The clinical characterization of the adult patient with an anxiety or related disorder aimed at personalization of management

Dan J. Stein[1], Michelle G. Craske[2], Barbara O. Rothbaum[3], Samuel R. Chamberlain[4], Naomi A. Fineberg[5,6], Karmel W. Choi[7], Peter de Jonge[8], David S. Baldwin[4], Mario Maj[9]

[1]South African Medical Research Council Unit on Risk & Resilience in Mental Disorders, Department of Psychiatry and Neuroscience Institute, University of Cape Town, Cape Town, South Africa; [2]Department of Psychology and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles (UCLA), Los Angeles, CA, USA; [3]Department of Psychiatry, Emory University, Atlanta, GA, USA; [4]Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, and Southern Health NHS Foundation Trust, Southampton, UK; [5]School of Life and Medical Sciences, University of Hertfordshire, and Hertfordshire Partnership University NHS Foundation Trust, Hatfield, UK; [6]University of Cambridge Clinical Medical School, Cambridge, UK; [7]Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; [8]Developmental Psychology, Department of Psychology, Rijksuniversiteit Groningen, Groningen, The Netherlands; [9]Department of Psychiatry, University of Campania "L. Vanvitelli", Naples, Italy

The clinical construct of "anxiety neurosis" was broad and poorly defined, so that the delineation of specific anxiety disorders in the DSM-III was an important advance. However, anxiety and related disorders are not only frequently comorbid, but each is also quite heterogeneous; thus diagnostic manuals provide only a first step towards formulating a management plan, and the development of additional decision support tools for the treatment of anxiety conditions is needed. This paper aims to describe systematically important domains that are relevant to the personalization of management of anxiety and related disorders in adults. For each domain, we summarize the available research evidence and review the relevant assessment instruments, paying special attention to their suitability for use in routine clinical practice. We emphasize areas where the available evidence allows the clinician to personalize the management of anxiety conditions, and we point out key unmet needs. Overall, the evidence suggests that we are becoming able to move from simply recommending that anxiety and related disorders be treated with selective serotonin reuptake inhibitors, cognitive-behavioral therapy, or their combination, to a more complex approach which emphasizes that the clinician has a broadening array of management modalities available, and that the treatment of anxiety and related disorders can already be personalized in a number of important respects.

Key words: Anxiety, anxiety and related disorders, obsessive-compulsive disorder, post-traumatic stress disorder, personalization of treatment, symptom profile, clinical subtypes, severity, neurocognition, functioning, quality of life, personality traits, psychiatric antecedents, psychiatric comorbidities, physical comorbidities, family history, early environmental exposures, recent environmental exposures, protective factors, dysfunctional cognitive schemas

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Anxiety disorders are the most prevalent mental disorders, with a global current prevalence estimate of 7.3%[1]. An early construct was "anxiety neurosis", but this was poorly operationalized. The differentiation of specific anxiety disorders in the DSM-III was therefore an important step forward for the field, giving impetus to the development of a more personalized approach to the treatment of the individual patient with anxiety[2]. An early hypothesis, for example, was that patients with social anxiety disorder would respond preferentially to monoamine oxidase inhibitors[3].

At the same time, anxiety disorders are characterized by significant comorbidity, and each disorder is heterogeneous in terms of phenomenology and psychobiology. Thus, for example, social anxiety disorder is often accompanied by generalized anxiety disorder (GAD), and ranges from discrete social anxiety disorder to generalized social anxiety disorder[4]. Although there is a large body of evidence on the value of selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral therapy (CBT) for anxiety disorders, this heterogeneity may explain why a significant proportion of individuals do not respond to first line therapy[5].

While current diagnostic systems are certainly useful in formulating an initial treatment plan, it behooves the field to develop additional decision support tools. These may allow us to move away from guidelines that focus solely on disorders and that emphasize SSRIs and CBT as first line steps towards more detailed assessments that provide the clinician with more specific guidance and facilitate a more personalized approach. More detailed and rigorous matching of presentation with management may ultimately improve treatment outcomes[6].

This paper aims to describe systematically important domains relevant to the personalization of management of anxiety disorders and related conditions such as obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) (Table 1). For each domain, we summarize the available research evidence and review the relevant assessment instruments, paying special attention to their suitability for use in routine clinical practice. We emphasize areas where the available evidence allows the clinician to personalize the management of anxiety and related conditions, and we point out key unmet needs. The research literatures on anxiety and depression have many important overlaps, so it is not surprising that this list of domains draws closely on previous work on depression[6].

In keeping with the aims of precision medicine, considerable effort has been paid to developing biomarkers for anxiety and related disorders. It is notable that fear conditioning and extinction provide an important paradigm for explaining the symptoms of these disorders, as well as conceptualizing treatment approaches[7]. Additional specific constructs, such as cognitive flexibility and inhibitory control, may be more relevant to particular disorders, such as OCD[8]. These concepts are emphasized in the translational neuroscience framework of the US National Institute of Mental Health's Research Domain Criteria (RDoC)[9] and contrib-

Table 1 Salient domains to be considered in the clinical characterization of a patient with an anxiety or related condition

1. Symptom profile
2. Clinical subtypes
3. Severity
4. Neurocognition
5. Functioning and quality of life
6. Personality traits
7. Antecedent and concomitant psychiatric conditions
8. Physical comorbidities
9. Family history
10. Early environmental exposures
11. Recent environmental exposures
12. Protective factors / Resilience
13. Dysfunctional cognitive schemas

uted in part to the separation of anxiety disorders in the DSM-5 and ICD-11 into anxiety or fear-related disorders, obsessive-compulsive and related disorders, and disorders specifically associated with stress (these are the terms used in the ICD-11)[10].

Despite the extent and rigor of research on the neurobiology of anxiety and related disorders, no biomarker of these conditions has to date proven sufficiently sensitive and specific for widespread adoption in clinical practice[11,12]. We therefore do not address biomarkers in detail in the current paper. However, we hypothesize that more personalized assessment of the sort proposed herein may be useful in advancing biomarker research, as well as work on the translational neuroscience of anxiety more generally, given the potential value of more fine-grained clinical assessments for delineating disorder heterogeneity in ways that may be neurobiologically informative and which may predict treatment response[6,13].

The paper focuses on anxiety and related disorders in the adult patient. These disorders often have an early onset, and pediatric anxiety is important both clinically and from a public health perspective; additional work is therefore needed to address the child and adolescent with anxiety. We also do not address in detail anxiety secondary to other mental disorders such as major depression or a psychotic disorder, or anxiety due to another medical condition, or anxiety induced by a substance or a medication, despite their clinical significance. Nor do we closely cover issues relevant to subthreshold anxiety and related disorders, despite their public health importance[14]. Gender- and culture-related issues are considered where relevant.

SYMPTOM PROFILE

Anxiety disorders share features of anxiety, fear and/or panic attacks, often accompanied by phobic avoidance or overly cautious behaviors, in reaction to perceived threats. In both the DSM-5 and ICD-11, anxiety disorders include agoraphobia, GAD, panic disorder, selective mutism, separation anxiety disorder, specific phobia, and social anxiety disorder. OCD and PTSD are included in separate but closely related groupings. In both nosologies, the diagnosis of anxiety disorders involves marked or substantial levels of fear or anxiety, that differ from stress-induced transient fear or anxiety by being persistent (i.e., lasting several months or more) and distressing or impairing.

Both the DSM-5 and ICD-11 differentiate among the anxiety disorders primarily by the focus of apprehension (i.e., perceived threat) and the types of objects or situations that induce anxiety, fear or panic attacks. The perceived threat and associated stimuli range from being tightly circumscribed (as in specific phobia), to domain-specific (as in agoraphobia, panic disorder, separation anxiety disorder, and social anxiety disorder), to pervasive (as in GAD). Thus, although highly comorbid with one another, anxiety and related disorders can be differentiated by close examination of the range and types of situations that are feared or avoided and the content of the associated thoughts or beliefs. For example, panic disorder is characterized by fears of interoceptive cues which are misappraised as being harmful, whereas social anxiety is characterized by fears of social or performance situations in which negative evaluation and rejection is anticipated to occur. Differentiation between the anxiety and related disorders is of high relevance to clinical management and treatment selection, since most evidence-based pharmacological and psychological treatments are tested for specific anxiety or related disorders.

The most significant difference between the DSM-5 and ICD-11 conceptualizations of anxiety and related disorders is in the diagnostic requirements for PTSD[15]. In the DSM-5, the criteria were expanded substantially, to include twenty symptoms across four clusters, in an attempt to capture the full scope of chronic post-traumatic expressions. In contrast, the ICD-11 simplified PTSD diagnostic requirements to three core symptoms that most clearly distinguish this disorder from other conditions, i.e. re-experiencing the traumatic event or events in the present, deliberate avoidance of reminders, and a sense of ongoing threat. Evidence suggests that the data better fit the simpler factor structure of the ICD-11 than the DSM-5 criteria[16]. The ICD-11 defines "complex PTSD" as consisting of the three core PTSD symptoms described above accompanied by problems in affect regulation, negative self-beliefs, and relationship difficulties[17]. Latent class analysis and latent profile analysis have supported the distinction between PSTD and complex PTSD as well as the association between complex PTSD and trauma in childhood in some studies[16].

Anxiety disorders are marked by fear or anxiety. Fear is conceptualized as the emotional response to perceived predictable or imminent threat when there is little or no time to consciously strategize escape, whereas anxiety is a future-oriented state of anticipation for uncertain, prolonged or distal threats when there is time to comprehend the foreboding nature of the situation. Both states are designed to activate cognitive, affective, physiological and behavioral processes that enhance safety. In the case of fear, rapid, involuntary, physiological reactions facili-

tate the selection and production of an appropriate fight or flight response; whereas anxiety activates physiological and cognitive strategic preparation for fight or flight if needed[18-20]. This view of fear and anxiety is supported by animal predatory imminence continuum models that posit distinct modes (from pre-encounter potential for threat, to post-encounter threat detection, to circa-strike predator attack) that each result in distinct well-defined behaviors and defensive circuits[21].

