard antidepressant treatment does not address cognitive symptoms fully, the adjunctive treatment, if effective, would show an advantage over the adjunctive placebo.

Monotherapy designs are, arguably, more complicated. In this case, a product would have to address both mood and cognitive symptoms. A number of complex issues would need to be considered in designing a monotherapy trial. These relate to whether the question is 1) is there an effect of the drug on cognitive function, or 2) does the test drug have a larger effect on cognitive function than other effective antidepressants? In the first case, a study with drug and placebo would be sufficient. For the second, an appropriate active control would be necessary and the study would need to show an advantage over the effective control. An additional question could be: how many active controls would be needed to support a claim?

6. Summary

Although the Division's perspective on cognitive dysfunction associated with MDD has evolved in recent years, a number of unresolved questions about this construct persist. The Division is asking the Committee to opine on these issues so that we can develop an appropriate path or paths to approval for this indication.

Points To Consider:

1. Is the cognitive dysfunction in MDD (Major Depressive Disorder) an appropriate drug development target? If so, which cognitive domains are mainly affected by the cognitive dysfunction in MDD and what is the best method to assess these affected domains?
2. What are the acceptable primary efficacy endpoints for a claim of the treatment of cognitive dysfunction in MDD?
3. Is a functional assessment necessary as a co-primary endpoint?

7. REFERENCE LIST

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8. Attachment: NIMH Memo

Assessment of Cognitive Impairment in Depression

- I. INTRODUCTION
- II. BACKGROUND
- III. COGNITIVE CONSTRUCTS OF INTEREST
- IV. CONSIDERATIONS FOR SELECTING A TEST BATTERY
- V. GENERAL ISSUES RELATED TO ASSESSMENT OF COGNITION
- VI. ANTIDEPRESSANTS AND COGNITION
- VII. RESEARCH AND STUDY DESIGNS
- VIII. SUMMARY

I. INTRODUCTION

This memo is intended to provide information to FDA related to the design and implementation of clinical trials to determine the efficacy of interventions for cognitive dysfunction in depression.

II. BACKGROUND

The diagnostic criteria for major depressive episodes, either using the DSM or the ICD nosologies, are clinical in nature and a depressive episode typically involves a mix of symptoms including disturbances in mood, cognition, and behavior. Only one of these symptoms – diminished ability to think or concentrate – specifically refers to cognition, although other symptoms could be seen as contributing factors; further, no formal quantitative measures of cognition are generally accepted for diagnostic purposes. While sometimes less apparent than mood disturbances, cognitive impairment occurs in about two-thirds of individuals with major depression [1, 2]. Cognitive impairment may play a role in the susceptibility to and maintenance of depression [3, 4], though the precise mechanisms are unclear. Given the prominence of functional disability in depression and its strong link to cognition [5, 6], this is a domain that warrants particular attention in clinical studies.

A major issue in evaluating cognition in depression concerns the marked heterogeneity in the nature of depression itself [7]. The DSM-5 diagnostic criteria for a Major Depressive Episode require 5 out of 9 possible symptoms; these must include either depressed mood, or loss of interest or pleasure in everyday activities. As the DSM was meant to be atheoretical, environmental or causal factors are generally not acknowledged in a diagnosis of the disorder. This, in conjunction with the number of possible permutations and combinations of symptoms that can be used to arrive at a diagnosis of the disorder, leads to the enrollment of patient groups for studies that vary widely in terms of symptomatology, severity, and etiology (even though all are classified under the umbrella term “depression”), and contributes to inconsistency of results across clinical trials.

An additional complicating factor is the problem of comorbidity. Depression often co-occurs with other physical and mental disorders [8, 9], suggesting a complex interplay among these disorders whereby one may cause or predispose to another, or may have a common cause. Epidemiological surveys have found that individuals with two or more disorders are the norm, rather than the exception [10, 11]. However, clinical trials often exclude patients with a comorbid condition from participation, reducing the generalizability of results. This is an important consideration since cognitive impairment has been shown to be more marked in individuals with medical and psychiatric co-morbidity [12-14].

