RESEARCH

Redefining Affective Disorders: Relevance for Drug Development

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The evaluation of new drug entities with specific modes of action may be hampered by rigid diagnostic classification systems and patient selection processes that do not focus on the anticipated symptomatic, behavioral, and functional outcomes to be achieved. Patients enrolled in central nervous system (CNS) clinical trials may present with a heterogeneous group of symptoms representing several syndromes or subtypes, subsumed under the same diagnosis in the DSM-IV classification system. As a result, enrolled patients may not have the valid illness characteristics of interest to the particular study. We propose that clinical drug development needs to focus on the primary nosological entity likely to be affected by a new drug entity's mode of action. Ideally, a valid patient will have the acute primary symptoms that the novel drug is supposed to influence. In this article, we propose operational criteria to delineate a more symptom-specific and ecologically valid approach to the identification of the valid patient for clinical trials.

Introduction

Newly developed medications possessing unique, targeted modes of action have a difficult hurdle to overcome in order to demonstrate significant efficacy in the broad population of patients with mood and anxiety disorders. It is well recognized, for instance, that currently approved antidepressants do not adequately treat many patients with major depressive disorder (MDD). For example, the recent NIMH-sponsored STAR*D study demonstrated that only 27.5% of depressed patients treated with a first-line, FDA-approved SSRI-antidepressant (citalopram) achieved remission despite adequate dose and treatment duration (Trivedi et al. 2006a). Since the same study has also shown that study participants who were Caucasian, female, employed, or had higher levels of education or income had higher HAM-D remission rates (Trivedi et al. 2006a), one may pose the following questions: *(1) What if the overall modest results of antidepressant monotherapy trials are due primarily to the marked heterogeneity of patients meeting current diagnostic criteria for depressive disorders?, and (2) What if antidepressants were 100% effective in a given subset of patients who have an authentic, ecologically valid depressive disorder?* Although a 100% success rate is an unlikely event, the question suggests an alternative world view to psychiatric diagnoses that departs from the currently employed, rigid classification system of the DSM-IV (APA 1987).

Limitations of DSM-IV Classification for Drug Development

The categorical system of defining psychiatric disorders as exemplified by the DSM-IV has yielded enormous utility for practicing clinicians. The diagnostic manuals provide a reliable operational language for communication between clinicians, patients, families, and insurers that facilitates both diagnostic assessment and treatment planning. The usefulness of the DSM system belies its limitations, which are amplified by the reification of these manuals with each new publication (Kendell and Jablensky 2003). The limitations of the DSM categorical system have been noted by numerous critics as well as the original authors of the manual (Andreason 1995; APA 1987; Kendell and Jablensky 2003; Kendler and Gardner 1998; Regier et al. 1998). The validity, not the reliability, of the diagnostic constructs defined in the DSM-IV has been challenged. For example, it has been argued that a large number of symptoms commonly reported by depressed patients are not captured by the current

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DSM-IV nosology (Cassano and Fava 2002) and that, in particular, there is a diagnostic focus on psychological symptoms rather than on somatic and physical symptoms, even though these may be presenting and chief complaints in MDD (Fava 2002). Similarly, the most recent iteration of the diagnostic criteria for generalized anxiety disorder (GAD) in DSM-IV has increased the focus on cognitive and psychic over somatic and autonomic symptoms compared to criteria from earlier versions of the manual. Examination of data from a number of treatment trials in GAD suggests that the somatic factor of the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton 1959) remains an important element in the overall severity of the disorder, contributing between 42% and 46% of the total HAM-A score (Dahl et al. 2005). Further, most patients with GAD in primary care settings present primarily with somatic rather than psychological symptoms (Wittchen et al. 2002). The relative weighting or inclusion/exclusion of different sets of symptoms in the diagnostic criteria may yield different patient populations of varying degrees of responsivity to particular types of pharmacotherapies—a potentially critical issue in demonstrating the efficacy of a novel therapeutic agent. For example, in GAD, current pharmacotherapies with different modes of action have been demonstrated to have differential effects on psychic and somatic symptoms, with benzodiazepines having greater efficacy on somatic than on psychic symptoms (Rickels et al. 1993); and tricyclic or serotonin reuptake inhibitors, and azapirones demonstrating enhanced efficacy against psychic relative to somatic symptoms (Feighner and Cohn 1989; Meoni et al. 2004; Pollack et al. 2001; Rickels et al. 1993; Rickels et al 2000). It is our belief that reliance on a categorical system of psychiatric nosology may be inappropriate for contemporary clinical drug development. Thus, the evaluation of new drug entities with specific, targeted modes of actions may be hampered by a rigid system of classification and measurement that does not focus on the anticipated symptomatic, behavioral, and functional outcomes. Instead, we propose a more symptom-specific and ecologically valid approach to the identification of the valid patient for clinical trials.