These canonical modes of threat are universal (although the responses are species-specific) and applicable not only to non-primates but also to humans[22,23]. Optogenetic studies in non-primates show that stimuli analogous to pre- and post-encounter threats evoke the ventromedial prefrontal cortex, hippocampus, and basolateral amygdala – regions involved in threat memory, prospection and avoidance[24,25]. In the circa-strike attack mode, activity is evoked in circuits that include the mid-cingulate cortex, central amygdala, hypothalamus, and periaqueductal gray – regions involved in fast reactions to threat (e.g., flight)[24,25]. Similar defensive circuits exist in humans: functional magnetic resonance imaging (MRI) studies show that distant threat is associated with increased activity in the ventromedial prefrontal cortex, and, as threat moves closer, more activation in midbrain periaqueductal gray is observed[26,27]. The RDoC, which take a dimensional approach to psychopathology, draw upon these models by suggesting that "responses to low imminence threats are qualitatively different than the high imminence threat behaviors that characterize fear"[9].

Whereas prototypes of fear and anxiety lie at different "places" upon a continuum of responding, clinical presentations are more fluid. For example, perceptions of threat can rapidly change from being distal to imminent through appraisals and imagery alone, without change in external circumstances. An exemplar is the person with PTSD who experiences a fearful flashback to trauma (i.e., imminent threat) in the midst of anxiety in unfamiliar surroundings (i.e., distal threat).

Anxiety and fear are expressed across multiple response modalities: behavior, physiology and subjective report[28]. States of anxiety are typically linked with behaviors of vigilance, caution and avoidance, physiological preparation for acute threat (e.g., startle response amplification, elevated muscle tension), statements of worry or concern, and appraisals of impending or uncertain threat (e.g., "What if I mispronounce a word at the dinner party next week – I will be so embarrassed" or "What if I faint in the movie theater"). States of fear are linked with behaviors of escape (or fight), autonomic arousal, statements of fear or fright, and appraisals of acute threats (e.g., "I am dying" or "I need to get out of here")[29].

Notably, these response modalities are not always concordant[30]. For example, individuals may report anxiety or fear in the absence of physiological changes or behavioral outputs, or may avoid situations in the absence of reported anxiety or fear. Even during panic attacks, people sometimes report fear without evidence of physiological changes[31]. Such discordance may be informative for treatment selection. For example, subjective distress in the absence of physiological changes may indicate the value of a cognitively oriented treatment approach rather than a biologically oriented one (such as respiratory regulation or pharmacotherapy), and behavioral avoidance in the absence of physiological changes may indicate the particular value of exposure therapy. However, evidence for such treatment matching remains only nascent, as clinical trials have focused primarily on particular anxiety diagnoses and clinical subtypes, rather than on detailed assessment of specific behaviors, physiological parameters, or cognitive appraisals.

In clinical practice, the key first step in the assessment of anxiety symptoms is the establishment of an anxiety or related disorder diagnosis on the basis of the symptom profile. The diagnosis of anxiety and related disorders in adults can be ascertained using validated clinical interviews. Examples of such interviews include the Structured Clinical Interview for DSM-5 (SCID-5)[32], the Mini International Neuropsychiatric Interview (MINI)[33] and the Composite International Diagnostic Interview (CIDI)[34]. The Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5) is particularly focused on the differential diagnosis among anxiety disorders[35]. A structured diagnostic interview for obsessive-compulsive and related disorders may be useful for assessing this range of often overlooked conditions[36].

Determining whether the anxiety symptoms (for example, panic attacks) are occurring as a manifestation of another mental disorder (such as major depression or bipolar disorder) is important. Substance use or intoxication (e.g., use of caffeine, stimulants) and withdrawal (e.g., from alcohol use) can lead to prominent anxiety symptoms. Certain medical conditions also produce anxiety symptoms, such as cardiopulmonary (e.g., asthma), endocrine (e.g., thyroid disease) and neurological (e.g., complex partial seizures) disorders, among others.

Identifying anxiety related to medical conditions is achieved through a detailed medical history and physical examination and, when warranted, specific blood (e.g., thyroid-stimulating hormone levels) or other (e.g., electrocardiography or electroencephalography) tests. Although structural (for example, voxel-based morphometric) and functional MRI have been used to learn more about the pathophysiology of anxiety and related disorders, they are not currently useful for diagnostic purposes[11,12].

Data on the underdiagnosis and undertreatment of anxiety and related disorders underscore the importance of screening for anxiety symptoms[37]. The Generalized Anxiety Disorder-7 (GAD-7)[38] is a 7-item self-report questionnaire that has been developed specifically for GAD, but has been found to be useful in identifying any anxiety disorder with adequate sensitivity and specificity[39]. Other screening tools include the Hospital Anxiety and Depression Scale[40] and the Overall Anxiety Severity and Impairment Scale (OASIS)[41], which includes measurement of avoidance behavior (an important feature, since anxiety levels may be masked without such measurement). The Perinatal Anxiety Screening Scale is suitable as a nonspecific screener for perinatal women[42].

If an anxiety or related disorder is present, several measures can be used to assess the profile of anxiety symptoms. The Interview for Mood and Anxiety Symptoms assesses all symptoms of

DSM and ICD emotional disorders as well as other manifestations of internalizing psychopathology[43]. Each item is rated from clearly absent, to partially present (subclinical, subthreshold) to clearly present, and thus symptom profile scores can be evaluated. Aside from interviews, self-report questionnaires exist for each of the anxiety and related disorders, and provide more detailed symptom profiles. These include the DSM-5 scales developed for agoraphobia, GAD, OCD, PTSD, social anxiety disorder, and specific phobia, each one including items for affective states of fear and anxiety, physiological, cognitive and behavioral symptoms[44]. With the exception of specific phobia, these scales have been shown to have adequate to strong psychometric properties[45-52].

A number of other well-validated standardized symptom questionnaires exist. They include the Penn State Worry Questionnaire[53] for GAD; the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)[54] for OCD; the Albany Panic and Phobia Questionnaire-Agoraphobia[55], the Mobility Inventory for Agoraphobia[56], the Panic Disorder Severity Scale[57], and the Panic and Agoraphobia Scale[58] for panic disorder and agoraphobia; the PTSD Checklist-5 for DSM-5 (PCL-5)[59] and the Clinician Administered PTSD Scale for the DSM-5 (CAPS-5)[60] for PTSD; and the Social Phobia and Anxiety Inventory[61] and the Liebowitz Social Anxiety Scale[62] for social phobia. Scales for each type of specific phobia are not available, but a generic measure is the Fear Survey Schedule[63], a 51-item questionnaire that asks respondents to indicate their discomfort, or felt anxiety, to each of fifty-one stimuli.

Distinguishing the anxiety and related disorders can guide clinicians to disorder-based treatment. Particular versions of CBT have been developed to target the specific focus of apprehension of each anxiety or related disorder. There is a substantial evidence for the efficacy of such targeted treatments[64-66], and they are recommended as first-line psychological treatments for anxiety and related disorders in several guidelines, including those by the UK National Institute for Health and Care Excellence (NICE)[67]. For example, CBT for panic disorder includes interoceptive exposure to feared bodily sensations; CBT for social anxiety disorder includes cognitive restructuring around post-event rumination; CBT for GAD addresses meta-beliefs about worry; CBT for OCD includes exposure to specific cues that trigger distress and the urge to perform compulsive rituals as well as response prevention aimed at eliminating the compulsions; and CBT for PTSD includes imaginal exposure or cognitive reprocessing regarding trauma memories. Thus, differential diagnosis facilitates choice of the most appropriate form of CBT. Even if using transdiagnostic CBT, a promising alternative to disorder-specific approaches[68], the clinician will still need to implement the therapeutic strategies in ways that are tailored to each person's focus of apprehension.

In terms of pharmacotherapy, SSRIs have demonstrated efficacy for all major anxiety and related disorders. Nevertheless, it is important to distinguish between the various disorders, for several reasons. First, SSRI pharmacotherapy guidelines differ across the various anxiety and related conditions[69]. Thus, for example, it is particularly important to begin with lower doses of an SSRI in panic disorder (as standard doses may not be tolerated), while a higher dose and longer duration of treatment is particularly important in OCD. Second, agents other than SSRIs have different efficacy across different anxiety and related disorders[69]. Thus, for example, the tricyclic antidepressant imipramine is efficacious in some anxiety and related disorders (e.g., GAD, panic disorder, PTSD) but not others (OCD, social anxiety disorder); the benzodiazepine alprazolam is efficacious in a different range of anxiety disorders (GAD, panic disorder, social anxiety disorder) but not in anxiety related disorders (OCD and PTSD); buspirone is efficacious in GAD but not in other anxiety and related disorders, while OCD appears unique among these conditions in being more responsive to serotonergic than noradrenergic reuptake inhibitors[69].

Greater precision and ultimate efficacy may derive from matching treatment to symptom clusters, given the heterogeneity that exists within diagnostic labels. Indeed, there is evidence that clinicians already view symptom clusters as more informative than diagnostic categories for pharmacotherapy selection[70,71]. For example, in a sample of 318 patients, the diagnosis of PTSD was not associated with the prescription of any specific medication class, while symptom clusters were: anticonvulsant prescription was linked to avoidance symptoms, antidepressant prescription to numbing symptoms, anxiolytic prescription to intrusions, and mood stabilizer prescription to hyperarousal[71]. Similarly, in panic disorder, anxiolytics were more often prescribed for physical symptoms of the fear response, whereas antidepressants and anticonvulsants as well as anxiolytics were prescribed for psychological symptoms. A similar matching of medication class with symptom profile was found for agoraphobia (public vs. enclosure), OCD (cleaning, checking), social anxiety disorder (interactive vs. performance), and specific phobia (animal, situational, blood). Clearly, the symptom profile is guiding prescribers' current pharmacotherapy choices, and the field of personalized medicine would be advanced by randomized controlled trials to validate (or not) such matching of symptom profile to medication.