III. COGNITIVE CONSTRUCTS OF INTEREST

Memory, attention, and executive function are the most common areas of cognitive dysfunction observed in depression [2, 15, 16] and they vary in the extent to which they normalize during periods of depression remission.

- a. **Memory:** The memory deficits seen in depression have been linked specifically to explicit, and not implicit, memory domains. Both recognition and recall studies have shown a significant association with depression [15, 17]. Studies using electroencephalography have shown a correlation between activity of the prefrontal (PFC) preceding memory task items and subsequent recall of the item. The PFC activation was thought to reflect strategy initiation and was modified by depression severity, indicating that poor strategy selection may be one cause of memory problems [18]. Memory deficits seen with depression may remit along with the mood symptoms upon treatment. Longitudinal studies following mood severity and cognitive dysfunction have shown that verbal memory improves as mood symptoms improve [19]. Likewise, a meta-analysis of literature comparing patients with remitted depression and controls has shown non-significant differences in memory performance between groups [2].

Examples of tasks that have been used to assess memory functioning in studies of depression include: delayed match to sample, paired associates learning, pattern recognition memory, spatial recognition memory, story and list learning.

- b. **Attention:** The attention deficits seen in patients with depression are associated with effortful attention, such as processing speed and selective attention, but not with implicit processing [20]. Unlike memory deficits, in a meta-analysis of current literature, Rock and colleagues [2] found that the deficits seen in attention were sustained in populations of patients whose depression symptoms were remitted.

Examples of tasks that have been used to assess attention in studies of depression include: simple and choice reaction time tasks, digit symbol coding, continuous performance task, sustained attention tasks, and rapid visual information processing tasks.

- c. **Executive Function:** Executive function encapsulates many higher-level cognitive functions, and patients with depression have shown deficits specifically in tasks that include planning, inhibition, problem-solving and set-shifting [2, 20]. One line of research posits that constructs such as working memory, response inhibition, and set

shifting/updating share a common substrate, and yet have components that are distinct and develop at slightly different rates from childhood to adulthood [21-25]. The variance in this common substrate factor is almost entirely heritable, both in adolescence and adulthood, lending support to (though not proving) the notion that there may be a single genetic basis for executive function components indexed by the various tests [23, 25]. Interestingly, almost all of the heritable variation in response inhibition was accounted for by this general factor, as compared to working memory and set shifting.

Examples of tasks that have been used to assess deficits in executive function in studies of depression include: Stroop, Wisconsin Card Sorting Task, Tower of London, Spatial Span.

IV. CONSIDERATIONS FOR SELECTING A TEST BATTERY

Given the heterogeneity of depression and the multi-faceted nature of cognition, here are some approaches to consider when selecting a test battery for use in clinical trials of cognition-enhancing treatments. We provide more traditional neuropsychological methods first and then novel, circuit-based approaches. These examples of batteries have been developed and used primarily in populations with schizophrenia.

MATRICES battery (traditional neuropsychological test battery). Perhaps the best-known battery for assessment of cognitive functioning was developed about a decade ago for schizophrenia research. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative resulted in a standardized battery for use in clinical trials of cognition-enhancing interventions. The MATRICS Consensus Cognitive Battery [MCCB; 26] assesses seven cognitive domains: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning, Visual Learning, Reasoning and Problem Solving, and Social Cognition. The battery includes converging measures for some of the domains and provides a composite score. Scores on individual tests all show palpable relationships to the composite score, such that the latter is most commonly used as an outcome measure.

A similar effort at developing a standardized battery has not been undertaken for cognition in depression, but the MCCB has been used in clinical trials of pharmacological treatment of depression [27] and is considered to be appropriate for use in studies of bipolar disorder [28]. In spite of these developments, some concern has been expressed as to whether the MCCB is suitable for widespread use in studies of depression due to possible ceiling effects, given the higher average levels of cognitive functioning in patients with depression as compared to those with schizophrenia.