The DSM-IV provides a broad checklist of symptoms of which some but not all must be endorsed to label a patient within a specific diagnostic category. Consequently, patients enrolled in clinical trials may present with a complex, heterogeneous group of symptoms representing several syndromes/subtypes within the category of illness operationally defined by DSM-IV. It is our contention that a more specific set of criteria tailored to the anticipated clinical effects of drugs with targeted modes of action is needed in some central nervous system (CNS) clinical trials. Further, the range of illness severity and extent of impact on function is not a requisite differentiator in the DSM-IV classification system. Eligibility criteria for clinical trials invariably add additional criteria to compensate for this limitation. However, the resultant compilation of inclusion/exclusion criteria rarely addresses the fundamental question to be asked about patient eligibility:

Does this patient have valid (authentic) illness characteristics of interest in this study?

As used in the present drug development process, the DSM-IV classification system may inadvertently contribute to misinterpretation of study results. As noted above, data from the NIMH-funded STAR*D study provide an illustrative example of potential misinterpretation generated by rigid classification of patients. In this large study, only 27.5% of patients broadly defined by DSM-IV as MDD achieved remission (Hamilton Depression scale score $\leq$7) when administered an adequate dose and duration of the first step treatment of the SSRI citalopram (Rush et al. 2006a; Trivedi et al. 2006a). This finding occurred despite the fact that patients with histories of previous nonresponse to treatment were excluded from the study. Similarly, only one-third of the nonremitters achieved remission when given a variety of second-step treatments that included switching to other antidepressants or combination treatments (Rush et al. 2006b; Trivedi et al. 2006b). Of note, 46% of the enrolled STAR*D patients also met criteria for anxious-depression, an entity not delineated as a depressive subtype in the DSM-IV, despite the evidence for unique clinical and sociodemographic features (Fava et al. 2004). This large subgroup revealed poorer treatment responses following citalopram treatment in Level 1 of STAR*D (Fava et al., in press). In particular, only 5% of the patients who had anxious-depression remitted when given the variety of treatment interventions offered in the second step (Fava et al. 2008).

A common interpretation of the STAR*D study data contends that the majority of patients with MDD did not achieve remission with their initial treatment intervention, and that remission was equally difficult to achieve in the second step regardless of the treatment strategies employed (Rush et al. 2006b). In fact, it has been pointed out that remission rates decreased after each STAR*D treatment step, while intolerance (dropouts for any reason during the first 4 weeks, or side effects afterwards) increased after each treatment step (Fava et al. 2007). This interpretation relies on the DSM-IV classification, which presumes that all of the enrolled STAR*D patients had *valid* MDD. If the criteria for MDD had included anxiety, the results would have been even worse (Fava et al., in press). An alternative interpretation of the results might be that the majority of patients with a more narrowly

defined affective syndrome that *excluded* anxiety were successfully treated in the first and second steps. Perhaps, it is the broad diagnostic category rather than a more circumscribed patient population that is truly treatment-resistant.

The STAR*D data example reflects the inherent problems those involved in drug development confront when they seek to evaluate a new drug with unique modes of action and targeted behavioral effects.

Ideally, clinical trials with new drug entities would include: 1) patients who actually have acute primary symptoms that an effective new drug is supposed to influence (a valid patient); 2) instruments that can reliably measure change in these primary symptoms from baseline to endpoint (a valid measurement).

These seemingly obvious requirements are complicated because regulatory authorities have traditionally recognized only the DSM-IV classification for drug approvals, forcing pharmaceutical companies to develop drugs according to this rigid, categorical method. Further, the interest of pharmaceutical companies to have their drugs indicated for the largest number of individuals reinforces the reliance on broad diagnostic categories that may obscure assessment in more carefully defined, individualized populations. On the other hand, more recently, regulatory authorities have allowed pharmaceutical companies to seek indications for specific symptoms within psychiatric disorders, opening up the possibility that newer regulatory paths to drug development may now take place. As noted above, the reification of the DSM-IV by insurers as well as the government has effectively discouraged more creative diagnostic strategies in clinical research. Kendell and Jablensky (2003) suggest that politics may be involved when an editor or a funding institution insists on the use of an "official" definition of a syndrome that has not been shown to be valid. They argue that researchers must be free to use other definitions to overcome the shortcomings of the standard definitions.