The same argument holds for psychotherapy, which has been confounded by utilization of CBT packages that combine multiple therapeutic strategies (e.g., breathing retraining, cognitive restructuring, exposure therapy, response prevention). There have been calls to match the core active ingredients of these therapy packages to specific symptom profiles (e.g., breathing retraining to arousal regulation, cognitive restructuring to cognitive distortions, exposure therapy to avoidance)[72,73]. This remains an important area of future research. Nonetheless, it is quite possible that the practicing clinician already tailors the core ingredients of CBT to symptom presentations, in the same way as observed for pharmacotherapies.

CLINICAL SUBTYPES

Each of the anxiety and related disorders is characterized by significant heterogeneity, and several clinical subtypes have been delineated. The content of the fear or anxiety (cognitive

component), the physiological reactions (such as a panic attack), and the behavioral response (which often includes avoidance and may include safety behaviors) can be useful in determining whether or not a distinctive clinical subtype is present. In addition, a range of other approaches to subtyping have been taken, including those based on age of onset and on comorbid symptoms. Here we consider the main clinical subtypes that have been posited for key anxiety and related disorders.

In GAD, it is useful to assess both the nature of the worries, as well as the range of psychic (psychological) versus somatic (physical) symptoms. The worries may focus on death (e.g., someone not calling when he said he would means he has died), disease (e.g., "headache means I have a brain tumor"), destruction (e.g., "the leak in the ceiling means I need a new roof and if I don't get it in time my house will be ruined"), and sometimes destitution (e.g., "If I lend my sister the money, she will never stop asking and I'll end up broke"). Tools such as the Penn State Worry Questionnaire[53] assess the range and focus of GAD worries, while the psychic and somatic subscales of the Hamilton Anxiety Rating Scale (HAM-A)[74] are useful for assessing the range of symptoms.

Knowing the precise nature of the worries is important for CBT, which may focus on cognitive restructuring of particular worries or exposure for particular kinds of fears. In terms of pharmacotherapy, an early suggestion was that tricyclic antidepressants are more useful for psychic symptoms, while benzodiazepines are more useful for somatic symptoms[75]. However, there has been relatively little subsequent evidence to support the selective response of psychic and somatic symptoms to different pharmacotherapies. A range of medications that are efficacious for GAD improve both psychic and somatic symptoms[76-79].

Concerning OCD, a substantial literature has emphasized that obsessions and compulsions tend to fall on a few symptom dimensions, including washing, checking, symmetry and hoarding[80]. Although many patients have symptoms that lie on different dimensions, or experience a range of symptoms from different dimensions over time, there is some evidence that symptom dimensions are associated with particular psychobiological characteristics and treatment outcomes. In particular, hoarding symptoms are less likely to respond to SSRIs. Further work is needed to determine whether patients with hoarding symptoms who do not respond to SSRIs may respond to augmentation with dopamine antagonists[81].

Insight in OCD can be ascertained by questioning the patient about the consequences of not engaging in the compulsions and the likelihood that the feared consequences will actually occur. It may be helpful to ask the patient if the feared consequences would be likely to occur for someone else, in order to assess their thought process without the influence of their own anxiety about not performing the compulsions. Insight in OCD can be formally assessed with measures such as the Brown Assessment of Beliefs Scale[82]. OCD patients with poor insight may be less likely to access or respond to pharmacotherapy and psychotherapy[83]. Such patients may require additional interventions such as family-based treatments[84] and adjunctive dopamine antagonists[85].

If OCD patients have current or past tics, it is important to determine if the compulsions are more tic-like (e.g., throat-clearing) or aimed to reduce anxiety (e.g., handwashing after feeling contaminated). Tic-related OCD is marked by a number of features, including early onset, male predominance, family history of tics, and more often having symptoms that involve responding to an urge (or premonitory sensory symptoms) or having to feel "just right". Tic severity may be formally assessed with a number of measures[86]. Tic-like compulsions do not respond well to exposure and response prevention, and may respond better to augmentation with dopamine antagonists[83].

A range of other subtypes of OCD has been proposed, including early onset OCD[83]. While such work has been valuable to better understand the heterogeneity of OCD, there is insufficient treatment evidence for such subtyping to have clinical utility.

Concerning panic disorder, a number of different sets of panic symptoms have been found to cluster together, including respiratory, nocturnal, non-fearful, cognitive and vestibular symptoms[31]. Investigation of the respiratory physiology in panic disorder has been particularly useful in advancing understanding of the neurobiology of the condition[87]. Nevertheless, there is no strong evidence to indicate that any of these subtypes has a distinctive psychobiology, nor is there good evidence that any has a selective treatment response[88]. It is possible, however, that more extensive study will lead to more specific treatment recommendations for panic disorder subtypes.

PTSD is diagnosed in the DSM-5 using twenty symptoms that fall in four symptom subgroups, namely intrusions (five symptoms), avoidance (two symptoms), negative alterations in cognition and mood (seven symptoms), and arousal (six symptoms). While it has long been suggested that different symptom dimensions of PTSD are underpinned by different neurobiological mechanisms[89,90], it seems that there are strong genetic correlations across PTSD symptom dimensions and that efficacious pharmacotherapy for PTSD reduces symptoms across dimensions[91]. As noted earlier, the prescription of anticonvulsants has been linked to avoidance, that of antidepressants to numbing symptoms, that of anxiolytics to intrusions, and that of mood stabilizers to hyperarousal[71], but further work is needed to provide the evidence base for such decision-making.

It has been hypothesized that there is a dissociative subtype of PTSD, with a distinctive neurobiology[92]. This subtype may be characterized by overmodulation of affect, rather than undermodulation of affect with re-experiencing and hyperarousal symptoms. Most clinicians assess dissociation via psychiatric history, but it may be useful to employ a formal tool such as the Dissociative Experiences Scale (DES)[93]. The DES-II is a 28-item self-report measure that assesses the frequency of dissociative experiences through daily life, with scores over 30 considered high[94].

Recording treatment sessions for later review may be helpful for patients with dissociation symptoms, as well as frequent grounding, breaks, and progressing more slowly with traumatic content in order to not overwhelm the patient. Further, in keeping with the hypothesis that dissociation is linked to avoidance,

there is evidence that cognitive processing therapy should include an exposure component when dissociation is present[95]. The ICD-11 construct of "complex PTSD" is marked by increased levels of early childhood trauma and dissociative symptoms, but further work is needed to determine what specific interventions would improve outcomes in this condition[96].

The DSM-IV included a "generalized" specifier for social anxiety disorder, referring to patients with a broader range of social fears. In the DSM-5, this has been replaced by a "performance only" specifier, which is used when the fear is limited to speaking or performing in public. There is a view that social anxiety disorder ranges from single fears through to multiple fears, and that patients with more fears have greater severity and impairment[97]. There is some evidence that patients with "performance only" social anxiety disorder may respond to beta-adrenergic blockers (such as propranolol or atenolol)[98]. SSRIs, on the other hand, may be useful for patients with both more limited or more generalized social anxiety disorder[99]. CBT seems to be effective for all types of social anxiety.

Specific phobias include an animal type (e.g., spiders, insects, dogs), a blood-injection-injury type (e.g., needles, invasive medical procedures), a natural environment type (e.g., heights, storms, water), a situational type (e.g., airplanes, elevators, enclosed places) and "other" types (e.g., phobic avoidance of situations that may lead to choking, vomiting, or contracting an illness). Exposure techniques tailored to particular phobias are helpful for this range of specific phobia types.

The blood-injection-injury type, in contrast to other phobias which result in persistent tachycardia in response to feared cues, may be characterized in some patients by a diphasic response, with an initial rise in heart rate followed by vasovagal bradycardia and, in some cases, syncope[100,101]. If patients faint upon exposure to cues, exposure therapy can be conducted with the patient lying down. It may be useful to teach patients an isometric muscle tensing technique that can help increase blood pressure during exposure to feared cues[102].

The situational type of specific phobia often overlaps with agoraphobia and/or panic disorder and therefore typically requires cognitive techniques in addition to exposure.

SEVERITY

Assessing the severity of anxiety symptoms is an important component of the evaluation of the patient with an anxiety or related condition.

The DSM-5 includes symptom severity measures for each of the anxiety and related disorders, and several standardized symptom measures are widely used in clinical practice and research. These include the GAD-7[38] and the Penn State Worry Questionnaire[53] for GAD; the Y-BOCS[54] for OCD; the Panic Disorder Severity Scale[57] and the Panic and Agoraphobia Scale[58] for panic disorder; the Mobility Inventory for Agoraphobia[56] and the Albany Panic and Phobia Questionnaire-Agoraphobia[55] for agoraphobia; the PCL-5[59] and the CAPS-5[60] for PTSD; the Fear Survey Schedule[63] for specific phobia; and the Social Phobia and Anxiety Inventory[61] and the Liebowitz Social Anxiety Scale[62] for social phobia (see Table 2).