CNTRACS battery (circuit-based battery). The MCCB tasks were selected for their psychometric properties rather than specificity in terms of related brain systems, and the overlapping processes required for accomplishing these tests are considered to be a primary reason for the large part-whole correlations and use of the composite score as an outcome. The CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) conference series [29] was initiated soon after the MCCB to review possibilities for more specific, circuit-based measures, followed by the CNTRACS research consortium (Cognitive Neuroscience Test

Reliability and Clinical Applications for Schizophrenia) to instantiate the most promising candidates [30]. Tests developed by the CNTRACS consortium have demonstrated associations with activation of specific circuits and disruption of those circuits in patients with schizophrenia. For example, impairment in relational encoding and retrieval was associated with reduced activation of prefrontal cortex and medial temporal lobe [31] and poor visual integration was associated with excessive activation in occipital and parietal areas [32].

True to its purpose, and unlike the MCCB, the initial CNTRACS study (largely with schizophrenia patients) suggested that scores on the various subtests of the battery showed only modest intercorrelations amongst themselves, indicating that they were tapping discrete cognitive circuits and processes [30]. A subsequent study [33] compared CNTRACS with two MCCB measures, and found higher intercorrelations than in the previous study (partly due to the fact that subjects in the latter trial completed all tasks on the same day). Overall, the set of tests appeared to measure both common and unique cognitive deficits, with a suggestion that the common factor involved cognitive control, “a well-characterized set of cognitive processes linked to the function of a common fronto-parietal network.” Further, the CNTRACS tasks were comparable to MCCB measures in correlating with functional measures such as the UPSA [33]. Interestingly, the same system was implicated in a new study of 461 patients from the Human Connectome project, indicating that the dorsal attention network accounted for a significant amount of variance in subject’s ranking on a composite measure of 280 variables related to effective functioning and life success [34]. Similar to the prior discussion of executive function, there was thus strong statistical evidence for a common factor amongst the various facets of this domain as well – highlighting the synchrony in findings from various methodologies.

The data are as yet insufficient to make firm conclusions about the optimal specificity for test batteries for depression (or other disorders). On the one hand, attempting to influence a more generalized cognitive target (presumably involving multiple circuits or more widely-distributed neural processes) may yield more robust impact on everyday functioning, given that everyday functioning requires multiple aspects of cognition functioning in concert. However, a treatment target defined by performance on a specific test and linked to functioning of an identified neural circuit is appealing in its translational simplicity, and the most recent data suggest that more specific, circuit-based tests can yield acceptable correlations with overall performance and with real-world functional measures.

Given the various sources of heterogeneity in both depression and cognition, it may be productive to base trials of cognitive deficits in depression on firmer ground, where more is known more about the pertinent neurobiology and its relationship to various aspects of performance. This can be achieved by using measures derived from cognitive neuroscience which assess more narrow aspects of cognition and offer the following:

- (1) Evidence for a valid behavioral/cognitive function,
- (2) Evidence for an implementing neural system,
- (3) Evidence of impairment in depression, and
- (4) Links to the mechanism of action of a pharmacological agent.

This assessment strategy would ensure that sponsors are studying a homogeneous mechanism that is anchored in both biology and behavior and will be informative with regard to the circuits affected by proposed treatments and will shed light on the neural substrate of the construct being tested.

Other classes of measurement. Event-related brain potentials (ERPs) may also have utility as circuit-based measures in clinical trials. These EEG-based measures are supported by a great deal of research in clinical populations, provide inexpensive and direct measurement of neural activity, and are suitable for use in clinical trials [35]. For example, an examination of the construct of performance monitoring (one aspect of cognitive control) would involve collecting an electroencephalogram (EEG) measure such as the error-related negativity [ERN; 36]. The ERN is a well-validated biomarker that has been reliably linked to the commission of errors. Extensive research also exists on its neural basis. Thus, the ERN could be tested before and after the administration of a particular antidepressant over some pre-specified period of time, which could help clarify which specific aspect of cognition (if any) the antidepressant may be affecting – thus serving as an endophenotypic measure of target engagement. In fact, similar experimental designs have been used to test whether the ERN can serve as a marker for response to treatment in obsessive-compulsive disorder after cognitive behavioral therapy in pediatric patients [37].