The inadvertent misinterpretation of data fostered by a rigid classification system is also present in the labeling of psychotropic medication. Categorization as antidepressants, anxiolytics, or even antipsychotics is challenged daily in clinical practice. Atypical antipsychotics, for instance, have been studied and are commonly used to treat nonpsychotic psychiatric disorders such as depression (Papakostas et al. 2007) and anxiety (Gao et al. 2006). The origin of the rigid "labeling" rests with the drug development process which requires that FDA approval can be given only for the "official" diagnoses as operationally defined by DSM-IV. Hence, every drug approval generates a label at launch. Consequently, drug development research has remained focused on these "official" diagnoses.

We propose that clinical drug development needs to focus on the primary nosological entity likely to be affected by the new drug entity's anticipated mode of action. Redirecting interest from a rigid DSM-IV diagnosis to a primary nosological entity facilitates identification of a *valid* patient. . .someone likely to have the acute *primary* symptoms of interest, which are correlated with the onset of the current illness episode and are subject to change with treatment intervention.

Robins and Guze (1974) proposed formal operational criteria for defining psychiatric disorder, which influenced the development of contemporary categorical diagnostic classification systems. Diagnostic assessment instruments derived from these categorical systems are useful vehicles to cordon populations of patients who approximate these operational definitions. However, these structured, checklist-type instruments do not distinguish between state or trait characteristics and consequently fail to ascertain the immediate relevance of the symptoms to the acute, current episode. We believe that a *valid* patient will have acute symptoms that reflect the *current* state of the illness and are not just longstanding trait characteristics unlikely to change during short treatment intervals with antidepressants. Although the duration issue may seem problematic for patients whose symptoms have been present for years and even decades, we believe that a focused approach may allow us to make the distinction between state and trait even in these cases.

The authors of the DSM-IV classification acknowledged that each category of mental disorder may not be a completely discrete entity with absolute boundaries dividing it from other mental disorders (APA 1987, DSM IV manual, pxxii). In fact, most clinicians would agree that a continuum of symptoms exists within the realm of affective and mood disorders and that the true threshold for illness resides more with functional impact than mere presence of symptoms. Maj (2005) suggested that the term "comorbidity" to indicate the concomitance of two psychiatric diagnoses may be incorrect because it is not always clear whether the presenting symptoms actually reflect two distinct clinical entities or refer to clinical manifestations of the same psychiatric entity. Consequently, a simple yes/no checklist system to identify patients for clinical trials is not consistent with clinical reality and may not represent the optimal approach to define syndromal eligibility for drug trials.

SAFER Criteria

We have developed operational requirements, called SAFER criteria, to facilitate identification of the *valid* patient for clinical trials (Appendix 1). These criteria seek to confirm that identified patients have acute symptoms

that reflect the current state of illness and that these symptoms can be reliably measured (assessed) with appropriate measurement tools. Beyond mere presence or absence, valid patients must have relevant symptoms that are pervasive, persistent (and not fluctuating over a defined period of time), and pathological in nature.

Further, the clinical presentation of eligible patients must have both face and ecological validity that go beyond mere symptom identification. For instance, how closely do the symptoms map to the primary nosological entity? Is the frequency, intensity, and duration of symptoms consistent with our knowledge of the illness? Also, do clinical changes of these symptoms actually impact the patient's real-life condition? In effect, do the symptoms really matter to the life and to the functioning ability of the patient?

Our proposal does not challenge the reliability of diagnoses that can be achieved between trained raters when applying the DSM-IV classification. The diagnosis may be reliable but not necessarily valid for a given clinical trial. Further, our proposal does not address the challenging issue of interrater reliability and competency in CNS clinical trials (Targum 2006). Rather, we seek reliable instruments that can measure *valid* symptoms regardless of the form of rating methodology (self-rating, clinician-rating, remote assessments). Our proposal *does* address the identification of a patient whose current illness is *valid* and whose symptoms can be measured for the nosological entity of interest in the clinical trial.