Table 2 Tools to assess severity of anxiety and related disorders

Agoraphobia	
Albany Panic and Phobia Questionnaire-Agoraphobia[55]	Number of items: 27 Scale: 0-8 Subscales: 9
Mobility Inventory for Agoraphobia[56]	Number of items: 26 Scale: 0-5
DSM-5 severity measure[44,47]	Number of items: 10 Scale: 0-4
Generalized anxiety disorder	
Generalized Anxiety Disorder-7 (GAD-7)[38]	Number of items: 7 Scale: 0-3
Penn State Worry Questionnaire[53]	Number of items: 16 Scale: 1-5
DSM-5 severity measure[44,46]	Number of items: 10 Scale: 0-4
Obsessive-compulsive disorder	
Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[54]	Number of items: 10 Scale: 0-4 Subscales: 2
DSM-5 severity measure[44,48]	Number of items: 10 Scale: 0-4
Panic disorder	
Panic Disorder Severity Scale[57]	Number of items: 7 Scale: 0-4
Panic and Agoraphobia Scale[58]	Number of items: 13 Scale: 0-4
DSM-5 severity measure[44,47]	Number of items: 10 Scale: 0-4
Post-traumatic stress disorder (PTSD)	
PTSD Checklist for DSM-5 (PCL-5)[59]	Number of items: 20 Scale: 1-5 Subscales: 4
Clinician Administered PTSD Scale for the DSM-5 (CAPS-5)[60]	Number of items: 30 Scale: 1-5 (frequency) Scale: 1-5 (intensity) Subscales: 4
DSM-5 severity measure[44,50]	Number of items: 10 Scale: 0-4
Specific phobia	
Fear Survey Schedule[63]	Number of items: 51 Scale: 0-6
DSM-5 severity measure[44]	Number of items: 10 Scale: 0-4
Social anxiety disorder	
Social Phobia and Anxiety Inventory[61]	Number of items: 45 Scale: 0-6
Liebowitz Social Anxiety Scale[62]	Number of items: 24 Scale: 0-3
DSM-5 severity measure[44,52]	Number of items: 10 Scale: 0-4

Measurement of symptom severity in anxiety is useful for a number of reasons. First, considering the full spectrum of symptom severity is relevant to stepped care models of treatment delivery. Stratified stepped care offers less intensive treatments (e.g., digital therapies) to those with lower symptom severity, while those with higher symptom severity are offered more intensive treatments[103-105]. Intensive approaches, including home visits or hospital admission, may be necessary for agoraphobia when patients are unable to leave their homes, for OCD patients when rituals make their homes unsafe or prevent clinic appointments or when they are suffering severe self-neglect as a result of their symptoms, or for the PTSD patient who has such severe symptoms that he/she is unable to attend outpatient treatment sessions.

Second, incorporation of symptom severity measures in treatment visits helps guide both the clinician and the patient, allowing them to be responsive to worsening symptoms, and to positively reinforce treatment gains[106,107]. Practical approaches to measurement-based care of both adult and pediatric anxiety have been implemented, and this promises to contribute to improvement in personalized care and optimization of clinical outcomes[108,109].

Third, guidelines for clinical management of anxiety and related disorders may advise treatment choice based on symptom severity. This is consistent with the point made above that mild symptoms may respond to less intensive treatments, while more severe symptoms may require more intensive treatments, including the use of more than one modality of treatment.

In GAD, symptom severity can be reliably assessed by the GAD-7 (patient-rated) and the HAM-A (observer-rated). With the GAD-7, cut points of 5, 10 and 15 can be interpreted as signifying mild, moderate and severe levels of anxiety: increasing scores on the scale are strongly associated with worsening functional impairment and increasing number of disability days[39]. With the HAM-A, scores of 9, 15 and 24 can be interpreted as representing the lower limits of borderline, mild and moderate illness, respectively[110]. Increasing symptom severity on the HAM-A is linearly related to increasing functional impairment in the three domains of the Sheehan Disability Scale (see below)[111].

The NICE guidance on the management of patients with GAD suggests that, if symptoms are mild, a period of active monitoring should initially be undertaken, as symptoms will often resolve without need for intervention. If symptoms have not resolved following a period of active monitoring, a low-intensity psychological intervention (essentially self-help or psychoeducational approaches) should be offered. In the presence of marked functional impairment, or when symptoms have not resolved with low-intensity psychological interventions, either a high-intensity psychological intervention (CBT or applied relaxation) or medication (typically an SSRI) should be offered, depending on the person's wishes[112].

In OCD, symptom severity can be evaluated with the Y-BOCS: in adults, scores of 14, 26 and 35 may indicate the lower limits of moderate, moderate-severe, and severe symptom intensity, respectively[113]. Increasing symptom severity is generally associated with increasing levels of disability. Severity of symptoms is one of several important clinical factors that should be considered when discussing treatment choices and sequencing with OCD patients[69]. Some guidelines indicate that severity is relevant to choosing between pharmacotherapy and psychotherapy (e.g., with psychotherapy a first line of intervention in mild OCD, and pharmacotherapy employed when patients are unable to undergo CBT)[114], but other guidelines indicate that pharmacotherapy and psychotherapy may be used irrespective of the level of symptom severity in OCD[69].

In PTSD, the assessment of symptom severity may be challenging, as a comprehensive evaluation requires systematic enquiries about multiple symptoms in different domains. The most widely used symptom severity measure is the CAPS-5[60], which comprises 30 items assessing symptom severity over the previous week. PTSD patients with severe symptoms may have more difficulty in tolerating CBT. However, intensive outpatient programs in which PTSD patients are seen daily may increase retention rates to over 90%[115,116], with associated decreases in both PTSD symptoms and suicidal ideation[117].

NEUROCOGNITION

Neurocognition represents one of the key mechanisms by which changes in brain structure and function ultimately give rise to clinical signs and symptoms. Lying closer to the putative biological substrate and being measurable on objective tests, neurocognitive markers may be more reliable, consistent and enduring than the variably expressed symptoms of a disorder[118-120]. Neurocognitive testing in patients with OCD and related disorders, for example, has been used to characterize abnormalities of fronto-striatal circuitry compared to controls[121], as well as to identify putative subtypes with different brain structure, function and connectedness[122].

Clinical assessment of neurocognition in anxiety and related disorders has been given impetus by the development of more reliable neurocognitive tasks with adequate specificity and sensitivity for domains of relevance to these conditions, as well as by technological advances such as delivery via the use of concise computerized batteries that are relatively cheap and easy to apply with little burden on patients or staff. Such testing may support evaluation and diagnosis, and may also be used to monitor the impact of treatment (although some neurocognitive deficits do not appear to change when symptoms respond to intervention, representing candidate vulnerability markers which also occur in asymptomatic first-degree relatives of such patients)[8,123].

Cognitive assessments are more commonly used in OCD than in other anxiety and related disorders. In a systematic review and meta-analysis of candidate biomarkers for OCD, only cognitive measures showed convincing or highly suggestive supportive evidence (class 1 or 2 evidence)[124]. Furthermore, assessment using standardized self-report tools such as the Cognitive Assessment Instrument of Obsessions and Compulsions (CAIOC-13)[125], a 13-item scale, shows a wide range of functional deficits in OCD which are thought to be derived from cognitive difficulties that interfere with many aspects of daily life. As these deficits are easily overlooked, a recent expert survey recommended routine cognitive-functional assessment using scales such as the CAIOC-13

in the clinical assessment for patients with OCD[126].

In the future, the hope is that neurocognitive testing may be used for detecting cases of anxiety and related disorders even prior to the onset of symptoms[126], and to predict treatment response *a priori*, improving overall outcomes[124]. Assessment of cognitive inflexibility is likely to be of particular value for predicting treatment outcomes in OCD. However, confirmatory evidence remains highly preliminary, with only a few small studies of OCD showing overall or differential response to pharmacotherapy or CBT depending on the degree of cognitive flexibility on set-shifting tasks[127].

FUNCTIONING AND QUALITY OF LIFE

Assessing functioning and quality of life in patients with anxiety and related disorders is important for several of the reasons discussed in the earlier section on symptom severity. First, the impact of the disorder on these domains helps determine whether standard outpatient management is to be used, or more intensive approaches are required. Second, assessing functioning and quality of life is part of measurement-based care; there is good evidence that treatment of anxiety and related disorders improves these domains[128]. Third, guidelines for treatment of anxiety and related disorders may be based in part on the degree of functional impairment. Although symptom severity, functional impairment and quality of life demonstrate significant correlations, it is important to note that in any particular patient they may not be entirely aligned, and hence each construct needs to be independently assessed[129,130].

According to the World Health Organization, quality of life is an individual's perception of his/her position in life in the context of the culture and value systems in which he/she lives and in relation to his/her goal, expectations and concerns. So, the assessment of quality of life can be distinguished from the measurement of functional impairment and symptom-related disability by its focus on the subjective experience of satisfaction with current functioning and the accompanying sense of general well-being.

The assessment of quality of life should ideally embrace both generic and specific measures, to maximize sensitivity and generalizability. However, studies in anxiety disorders, PTSD and OCD have largely employed generic instruments. The Sheehan Disability Scale[131], the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[132] and the Medical Outcomes Study 36-item Short Form Health Survey (SF-36)[133] have been most commonly employed, with the EuroQoL (EQ-5D)[134] and the Quality of life Inventory (QOLI)[135] also used. Disorder-specific scales include the CAIOC-13[125] for OCD and the Veterans Rand 12 Item Health Survey (VR-12) for PTSD[136].

Some clinical guidelines for treatment of anxiety and related disorders have focused on functional impairment. In the NICE guidelines for OCD, for example, low intensity psychological treatment is suggested for patients with mild functional impairment (or when a patient prefers this type of treatment), whereas SSRIs or more intensive CBT are suggested in the case of moderate functional impairment[137].