Finally, given the uncertain relationship between functional outcomes, cognitive testing, and neurobiological measures, patient-reported outcomes of mood and daily functioning will also need to be assessed both over the immediate and longer term, and the inter-relationships between these various domains (i.e., functional outcomes, cognitive tests, and neurobiology) examined in depth.

V. GENERAL CONSIDERATIONS RELATED TO ASSESSMENT OF COGNITION

Cognition is not a unitary psychological concept, but rather includes a variety of basic and overlapping mental functions such as attention, working memory, concentration, processing speed, motor functioning, and executive functioning. Research to date does not allow for strong conclusions about the cause of cognitive deficits in depression and, thus, it is difficult to identify a neural or cognitive target for intervention.

(1) State versus trait effects

Although cognitive impairment is frequently observed in depressed individuals, it is not clear whether the impairment is a stable, trait-like feature or is transitory. Studies of patients whose depression is remitted reveal persistent cognitive deficits, suggesting that these deficits are trait-like in nature or perhaps a scar effect of depression [38]. In contrast, a longitudinal study that monitored cognitive function with depression severity showed that improvements in cognitive abilities were closely related to mood improvements, indicating that the deficits are more state-like in nature [19]. Although mood and cognition are colloquially considered to be separate domains, they are, to an extent, inter-related via factors such as motivation and effort, and sometimes cannot be entirely disentangled from one another.

(2) Relationships between cognition and everyday functioning

There is as yet no clear evidence that any one narrow cognitive process is differentially impaired in depression or that any single aspect of cognition is more strongly predictive of everyday functioning than another. In addition, performance on lab- or clinic-based tests may improve in response to treatment, but the extent to which this translates to observable life gains, such as improved job performance, is unclear. Everyday functioning is multiply-determined and, although performance on laboratory-based tests of cognition is associated with functioning, it accounts for only approximately one-third of the variance in functioning in individuals with serious mental illness [39, 40]; it is thus difficult to define the relationship between performance on clinic-based measures and everyday functioning. There are no empirically-based thresholds for determining the degree of change in cognitive test performance that predicts meaningful changes in everyday functioning, although one could reasonably argue that any improvement in cognition is, in and of itself, of benefit to the patient.

Relatedly, assessing real-world functioning is a challenge as well because self-report of functioning does not necessarily accurately reflect actual functioning and is affected by symptoms and mood state. For example, in individuals with bipolar disorder [41] and schizophrenia [42], depression severity is inversely associated with self-ratings of functioning. Ratings of functioning made by high-contact clinicians tend to be more accurate than those made by patients, but collecting data from informants adds to the cost and complexity of a study. Novel methods such as passive data collection via wearable devices and ecological momentary assessment [43] might help bridge the clinic-community gap in assessment of functioning.

(3) The “task impurity” problem

Given the degree of intercorrelation and overlap among tests of cognition, no single cognitive task is a pure measure of any cognitive construct; this is referred to as the “task impurity” problem [21]. The problem can stem from a situation in which a task measures a relatively pure function, but the exact nature of the function has not yet been fully and accurately understood; or from the not uncommon situation in which the task indexes multiple functions (e.g., the Wisconsin Card Sorting Test); or it could be that the task measures only a subset of the totality of what it is intended to measure.

(4) Subjective versus objective evaluation of cognition

Data are not clear whether improving patients’ subjective sense of their cognitive abilities is related to improvement in functioning. It is not certain from existing research whether subjective versus performance-based measures are more strongly predictive of improvement in functioning. It may be that improved perception of cognitive abilities is more impactful to patient functioning, but in the absence of performance-based improvement, this would not provide a strong argument for an indication for cognitive improvement. For example, in schizophrenia, the ability to accurately estimate one’s own cognitive ability and real-world functioning is a stronger predictor of functioning than performance on cognitive and functional capacity tests [44], suggesting that this might be an aspect of cognition suitable for remediation. Perception of cognitive deficits, independent of actual cognitive performance, is also associated with functioning [45].

Motivation, activation, and self-efficacy, all of which affect cognition and emotion, are additional targets that, if they could be successfully modulated, might prove beneficial to everyday functioning.