If our proposed approach were to be adopted in clinical trials, investigators would then face the issue of making it operational. We have therefore developed a SAFER Criteria Inventory (Appendix 2) aimed at allowing investigators to determine the "validity" of their patients with respect to the disorder under investigation. The inventory addresses eight specific elements adapted from the SAFER criteria that comprise a valid symptom and one SAFER element (face validity) that considers the entire symptom cluster as a valid nosological entity. The utilization of the SAFER criteria inventory requires:

1. Identification of the presence and clinical relevance of target symptoms
2. Assurance that the selected rating instruments actually measure the targeted symptoms

In addition, it is necessary to determine in advance the minimum number of valid targeted symptoms necessary to satisfy the SAFER criteria for a valid patient.

A case illustration follows:

A patient is being evaluated for a clinical study of melancholic depression in which the Inventory of Depressive Symptomatology (IDS) 30-item version is employed (Rush et al. 1996) and at least four valid symptoms of melancholic depression are required.

Pt. X is a 34-year-old woman who presents with numerous acute symptoms including:

- feelings of despondency over the past month affecting her ability to work and relate to friends
- sleep disturbance (particularly early morning awakenings) for the past month causing daytime fatigue and irritability
- loss of appetite and possible weight loss for the past 6 weeks
- anhedonia contributing to loss of interest, decreased work productivity, and decreased social activities
- excessive guilt affecting her sense of self and very different from her usual self.

These symptoms have impacted the quality of the patient's life across multiple domains, and are clearly seen as markedly different and distinct from previous levels of functioning during the examination. In addition, the symptoms are judged to be specific to the depressive syndrome and are not attributable to other comorbid or concomitant conditions.

In this case example, the five presenting symptoms reflect acute state symptoms (SAFER inventory items 1 and 2) that have been persistent for at least 4 weeks (item 3), pathological (item 4), pervasive (item 5) by affecting multiple life contexts, syndrome specific and not attributable to another cause (item 6), ecologically valid (item 7) and assessable by the IDS-C30 instrument (item 8). Further, these symptoms clearly map to the nosological entity of interest (DSM-IV-R melancholic depression). Consequently, the SAFER inventory would conclude that the patient meets SAFER criteria (scored definitely/yes) and is a valid patient for this clinical trial.

Summary

In this article, we have emphasized that clinical trials evaluating new medications with unique, targeted modes of action may not be able to demonstrate efficacy within the broad heterogeneous population of patients with mood and anxiety disorders as defined by the DSM-IV-R. Instead, new drug development needs to focus on the primary nosological entity likely to be affected by a new drug entity's mode of action. We have proposed that a valid patient for clinical trials will have the acute primary symptoms that the novel drug of interest is supposed to influence. In this article, we have described operational criteria (SAFER criteria) to delineate a more symptom-specific and ecologically sound approach to the identification of the valid patient for clinical trials and offered a tool (SAFER criteria inventory) to ascertain valid patients

by these criteria. The usefulness of these criteria and the inventory will need to be demonstrated in clinical studies.