PERSONALITY TRAITS

Among the "classic" traits from the five-factor (Big Five) model of personality, neuroticism – which refers to negative emotionality, or the persistent tendency to readily experience strong negative emotions – has shown the most robust association with anxiety[138]. Neuroticism has been linked to increased symptoms of general anxiety, as well as symptoms of OCD, panic disorder, phobias, PTSD, and social anxiety disorder. According to the tripartite model of Clark and Watson[139], neuroticism is a core risk factor shared across anxiety and depressive disorders, with the added component of anxious arousal being more specific to anxiety conditions, and anhedonia being more characteristic of depression[140].

In a clinical context, understanding the patient's degree and history of negative emotionality as a vulnerability factor could help contextualize the initial onset and maintenance of anxiety symptoms. If neuroticism is impacting current coping and functioning, for example by exacerbating anxiety and related distress, its levels can be reduced through psychological therapies based on acceptance-based and cognitive-behavioral approaches that specifically target responses to negative emotions[141].

Another Big Five personality trait, extraversion – which refers to sociability and the tendency to draw energy from interacting with others – has clinical relevance for understanding certain anxiety disorders, including agoraphobia, specific phobia, and social anxiety disorder[138]. Social anxiety has been found to correlate genetically with decreased extraversion, but not with neuroticism[142]. Knowledge of a patient's level of extraversion could be particularly beneficial in informing the treatment of social anxiety, for example the selection of a hierarchy of social exposures.

Patients with generalized anxiety tend to present with higher than average levels of conscientiousness[143], another Big Five personality trait. High conscientiousness may raise both opportunities and challenges for treatment adherence in the course of psychotherapy for an anxiety or related disorder: it may result in higher levels of therapeutic homework completion, but also more worry and preoccupation around assigned practices or tasks. In the latter case, clinical reasoning suggests that explicit discussion around realistic expectations and normalizing incremental progress may be helpful. High levels of conscientiousness can also flag the possibility of an underlying obsessive-compulsive personality disorder, and the potential value of treatments developed for this condition[144].

Some literature has indicated that the Big Five personality traits are best considered in combination when it comes to understanding anxiety, with higher levels of extraversion and conscientiousness linked to lower risk of anxiety disorders among individuals with high neuroticism[145]. Consistent with this, higher levels of conscientiousness have been linked to more rapid recovery from negative emotional information in adults[146], perhaps buffering the effects of neuroticism.

Thus, a clinician may consider where a patient with anxi-

ety falls along multiple personality domains. If a patient demonstrates high neuroticism but low conscientiousness, he/she may be at particularly risk for emotion regulation difficulties, and thus benefit from adjunctive strategies to improve emotion regulation, such as those from dialectical behavior therapy. By contrast, a patient with high neuroticism but also high extraversion and conscientiousness may benefit from standard strategies such as cognitive restructuring or exposure. However, further research is needed to establish whether treatment recommendations can be guided by assessment of the Big Five traits.

In terms of how a clinician should evaluate personality traits in an anxious patient, assessment of the Big Five traits has been the subject of growing attention, and a number of validated scales, such as the NEO Personality Inventory-3[147] and the Big Five Inventory-2[148], are available. However, because these scales are relatively lengthy, clinicians may find it useful to select the most relevant subdomains – such as neuroticism – for assessment, or use brief personality trait scales (e.g., the Ten-Item Personality Measure[149]) with trade-offs of precision and reliability. In assessing personality, clinicians should keep potential bidirectional influences between reported personality traits and anxiety outcomes in mind, as the presence of an anxiety or related disorder may impact the experience and reporting of neuroticism over time[150].

Importantly, each of the Big Five personality traits has been posited to consist of "facets" that could further prove useful for understanding the development and maintenance of symptoms in anxiety patients. For example, recent efforts to probe personality facets within neuroticism have identified five potential subdomains, including anxiety, depression, anger proneness, somatic complaints, and envy[151]. Nuanced assessment of personality facets may point to specific intervention targets that could be productive in the course of psychotherapy, such as addressing somatic issues with mind-body strategies, or anxiety sensitivity with cognitive-behavioral techniques.

Finally, personality traits may manifest in the form of personality disorders as outlined in the DSM-5. In particular, Cluster C personality disorders may be overrepresented in patients with anxiety disorders: these include avoidant personality disorder (characterized by social inhibition and sensitivity to rejection); dependent personality disorder (characterized by separation anxiety and passive behavior); and obsessive-compulsive personality disorder (characterized by strong need for order and control). Cluster C personality disorders that co-occur with anxiety and related disorders may complicate treatment, for example by interfering with treatment engagement in the case of avoidant personality or leading to excessive reliance in the case of dependent personality. These personality disorders can be assessed using the Personality Inventory for DSM-5 (PID-5)[152].

ANTECEDENT AND CONCOMITANT PSYCHIATRIC CONDITIONS

Many persons suffering from an anxiety or related disorder will experience a comorbid psychiatric condition during their life[153]. Anxiety disorders are relatively central in the multidimensional domain of psychopathology[154], and high levels of comorbidity between these disorders and other mental disorders have been consistently reported, especially with depression. As noted earlier, some view anxiety and depressive disorders as expressions of a common internalizing psychopathology, that may be further divided into fear (e.g., panic, phobia) and distress (e.g., GAD, PTSD, depression) disorders[155].

Some authors have expressed concerns that comorbidity may be an artifact of our current diagnostic systems[156], being better viewed as a reflection of the severity and/or magnitude of the underlying problem rather than as the co-occurrence of distinct clinical entities. Such a perspective may emphasize the importance of measuring transdiagnostic constructs such as neuroticism, as above. Notably, in the DSM-5, the presence of panic attacks is now used as a generic specifier (e.g., social anxiety with or without panic attacks), and may be useful in signaling severity across different disorders.

The median age of onset of anxiety disorders is earlier than many other psychiatric disorders, leading to the question of how far anxiety disorders are antecedents of comorbid conditions. In the World Mental Health Surveys, a very early median age of onset (7-14 years of age) was found for separation anxiety and specific phobia, while GAD, panic disorder and PTSD had a much later age of onset (24-50 years of age). Still, in the majority of comorbidity pairs, anxiety disorders are either concurrent or antecedent to the other disorder. The clearest pattern is seen regarding specific phobia: in 75% of comorbidity pairs, specific phobia is antecedent[153]. From this perspective, early recognition and treatment of anxiety disorders may be key for preventing subsequent psychiatric morbidity[157]. Future research is needed to determine whether treatment of specific phobia, a particularly important marker of internalizing psychopathology, prevents the onset of later psychiatric conditions[158].

Several diagnostic interviews can be used to assess comorbidity. The SCID-5 is useful, but its administration takes about 90 min and requires considerable training. The MINI is quicker to administer, but has the disadvantage of being entirely structured. The DSM-5 includes "cross-cutting" symptom measures which may be helpful in screening for a range of comorbid conditions. The Psychiatric Diagnostic Screening Questionnaire (PDSQ)[159] covers multiple psychiatric disorders, including mood, anxiety, substance abuse, eating and somatoform disorders.

In individuals with an anxiety or related disorder, identifying other psychiatric conditions is key in personalizing management. If the two conditions are judged to be independent, then both are likely to require condition-specific treatments. If interdependent, five principal models come into play[6].

First, a sequential model: for example, in a patient with social anxiety disorder and a substance use disorder, stabilizing the substance use disorder may be the priority before addressing the anxiety disorder. Second, a hierarchically-weighted model (a single treatment may address an underlying factor such as neuroticism, and so improve comorbid conditions): for example, an SSRI and/or CBT may be of benefit for comorbid states of anxiety and depression. Third, a severity-weighted model (treatment of a primary anxiety condition might correct any secondary condi-

tions or consequences): for example, if panic attacks lead to agoraphobia, then targeting the panic attacks may be the first step towards managing the agoraphobia. Fourth, a "motivational bypass" model: for example, an individual with a borderline personality disorder leading to severe anxiety may not be motivated to undergo psychotherapy, but may be willing to take medication for anxiety, which may also have a positive impact on impulsive personality traits. Fifth, a risk management model: for example, if an individual with PTSD has developed a substance use disorder and is displaying severe aggression, then hospitalization and other relevant strategies that target patient and family safety may be an immediate priority.

While there is a substantial evidence base on the treatment of anxiety and related disorders, and a growing evidence base on the management of patients with comorbidity, any particular patient requires individualized assessment, weighing up of possible causal models, and clinical judgment to address these optimally.

PHYSICAL COMORBIDITIES

Anxiety and related disorders may arise as a consequence of a physical disorder, be an antecedent of a physical disorder, or be a co-occurring phenomenon.

A broad range of physical disorders may lead to or exacerbate anxiety symptoms, with some evidence of specificity across the anxiety and related disorders. Thus, for example, there are important causal associations between respiratory conditions and panic disorder[87], and it has been suggested (though also disputed) that there are causal links between panic disorder and a range of physical conditions, including mitral valve prolapse[160] and joint hypermobility[161]. Furthermore, there has been particular attention to the causal role of traumatic brain injury in PTSD[162], and to the causal role of some infections in OCD[163].

The majority of studies on the physical comorbidity of anxiety disorders are focused on cardiovascular disease. A meta-analysis showed that persons with a lifetime diagnosis of anxiety disorder have a 60% increased risk of cardiovascular disease onset[164]. Notably, the risk of an anxiety condition increases substantially after an acute illness event, e.g. an acute myocardial infarction. The awareness of the illness event may play a major role, as "silent" myocardial infarction (in which the person is not aware of the cardiac event[165]) is not followed by an increased risk of anxiety disorders, contrary to manifest infarction. Post-myocardial infarction anxiety is in turn associated with negative cardiovascular consequences[166].