(5) Norming test batteries

It should be noted that it is often difficult to disentangle differences in cognitive performance from differences in the measurement characteristics of different tests. In order to make a claim about an effect on a specific cognitive domain, it would be optimal to administer more than one test of each domain of interest in order to minimize test-specific variance. These considerations suggest that a broad battery consisting of multiple tests of diverse cognitive domains could be appropriate. On the other hand, obviously the administration of a larger number of tests requires more time, and can result in spurious variance due to subject fatigue.

Further, a very important point concerns the importance of co-norming a battery [46]. If sponsors merely pull together existing tests with independent normative datasets, it is nearly impossible to know whether differences in the resulting norm-referenced scores for each test reflect actual differential performance among tests, or are due to test-specific idiosyncrasies among the normative datasets (due to differences in the characteristics of the populations upon which the test was normed, testing procedures, etc.). In this regard, both the MCCB and the CNTRACS tests have normative data available as a whole, although there are more data available to date (and more tests per construct) for the former battery.

VI. ANTIDEPRESSANTS AND COGNITION

The question of whether antidepressants can improve cognitive ability has generated a great deal of interest recently. For example, vortioxetine has been reported to provide cognitive benefits that are not observed with other antidepressants such as duloxetine [47], perhaps via increased glutamatergic neurotransmission, long-term potentiation, and neuroplasticity [48]. The profile of cognitive improvements associated with vortioxetine is variable, with somewhat selective improvement on the Digit Symbol Substitution Test and the Trailmaking Test – Part B in one study [49, but see also 50] and more generalized cognitive benefits in another [51].

The research on pro-cognitive effects of antidepressants is difficult to interpret due to heterogeneity among studies in the type and dose of medications that have been tested [52] and the diversity of cognitive tests used as outcome measures. Definitive conclusions about cognitive enhancement via antidepressant medication await further study using the experimental therapeutics approach in which a specific treatment target is defined, the degree to which the treatment affects the target is directly measured, and the extent to which target engagement relates to clinical outcome is evaluated. More rigorous studies testing hypothesized mechanisms of neural action in humans are needed before a particular antidepressant can be endorsed as having a specific effect on cognition or any other domain of behavior.

VII. RESEARCH AND STUDY DESIGNS

- a. **Subject sampling:** Compelling trials would include a theoretically motivated rationale for addressing the heterogeneity of depression, and evaluating whether particular subgroups are optimally responsive to treatment. This might represent a design in which subtypes of depression (or degrees of elevation along a particular dimension) would function as moderator variables with respect to the overall treatment effect in a large sample of subjects with depression. Alternatively, the design might involve specifying in advance particular subtypes or dimensional components for which the treatment would be predicted to show significant separation from a placebo or control treatment, versus other subtypes for which treatment would be predicted to be ineffective. Subtypes or dimensions might be defined on the basis of traditional clinically-defined groups, such as atypical depression or vegetative signs. However, given the considerations above, stronger studies would involve measurements that link activity in neural systems, cognitive performance, and symptomatic outcomes.
- b. **Experimental Design:** With respect to research designs, the considerations above suggest that trials are likely to involve a sequential design in which the investigator assesses the presence of impaired cognition at the start of the trial, and then re-evaluates both mood symptoms and cognition at the end of an intervention treating mood symptoms. Persisting cognitive impairments following remission or partial response in mood symptoms will help provide evidence that cognition represents an independent component of the syndrome rather than constituting pseudo-specificity. The second phase of a trial for an agent targeting cognitive symptoms could then include patients with persisting cognitive impairment. Separate arms of such a study might be conducted with patients whose mood symptoms remitted or responded versus those who showed no change in mood symptoms. Improvement in cognitive function, but not mood, in the latter group might provide further evidence for the specificity of the compound targeting cognition.

VIII. SUMMARY

Both depression and cognition, as currently conceptualized, are heterogeneous and somewhat imprecisely defined, with several overlapping subconstructs. We have discussed what we view as the primary considerations in addressing these issues as they relate to clinical trials of cognition-enhancing interventions, and provided some thoughts about test selections, subject recruitment, and experimental design.

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