Conflict of Interest

Dr. S. D. Targum has equity interests in United BioSource Corporation (UBC), BrainCells Inc., and Prana Biotechnology Ltd. He has received consultation fees for clinical trial design, execution, or training from BrainCells Inc., Prana Biotechnology, Nupathe, Dynogen, and Memory Pharmaceuticals within the last 12 months. He is an executive-in-residence at Oxford Bioscience Partners (Boston, Massachusetts) and a consultant in psychiatry at the Massachusetts General Hospital. Dr. M.H. Pollack has equity interests in Medavante and Mensante Corporation. He has received research grants from AstraZeneca, Bristol Myers Squibb, Cephalon, Cyberonics, Forest Laboratories, GlaxoSmithKline, Janssen, Eli Lilly & Co., NARSAD, NIDA NIMH, Pfizer, Sepracor, UCB Pharma, and Wyeth. He sits on the Advisory Boards and is a consultant for AstraZeneca, Brain Cells Inc., Bristol Myers Squibb, Cephalon, Dov Pharmaceuticals, Forest Laboratories, GlaxoSmithKline, Janssen, Jazz Pharmaceuticals, Eli Lilly & Co., Medavante, Neurocrine, Neurogen, Novartis, Otsuka Pharmaceuticals, Pfizer, Predix, Roche Laboratories, Sanofi, Sepracor, Solvay, Tikvah Therapeutics, Transcept Inc., UCB Pharma, and Wyeth. Also, Speaker Programs for Bristol Myers Squibb, Forest Laboratories, GlaxoSmithKline, Janssen, Lilly, Pfizer, Solvay, and Wyeth. Dr. M. Fava has research support from Abbott Laboratories, Alkermes, Aspect Medical Systems, Astra-Zeneca, Bristol-Myers Squibb Company, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc., GlaxoSmithkline, J & J Pharmaceuticals, Lichtwer Pharma GmbH, Lorex Pharmaceuticals, Novartis, Organon Inc., PamLab, LLC, Pfizer Inc., Pharmavite, Roche, Sanofi/Synthelabo, Solvay Pharmaceuticals, Inc., Wyeth-Ayerst Laboratories. Advisory/consulting from Aspect Medical Systems, Astra-Zeneca, Bayer AG, Auspex Pharmaceuticals, Best Practice Project Management, Inc., Biovail Pharmaceuticals, Inc., BrainCells, Inc. Bristol-Myers Squibb Company, Cephalon, Compellis, CNS Response, Cypress Pharmaceuticals, Dov Pharmaceuticals, Eli Lilly & Company, EPIX Pharmaceuticals, Fabre-Kramer Pharmaceuticals, Inc., Forest Pharmaceuticals Inc., GlaxoSmithkline, Grunenthal GmBH, Janssen Pharmaceutica, Jazz Pharmaceuticals, J & J Pharmaceuticals, Knoll Pharmaceutical Company, Lundbeck, MedAvante, Inc., Merck, Neuronetics, Novartis, Nutrition 21, Organon Inc., PamLab, LLC, Pfizer Inc., PharmaStar, Pharmavite, Precision Human Biolaboratory, Roche, Sanofi/Synthelabo, Sepracor,Solvay Pharmaceuticals, Inc., Somaxon, Somerset Pharmaceuticals, Takeda, TetraGenex Inc., Transcept Pharmaceuticals, Wyeth-Ayerst Laboratories. Speaking from Astra-Zeneca, Boehringer-Ingelheim, Bristol-Myers Squibb Company, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc., GlaxoSmithkline, Novartis, Organon Inc., Pfizer Inc., PharmaStar, Wyeth-Ayerst Laboratories and equity holdings in Compellis, MedAvante.

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APPENDIX 1: General Requirements (SAFER) for a Valid Patient/Illness

- **State versus Trait:**

The identified symptoms must reflect the current *state* of illness and not longstanding traits

- Traits do not generally change in 4–12 weeks

- **Assessability:**

The patient's symptoms are measurable with standard, reliable rating instruments

- The symptoms of valid patients *can be reliably assessed* with standardized measurement tools

- **Face validity:**

The patient's presentation is consistent with our knowledge of the illness

- **Ecological validity:**

The patient's symptoms reflect the characteristics of the illness in a real-world setting

- **Rule of the Three Ps:**

Identified symptoms must be pervasive, persistent, and pathological

- The three Ps must interfere with function and quality of life

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APPENDIX 2: SAFER Criteria Inventory

The SAFER criteria seek to reduce the variance in patient selection and qualification for clinical trials by confirming the presence of key elements of a clinical presentation contributing to a valid patient profile (Targum, Pollack, Fava, 2008). The criteria identify patients whose acute presenting symptoms are likely to be affected by a new drug entity's mode of action and therefore lie within the context of the primary nosological entity of interest.

The SAFER CRITERIA INVENTORY operationalizes these criteria in a straightforward format that can be applied in most clinical trial designs.

Instructions

1. Identify the targeted symptoms for the primary nosological entity of interest
   a. Symptom constructs may or may not approximate disease entities as defined in the DSM-IV-R

   i. for melancholic depression (based upon DSM-IV-R) it might include depression, anhedonia, guilt, despondency in the morning, early morning awakening, etc.
   ii. for anxious depression, an alternative group of symptoms, which include symptoms of hyperarousal and hypervigilance, would be identified
   iii. for generalized anxiety disorder may focus on particular subgroups of symptomatology including psychic and/or somatic symptomatology
2. Ascertain which rating instruments will be employed and confirm that the targeted symptoms are included in the scale
3. For a clinical trial, determine the minimum number of valid target symptoms necessary/sufficient to confirm that criteria are met for a *valid* patient
   a. For instance: patient must have at least four valid symptoms meeting SAFER criteria of which one must be depression or anxiety (depending on the target disorder under study).
4. Conduct the Patient/Symptom Review using the SAFER criteria inventory
   a. Identify current, acute symptoms presented by the patient during the psychiatric examination. Use any and all available resources including diagnostic surveys, symptom-specific rating instruments, medical records, narrative reports, corroborative information (if available) from friends, family, and other professionals.
   b. Administer the SAFER inventory for each targeted symptom
      i. It may be necessary to obtain additional information from the patient
   c. Using the pre-determined minimum criteria for sufficient and valid target symptoms (established in item 3 above), confirm that the patient meets SAFER criteria for a valid patient for this clinical trial/assessment