Despite considerable attention to the association between anxiety disorders and cardiovascular disease, causality in the association remains to be proven. Perhaps even more important, the association is not specific, as anxiety disorders are associated with a whole range of physical disorders, with hazard ratios in the range of 1.17-1.73 for ten condition groups and between 1.13 and 2.40 for the individual conditions[167]. The strength of the association of anxiety disorders with cardiovascular disease is only in the middle of that range. In other words, the over-specific focus on the comorbidity of anxiety disorders with cardiovascular disease is not warranted, and attention should be extended to other physical conditions.

Given the lack of specificity in the associations of anxiety disorders with physical diseases, we emphasize the importance of screening for and evaluating physical disorders in all patients with anxiety and related disorders, and of paying particular attention to the possibility that physical conditions play a causal role in anxiety and related disorders, particularly in patients with unusual or refractory presentations[168]. More specific recommendations regarding assessment of physical conditions have been provided for depression, which is often comorbid with anxiety and related disorders[6]. These recommendations are consistent with a general emphasis on the integration of mental health into the care of non-communicable diseases, including the identification and management of modifiable risk factors such as tobacco use, unhealthy diet, physical inactivity, and harmful use of alcohol[169,170].

Clinicians should consider how a patient's particular anxiety symptoms may affect the interfaces with physical health care settings. For example, anxiety might lead to patients not seeking help for physical health symptoms, or make it hard for them to attend medical appointments. On the other hand, certain anxiety concerns (e.g., health anxiety) may lead to repeated presentations in particular medical settings where over-investigation can lead to reinforcement of underlying anxiety-related concerns. In these circumstances, measures such as the Short Health Anxiety Inventory[171], and treatments that specifically target health anxiety[172] may be appropriate.

When pediatric acute-onset neuropsychiatric syndrome (PANS) is suspected as the cause of OCD symptoms, a comprehensive psychiatric and physical assessment is required[163], and specific immunotherapies may be considered in addition to standard OCD treatments[173]. Given the high rates of co-occurrence of PTSD and traumatic brain injury, screening for this condition in patients with PTSD may be recommended: there is a growing literature demonstrating that existing treatments for PTSD are efficacious in this population[174], but additional targeting of brain trauma symptoms may be appropriate. Assessing and treating obstructive sleep apnea may improve management of PTSD.

In general, the presence of physical comorbidities requires specific treatment targeting. This may include interventions focused on particular illnesses as well as on healthy lifestyles. Notably, there is growing evidence that engaging in physical activity protects against anxiety symptoms and disorders[175]. Evidence for the efficacy of aerobic exercise – as well as for a range of complementary and alternative medicine approaches – in the management of anxiety and related disorders remains, however, preliminary[176,177].

FAMILY HISTORY

Anxiety and related disorders are known to run in families, and the clustering of anxiety conditions among related individuals, ranging from GAD to OCD, phobias and panic disorder, is well documented in clinical and population-based samples[178].

Knowledge of family history – where possible including the

specific relatives affected, their relationship to the patient, the age of onset and course of the disorder – may inform the clinician's understanding of the patient's presenting condition and help the patient to contextualize his/her current and past challenges with anxiety.

Meta-analytic data indicate that having a first-degree relative with any anxiety disorder may increase a person's odds of developing an anxiety disorder by four- to six-fold. This risk may be similarly elevated regardless of whether the first-degree relative is a parent, sibling or child, suggesting that systematically inquiring about a range of family members may be most informative. This familial aggregation of clinical anxiety has been attributed in large part to genetic factors, with twin studies indicating heritability of anxiety conditions of 30 to 40%[178].

Studies have suggested disorder-specific patterns of familial transmission, in which a family history of a particular anxiety or related disorder is more strongly linked to heightened risk for that same disorder rather than other anxiety disorders or psychopathology more broadly. Where relevant, this disorder specificity can be informative for making a differential diagnosis of anxiety conditions, as a reported history of multiple family members with a given disorder may point to a similar diagnosis to be considered. This specificity has been demonstrated for OCD, panic disorder, social anxiety disorder, and in some cases GAD[179].

Obtaining a family history from adult patients themselves is the most straightforward approach, but such information can also be gleaned from family members when available. Research comparing direct interview with family member reports has indicated satisfactory agreement between informants. Data suggests that, when individuals positively endorse a family history of an anxiety or related disorder in one or more of their relatives, this information can be considered reliable; however, clinicians should keep in mind that it is possible for individuals to be unaware of anxiety and other psychiatric conditions in their relatives, and reporting may be biased by various patient characteristics[180].

Multiple informants have been recommended for optimum accuracy, but this may be challenging in standard clinical contexts. Relatively brief screening tools for family psychiatric history, such as the Family History Screen[181], have been designed to take 5 to 20 min and may be more feasible.

Importantly, a positive family history has not only been associated with the lifetime development of an anxiety or related disorder, but also with meaningful clinical outcomes. For example, a prospective cohort study showed that family history of an anxiety disorder, defined as the weighted proportion of first- and second-degree members in the family with a positive history of any such disorder, was associated with greater recurrence of anxiety and worse functioning, as well as greater service utilization, across adulthood[182]. Thus, assessing family history can inform prognosis and guide the formulation of follow-up treatment plans.

If a family history of an anxiety or related disorder is identified, it would seem appropriate to determine whether specific medications have been useful in the affected relative. However, to date there is little evidence of a high concordance of medication response in members of the same family. A family history of tics may point to the potential value of augmentation with dopamine antagonists in OCD, but further research is needed to validate this clinical suggestion.

EARLY ENVIRONMENTAL EXPOSURES

A broad range of early environmental exposures have been examined in relation to anxiety and related disorders. These include perinatal complications, season of birth, socioeconomic status, parental rearing practices, infections, and traumatic brain injury. Studies have been characterized by methodological limitations, and conclusions remain tentative[183-185]. Nevertheless, a number of early environmental exposures should be specifically assessed, as they may influence treatment planning.

First, there is growing evidence that acute onset of obsessive-compulsive symptoms in childhood may sometimes be due to streptococcal infections (i.e., autoimmune neuropsychiatric disorders associated with streptococcal infections, PANDAS) or to a broad range of other insults (i.e., PANS). As noted earlier, when PANS is suspected, a comprehensive psychiatric and physical assessment is required[163], and augmentation of standard treatments with specific immunotherapies may be considered[173].

Second, a growing evidence base supports an association between early childhood adversity and subsequent anxiety and related disorders. Examples include physical and sexual abuse[186,187], parental separation[188] and emotional maltreatment[189]. More childhood and adolescent major adversities predicted the subsequent onset of anxiety disorders over the next several years in a sample of late adolescents[190]. Data from the World Mental Health Surveys indicate that eradication of childhood adversities would lead to a 31% reduction in anxiety disorders[191]. A range of questions continue to be explored in the literature, including associations of different types of early adversity with anxiety, the timing of early adversity, causal mediators between such adversity and subsequent anxiety, and associations of early adversity with different features of anxiety.

Given the importance of this association, assessing the history of childhood adversity should be part of a comprehensive evaluation of patients with an anxiety or related disorder. As discussed in relation to depression, a number of key issues must be kept in mind when assessing early adversity in a patient with anxiety[6]. First, reports of adversity are largely subjective, and there is the possibility of recall bias. Second, it is important to explore not only the events that occurred, but also key aspects of the subjective experience and meaning assigned. Third, personality and sociocultural background may influence both the experience and reporting of early adversity. Obtaining a history of childhood adversity that also includes a focus on coping and resilience may be useful in helping to address these issues.

The Childhood Experience of Care and Abuse (CECA)[192] is a comprehensive interview measure for the assessment of childhood adversity. It allows for detailed collection of information, but is time-consuming to administer, requires interviewer train-

ing, and information on its clinical utility is limited. Several shorter self-report questionnaires have been used in research settings and can be considered in clinical practice. These include a shorter self-report questionnaire based on the CECA (CECA.Q)[193] and the Childhood Trauma Questionnaire (CTQ)[194]. The short form of the CTQ has 28 items, assessing five domains of childhood adversity: emotional neglect, physical neglect, emotional abuse, physical abuse, and sexual abuse.

A number of measures are available for assessing the parenting patterns of early caregivers. The Young Parenting Inventory (YPI) has been used in schema therapy and provides a useful way of assessing early parenting styles, and how these might be related to an individual's early maladaptive schemas[195]. The inventory has 72 items that retrospectively assess perceived parenting experiences in respect of each key caregiver. This measure is designed to be used in conjunction with the Young Schema Questionnaire (YSQ)[196], which assesses eighteen early maladaptive schemas.

Although much of the potentially relevant evidence base is from work on depression[6], the presence of early adversity may impact treatment planning for anxiety and related disorders in a number of ways. First, the presence of early adversity may be associated with premature treatment termination, perhaps because of a weaker therapeutic alliance. Particular attention to shared decision-making in such cases would seem appropriate. Second, specific evidence-based psychotherapies developed for patients with childhood adversity, such as trauma-focused treatment, can be considered. Third, it is possible that early adversity is associated with a reduced response to treatment, pointing to the need for robust management.

RECENT ENVIRONMENTAL EXPOSURES

A broad range of environmental stressors are associated with increased rates of anxiety and related disorders[197]. These include minority status (especially linked with risk for PTSD, which has been attributed to experiences of discrimination and exclusion), income insecurity, unemployment, homelessness, natural hazards, armed conflict, crime and displacement.

Individuals exposed to childhood adversity are more vulnerable to anxiety and related disorders from proximal stressors (i.e., stress sensitization). For example, data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) indicated that the magnitude of influence of past-year stressful life events upon risk of anxiety disorders and PTSD was amplified by a history of childhood adversity, especially three or more childhood adversities[198]. This pattern was moderated by gender, in that fewer major life stressors were necessary to trigger stress sensitization in liability for PTSD in women compared to men.

Data from twin studies indicate that almost all types of environmental stress are genetically influenced (for example, a genetic propensity for risk-seeking may lead to increased exposure to dangerous environments)[199]. Evidence for diathesis-stress effects is weak thus far, with data from twin studies indicating none to modest interaction effects[200,201]. Genome-wide methods have produced promising initial effects: for example, a genome-wide polygenic score of emotional responsivity to the environment was found to interact with negative parenting to produce higher rates of anxiety-related symptoms[202].

Consideration of proximal life stressors is important in the assessment of anxiety and related disorders. Semi-structured interview measures include the Life Event and Difficulty Schedule (LEDS)[203], which assesses objective aspects of life events and chronic stressors, as well as the person's subjective experience of how threatening or disruptive they were. Another useful tool is the UCLA Life Stress Interview[204], which assesses both chronic and episodic stress and rates severity within the context of other life circumstances. Training is required for both interviews.

A range of self-rated checklist measures for assessing life events and chronic stressors may be suitable for use in clinical practice. These include the Psychiatric Epidemiology Research Interview Life Events Scale (PERI-LES)[205], the List of Threatening Experiences (LTE)[206], and the Questionnaire of Stressful Life Events (QSLE)[207]. All have good to strong psychometric properties. The PERI-LES lists 102 events, and has been widely used in epidemiological research. The LTE was specifically developed in order to be shorter; it assesses twelve recent life events that are associated with long-term threat. The QSLE was developed to cover the lifespan; it assesses eighteen life events that occur during childhood, adolescence and adulthood, noting the age at which they occurred and their impact. Perceived discrimination can be assessed using self-report questionnaires such as the Everyday Discrimination Scale[208].

Stressful life events and chronic stressors may impact clinical management in a number of ways. First, they may hamper self-management and adherence/response to medical care, especially when combined with high personal demands (such as school or job responsibilities)[209]. CBT homework practice, for example, may be completed less often as a function of multiple life stressors and, although cognitive and behavioral skill practice is important to overall success rates, understanding and allowance for personal impedances to practice is essential to continued treatment engagement.

Second, high levels of chronic stress can lead to persistent sensitization of the pituitary-adrenal and autonomic stress response[210], thereby contributing to the physiological and cognitive disruptions already present in persons with anxiety and related disorders. The combination of high arousal and attention deficits can interfere with attending to and encoding treatment-relevant information, whether it be about medications or cognitive and behavioral skills. Arousal regulatory strategies (e.g., breathing retraining, muscle relaxation, mindfulness training) may be of particular value for the person facing significant life stressors.

Third, for some individuals, traumatic experiences may warrant trauma-focused therapies targeting the intrusive and distressing memories and the behavioral and physiological consequences. On the other hand, understanding of contextual factors such as

neighborhood violence can moderate the therapeutic approach to traumatization; for example, *in vivo* exposures to places that are reminders of the trauma will be contraindicated whenever there is a potential for re-traumatization.

Fourth, understanding of recent life stressors can guide tailoring of psychological treatment. For example, patients with panic disorder sometimes report histories of medical trauma in themselves or other family members that prime their fearful response to bodily sensations. Understanding those medical traumas can help the clinician to tailor cognitive restructuring about personal risk or design exposures most effectively[211]. Similarly, patients with social anxiety disorder who were recently laid off from work may experience elevated perceptions of rejection, and that information can inform tailoring of cognitive skill practice.

PROTECTIVE FACTORS / RESILIENCE

Protective and resilience factors can be generally grouped as individual trait characteristics or environmental supports, although the two are likely to interrelate for reasons of "support generation", as individuals with resilient traits may self-select into supportive environments and conduct their lives in ways that increase support.

Extraversion is an individual trait shown to function as a protective factor for anxiety disorders (see above). One aspect of extraversion is positive affect such as happiness, joy, interest, excitement, confidence, and alertness; this has been shown to promote flexibility in thinking and problem solving, reduce the physiological effects of negative emotions, build enduring social resources, promote effective coping strategies and create upward spirals of improved emotional well-being[212].

High levels of trait positive affect functioned as a protective factor in predicting lower rates of anxiety disorders prospectively, and as a protective factor in buffering the effects of stressful life events upon the risk for social anxiety disorder[213]. Related traits that have shown to reduce the risk for anxiety disorders in adolescents include optimism, perceived competence, and self-esteem[214].

In a review of protective factors for anxiety disorders among adults in the general population, individual characteristics of physical activity and coping styles (ways of responding to perceived stressors) were also highlighted[215].

Supportive interpersonal environments may act as a protective factor for anxiety. Interpersonal relationships are presumed to promote well-being by increasing social contacts and interactions as well as access to resources. The protective function of social support for anxiety has been demonstrated in different risk contexts, including childhood adversity[216]. Social support is also associated with reduced risk for anxiety disorders prospectively[214,217] and can mitigate the development of PTSD following exposure to trauma. Given the role of financial strain in anxiety[197], it is not surprising that employment is robustly associated with reduced symptoms of depression and anxiety and decreased suicide risk, especially among men[218-220].

A comprehensive clinical interview for patients with anxiety and related disorders should cover protective factors and resilience. As described in the case of depression[6], the acronym SOCIAL can guide questioning of key protective factors; Social resources, including friends, groups and social influence; Occupation (paid or not); Children and family; Income and sources of material resources; Abilities, appearance, health, time and other personal resources; and Love and sex in intimate relationships[221]. More in-depth questioning around these topics can gauge the personal and environmental strengths to be reinforced and potentially leveraged throughout the treatment process (e.g., engaging a supportive partner in aspects of cognitive behavioral skills practice) as well as the areas of weakness to be improved upon.

There are a number of standardized scales to measure various aspects of resource and protection. Trait positive affect can be measured using the Positive Affect Scale of the Positive and Negative Affective Schedule (PANAS)[222], a widely used 20-item tool. Self-esteem can be assessed using the Rosenberg's Self-Esteem Scale[223], a ten-item scale of overall self-worth or self-acceptance. An alternative to these would be the Patient-Reported Outcomes Measurement Information System (PROMIS)[224] scales for meaning and purpose (the sense that life has purpose and there are good reasons for living, including hopefulness, optimism, goal-directedness, and feelings that one's life is worthy), positive affect (feelings that reflect a level of pleasurable engagement with the environment, such as happiness, joy, excitement, enthusiasm, and contentment), and self-efficacy (the confidence in ability to deal effectively with a variety of stressful situations), all of which have short forms.

A number of self-report scales of perceived resilience, broadly construed, have been developed[225], and parallel those recommended for use in the clinical management of depression. These include the Connor-Davidson Resilience Scale[226], a 25-item measure of personal competence, tenacity, trust in one's instincts, tolerance of negative affect, acceptance of change, secure relationships and spiritual influences, that is sensitive to treatment change. A shortened 10-item version of this scale may be more practical[227]. The Brief Resilience Scale comprises only six items and measures ability to bounce back from life stressors[228].

A large number of scales measure social support. Examples include the Multidimensional Scale of Perceived Social Support[229], a 12-item measure of perceived support from family, friends and significant others. Another option is the Medical Outcome Study Social Support Survey[230], that measures emotional/informational support, tangible support, affectionate support, and social interaction. In addition, the PROMIS[224] scales include measures of companionship, emotional support, informational support, and instrumental support, all with short forms available.

Coping skills can be measured using the Ways of Coping Checklist[231]. Albeit lengthy (66 items), this scale measures thoughts and acts that people use to deal with the internal or external demands of specific stressful encounters. A briefer alternative is the Brief Coping Orientation to Problems Experienced inventory[232] (28 items), which assesses problem-focused coping (e.g., active coping, planning, suppression of competing activities, restraint coping, and seeking of instrumental social sup-

port) and emotion-focused coping (e.g., seeking of emotional social support, positive reinterpretation, acceptance, denial, and turning to religion). These scales provide insight into the type of coping skills, some of which are adaptive and can be reinforced, while others are maladaptive (e.g., wishful thinking, denial) and can be the target of intervention.

Understanding of protective factors, or lack thereof, can guide clinical management in a number of ways. First, those protective factors already present can be reinforced, encouraged and leveraged in treatment. For example, supportive significant others can be incorporated into the treatment process, such as when significant others co-learn cognitive-behavioral skills and facilitate *in vivo* exposure practices for patients with agoraphobia[233]. Supportive family members may be similarly helpful partners for patients with OCD or PTSD as they engage in exposure and response prevention of avoidance or rituals, with care to correct over-accommodation on the part of the family member (e.g., complying with patient requests to wash excessively due to fears of contamination), since such accommodation inadvertently reinforces avoidance behavior[234]. Positive affect can be a facilitator of exposure therapy for phobias[235].

When protective factors are lacking, they can become the target of intervention. In essence, CBT builds greater protection through coping skills for managing internal (i.e., symptoms of anxiety) and external stressors. Building more robust social support networks can become a particular target of intervention, especially when anxious avoidance behavior has diminished social connection and support. Low levels of positive affect can be targeted directly through newer psychological interventions designed specifically to improve reward sensitivity[236,237], with initial results showing effectiveness in both anxious and depressed patients, albeit in need of replication. Mindfulness based practices also improve positive affect[238].

DYSFUNCTIONAL COGNITIVE SCHEMAS

Anxious people display hypersensitivity in recognizing, processing and responding to threat-related information even in the absence of actual threat. Biases towards threat occur within processes of attention and appraisal.

Attentional biases mean that anxious individuals have a tendency to be easily distracted by potential threats at the expense of attending to other, perhaps more important, features of the environment[239]. In clinically anxious groups, the attention bias is often specific to their focus of apprehension (e.g., socially anxious individuals show an attention bias to detect social dangers, whereas individuals with GAD show a broader attentional bias to physical and social threats). Attention biases involve a number of components, ranging from sensory-perceptual processes (early processing and detection of stimuli), to attentional control (ability to attend to some stimuli and ignore others), memory (maintenance and retrieval of information) and executive function (complex integrative and decision-making processes).