CRITERIA	OPERATIONAL DEFINITION	SCORING
1. Acute Symptoms	Symptoms have been present during the current episode	1 = DEFINITELY/YES 2 = POSSIBLY/PROBABLY YES 3 = UNLIKELY/NO
2. State versus Trait Symptoms	Symptoms are present primarily during episodes of acute illness (state-dependent)	1 = DEFINITELY/YES
	Symptoms are NOT just a trait characteristic	2 = POSSIBLY/PROBABLY YES
(Pre-existing symptoms)	Symptoms that are present steadily throughout the person's life are unlikely to change during current treatment intervention (score 3 = NO)*	3 = UNLIKELY/NO
	Exacerbation of pre-existing symptoms may be measurable in the current episode and may be valid (score 1 or 2)	
3. Persistent Symptoms	Symptoms are present most of the day nearly every day since the onset of current episode *and* have been present at least 4 weeks	1 = DEFINITELY/YES 2 = POSSIBLY/PROBABLY YES 3 = UNLIKELY/NO
4. Pathological Symptoms	Symptom are disruptive and have had some impact on behavior or function in the past 4 weeks	
	Symptoms are distinguishable from normal behavior according to rater, patient, and others (if corroboration is available)	1 = DEFINITELY/YES 2 = POSSIBLY/PROBABLY YES 3 = UNLIKELY/NO
5. Pervasive Symptoms	Symptoms impact multiple domains (cognitive, symptomatic, behavioral, functional) and/or contexts (school, work, home, social relations)**	1 = DEFINITELY/YES 2 = POSSIBLY/PROBABLY YES 3 = UNLIKELY/NO
6. Specificity of Symptoms	Symptoms are specific to the primary nosological entity and are NOT attributable to:	
	Comorbid conditions	1 = DEFINITELY/YES
	Concurrent medications	2 = POSSIBLY/PROBABLY YES
	External circumstances	3 = UNLIKELY/NO

CRITERIA	OPERATIONAL DEFINITION	SCORING
7. Ecologically Valid Symptoms	Symptoms occur with the frequency, intensity, duration, course, and impact consistent with our knowledge of its occurrence in a real-world setting	
	Symptoms are not exaggerated and have had real impact on behavior or function in past 4 weeks	1 = DEFINITELY/YES 2 = POSSIBLY/PROBABLY YES
	Symptomatic change is likely to matter to the patient's quality of life	3 = UNLIKELY/NO
8. Assessable Symptoms	Symptoms can be reliably and sensitively measured with employed rating instruments	1 = DEFINITELY/ YES 2 = POSSIBLY/PROBABLY YES 3 = UNLIKELY/ NO
Valid Symptom (meets SAFER symptom criteria)	All eight symptom criteria scored yes or probably yes (1 or 2);	1 = DEFINITELY/YES
	Items 1, 6, 7, and 8 scored definitely yes	3 = UNLIKELY/NO
9. Face Validity for *all t*argeted symptoms	Presenting symptom cluster clearly maps to the primary nosological entity	
	Symptoms have clearly affected behavior/function in past 4 weeks	1 = DEFINITELY/YES
	Current illness represents a clear change from previous level of functioning	2 = POSSIBLY/PROBABLY YES 3 = UNLIKELY/NO
	If recurrent, the characteristics of the current episode are similar to previous episodes	
Valid Patient (meets ALL SAFER clinical trial criteria)	Patient has sufficient and valid target symptoms of the primary nosological entity for at least 4 weeks to yield meaningful, measurable scores in a clinical trial	1 = DEFINITELY/YES 3 = UNLIKELY/NO

*There may be some disease entities (e.g., social phobia, GAD) where the symptoms have been longstanding and presented early in the course of illness, but are the targets for symptomatic change of the treatment intervention. In these instances, score state vs. trait as 2 (possibly yes).
**Exceptions: Multiple domains or contexts may not be relevant for some disease entities (e.g., specific phobias) or when targeted symptoms of interest are narrow (e.g., cognition, sleep). In these instances, score pervasive symptoms as 2 (possibly yes).

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