Furthermore, anxious individuals tend to show slowed disengagement from threat-relevant stimuli. A particular type of bias in attentional engagement occurs with respect to interoceptive cues. Interoceptive awareness (or awareness of internal bodily states) has been studied mostly in the context of panic disorder, but is elevated in other anxiety disorders as well[240,241]. Notably, heightened awareness of bodily states is not synonymous with heightened accuracy, which may contribute to errors in symptom reporting and misappraisals of threat.

Anxious individuals are likely to position themselves at various points along the continuum of attentional bias, with some showing more bias in initial detection, others showing more bias at the stage of disengagement, and others still showing more strategic avoidance[242,243]. Such attentional biases likely underlie the common complaints of distractibility and poor concentration in persons with GAD and in phobic individuals as they face their feared situations.

Alongside attentional biases toward threat, anxious individuals interpret ambiguous stimuli in a threat-laden manner[244,245]. Attentional biases likely influence interpretation of threat, which in turn is presumed to influence attention to threat. Interpretation biases are most directly observed in response to ambiguous stimuli, such as interpretations given to the meaning of ambiguous sentences.

As with attentional biases, interpretation biases tend to be specific to the foci of apprehension. Thus, persons with panic disorder are more likely to resolve ambiguous stimuli related to physical sensations in a threat-congruent fashion, whereas persons with social anxiety disorder tend to interpret ambiguous social events as more negative, and mildly negative social events as more catastrophic than other anxious patients or controls. Individuals with high trait anxiety or GAD tend to interpret ambiguous events in general as threatening[20].

Aside from disorder-specific interpretation biases, anxiety sensitivity is relevant to most anxiety disorders, although especially panic disorder, and refers to a tendency to interpret anxiety *per se* as harmful physically, socially or mentally[246]. Anxiety sensitivity has been shown to be both a predictor of subsequent anxiety symptomatology and a correlate that contributes to the persistence of anxiety disorders. It is responsive to cognitive, behavioral and pharmacological interventions[246].

Many of the research instruments for evaluating attentional bias are not suitable for clinical practice. Online or web-based programs for attentional bias modification (described below) typically include tests of attentional bias before training, and these may therefore be available. More practical are standardized self-report scales that measure aspects of engagement and disengagement from threat-relevant stimuli. One example is the 20-item Attentional Control Scale[247], assessing attention focusing and shifting.

The Interpretation Questionnaire[248] assesses individuals' interpretation of ambiguous social scenarios. This questionnaire comprises twenty-two ambiguous scenarios (e.g., "You see a group of friends having lunch, they stop talking when you approach") and three interpretations of each scenario (i.e., positive: "They are about to ask you to join"; negative: "They were saying negative

things about you"; and neutral: "They just ended their conversation"). Participants are asked to rank how likely each interpretation would come to mind if they were in a similar situation.

For OCD, the Obsessive Beliefs Questionnaire[249] is a 44-item measure of cognitive biases that lead to misinterpretation of normally occurring intrusive thoughts as threatening. The Multidimensional Assessment of Interoceptive Awareness-2 (MAIA-2)[250] is a state-trait questionnaire with thirty-seven items to measure multiple dimensions of interoception by self-report. The Anxiety Sensitivity Index-3[251] is an 18-item scale with three subscales representing physical concerns (e.g., death, faint), cognitive concerns (e.g., loss of control) and social concerns (e.g., embarrassment) about anxiety and related symptoms.

Cognitive biases towards threat are directly targeted through CBT for anxiety disorders. Psychoeducation, the initial therapeutic strategy, typically includes information designed to correct mistaken beliefs particularly about anxiety symptoms. Cognitive restructuring teaches skills for identifying overestimates of danger and ways of balancing estimates with more evidence-based interpretations. Exposure therapy targets prediction error correction (i.e., violation of negative expectancies) through direct experience. High levels of threat misappraisal may suggest the need for CBT, although there is insufficient evidence for matching the treatment approach (medication vs. CBT vs. other psychotherapies) to such cognitive biases. In fact, one study has shown that higher scores on anxiety sensitivity predicted poorer response to both CBT and medications for panic disorder[252].

Bias modification programs have emerged as a more specifically targeted treatment for cognitive biases. The attention training technique[253] consists of auditory attentional exercises that require individuals to engage in executive control skills including selective attention, divided attention, and attention switching, in order to lessen inflexible self-focused attention, threat-oriented attention biases, and worry and rumination. This technique has demonstrated efficacy for anxiety disorders[254]. Attention bias training (i.e., training attentional bias away from threat-relevant stimuli towards neutral or positive stimuli by reinforcing dot probe selection) and interpretation bias training (i.e., training to interpret ambiguous scenarios in a neutral or positive manner by reinforcing word selection) have also gathered evidence. However, while such training has robust effects upon attentional or interpretation bias *per se*, studies tend to show small effect sizes on anxiety symptoms in clinical samples[255,256].

Understanding cognitive biases is relevant to pharmacotherapy approaches as well, particularly when patients judge their bodily sensations to be indicative of injury or danger, which can lead to excessive fears of medications and their side effects. Graduated approaches to medication may be advised in these scenarios.

Threat-laden cognitive biases can subtly influence the ways in which information is received and encoded, such that what are benign comments from the clinician can be easily misunderstood to involve threat to the patient. Care in presenting information, taking the patient's biases into account, may be beneficial.

There is some evidence that change in cognitive biases mediate therapeutic outcomes, especially for social anxiety disorder[257-259] and panic disorder[64]. Hence, lack of change in cognitive processes may be an indicator of poor treatment response and the need to reevaluate the treatment approach. Evidence regarding cognitive mediation of pharmacotherapy for anxiety disorders remains nascent.

DISCUSSION

This paper has aimed to describe systematically important domains that are relevant to the personalization of management of anxiety and related disorders. Careful assessment of anxiety symptoms to ensure appropriate clinical diagnosis is key, given that the majority of the evidence in this area is based on trials of specific disorders. However, there is growing work supporting the view that the assessment of other domains is also useful in clinical decision-making.

Taken together, the evidence suggests that we are beginning to be able to move from simply recommending that anxiety and related disorders are treated with SSRIs, CBT, or their combination, to a more complex approach which emphasizes that the clinician has an increasingly broad array of management modalities available, and that treatment of anxiety and related disorders can start to be personalized in a number of important respects.

This review of what is currently known, as well as of key areas for future research, seems timely and valuable for a number of reasons. First, it is consonant with a growing re-emergence of interest in the establishment of a personalized psychiatry, and with similar reviews in other important areas of psychiatry[6,260]. Second, it resonates with systematic work on identification of treatment outcomes, and may help identify variables for potential inclusion in complex predictive models, including machine learning approaches[261,262]. Third, the literature suggests a number of clinically feasible measures, including self-report scales, that can potentially be included in future observational or intervention research. Fourth, the review identifies a number of scales that can begin to be employed by clinicians in practice, as they attempt to personalize treatment of anxiety and related disorders, recognizing that additional research is needed to validate their use.

A number of potential criticisms of our approach here deserve discussion. First, it may be argued that clinicians are already aware of the heterogeneity of anxiety and related conditions. While this is certainly true, there is a lack of systematic efforts to provide the clinician with practical ways of assessing such heterogeneity. Second, it may be argued that use of formal assessments is not practical or efficacious in standard clinical practice. However, even if clinicians do not always formally rely on diagnostic criteria, the introduction of a reliable nosological system has usefully impacted clinicians' approach to assessment, and there is a growing evidence base suggesting the value of routine outcome monitoring[106,107]. Third, it may be argued that ultimately a translational neuroscience approach is needed to optimally personalize the management of anxiety and related disorders.

Our aim is certainly not to downplay the importance of such work, but rather to argue that refinement of clinical assessment can usefully contribute to both neurobiological and interventional work in the future.

A key issue that emerges from this and similar reviews is the abundance and complexity of available relevant measures. This abundance presents a number of important problems for the field[263]. First, even if clinicians agree on the importance of assessing a particular construct, the use of different instruments may lead to disagreements about findings. Second, measures may yield information that is difficult for clinicians to interpret, and may therefore reinforce a view that clinical judgment is more helpful than clinical measures. Third, the use of a range of metrics may impede communication between clinicians and consumers, making shared decision-making more difficult. The review here is consonant with calls in the field to develop common metrics[264], to agree on core outcome sets[265,266], and to harmonize measurement results[263].

It may be instructive to compare existing work on personalized approaches to depression and anxiety[6]. At first glance, it seems that the field of depression is much more advanced, with more evidence available on a range of important domains and how these can be used to personalize treatment. By contrast, major depression is an enormously heterogenous condition, whereas some anxiety and related disorders appear more homogeneous. Although no particular anxiety or related condition has received as much attention as depression, the recognition of specific anxiety and related conditions has created the opportunity for more fine-grained work on each of these disorders, and subtyping of specific conditions has contributed towards personalization of management.

Clearly, much further work needs to be done to achieve a detailed and evidence-based approach to the personalization of interventions for anxiety and related disorders. Hierarchical models of self-reported symptoms such as the Hierarchical Taxonomy of Psychopathology (HiTOP) model[155], or the tri-level model of depression and anxiety[267,268], provide useful frameworks for understanding genetic, neurobiological and environmental risk factors and symptom covariation patterns. In the future, it would be useful for clinical trials to include not only anxiety diagnoses and symptom severity, but also more detailed assessment of symptomatology (e.g., evaluation of specific behaviors, physiological parameters, and cognitive appraisals), as well as of the range of other domains reviewed here. Such work will hopefully strengthen the personalization of treatment for anxiety and related conditions.

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