The definition of treatment resistance in anxiety disorders: a Delphi method-based consensus guideline

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Anxiety disorders are very prevalent and often persistent mental disorders, with a considerable rate of treatment resistance which requires regulatory clinical trials of innovative therapeutic interventions. However, an explicit definition of treatment-resistant anxiety disorders (TR-AD) informing such trials is currently lacking. We used a Delphi method-based consensus approach to provide internationally agreed, consistent and clinically useful operational criteria for TR-AD in adults. Following a summary of the current state of knowledge based on international guidelines and an available systematic review, a survey of free-text responses to a 29-item questionnaire on relevant aspects of TR-AD, and an online consensus meeting, a panel of 36 multidisciplinary international experts and stakeholders voted anonymously on written statements in three survey rounds. Consensus was defined as ≥75% of the panel agreeing with a statement. The panel agreed on a set of 14 recommendations for the definition of TR-AD, providing detailed operational criteria for resistance to pharmacological and/or psychotherapeutic treatment, as well as a potential staging model. The panel also evaluated further aspects regarding epidemiological subgroups, comorbidities and biographical factors, the terminology of TR-AD vs. "difficult-to-treat" anxiety disorders, preferences and attitudes of persons with these disorders, and future research directions. This Delphi method-based consensus on operational criteria for TR-AD is expected to serve as a systematic, consistent and practical clinical guideline to aid in designing future mechanistic studies and facilitate clinical trials for regulatory purposes. This effort could ultimately lead to the development of more effective evidence-based stepped-care treatment algorithms for patients with anxiety disorders.

Anxiety disorders – including specific phobias, social anxiety disorder, panic disorder, agoraphobia, generalized anxiety disorder (GAD), as well as separation anxiety disorder and selective mutism[1] – represent the most common mental disorders, with an estimated combined 12-month prevalence of 10-14%[2-4]. They confer a substantial socioeconomic burden[5-7] and often take a debilitating course, with a high proportion of cases having only intermittent recovery (32.1%) or consistent chronicity (8.6%) at 9-year follow-up[8]. Accordingly, they rank sixth among all disorders regarding years lived with disability (YLDs)[9], and seventh in the group of 15-24 year olds and 15th among 25-49 year olds in terms of disability-adjusted life years (DALYs)[10].

One factor contributing to the chronicity of anxiety disorders is the clinical challenge of treatment resistance, particularly in panic disorder/agoraphobia, GAD, and social anxiety disorder[11-14]. While effective pharmacological and psychotherapeutic options are available for these disorders as first-line treatments endorsed by clinical guidelines[15] – i.e., selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and cognitive behavioral therapy (CBT) – only 50 to 67% of patients show an adequate clinical response after the first treatment trial[16-21]. There is, therefore, a pressing need for clinical trials probing novel pharmacological and psychotherapeutic interventions specifically for patients with treatment-resistant anxiety disorders (TR-AD)[22], and for studies exploring predictive markers and mechanistic underpinnings of treatment resistance in anxiety disorders[23-25].

A prerequisite for conducting these clinical trials and mechanistic studies is an international consensus on the definition of TR-AD, which is currently lacking[17,26]. International guidelines focusing on anxiety disorders do not provide explicit criteria aiding in the identification or treatment of patients with TR-AD[15,27-50], with only two exceptions. First, the Canadian Clinical Practice Guidelines for the Management of Anxiety Disorders[51] suggest that patients who "do not respond to first- or second-line agents" (in panic disorder), who "do not respond to several medication trials and/or CBT" (in social anxiety disorder), or who "do not respond to multiple courses of therapy" (in GAD) should be considered treatment-refractory. Second, the most recent version of the Australian Therapeutic Guidelines[52] states that "non-response to initial pharmacotherapy for GAD, panic disorder and social anxiety disorder in adults and young people is assumed if symptoms persist despite using an effective dose of at least two SSRIs or SNRIs as sequential monotherapy, each for a minimum of 4 weeks (full benefit may take 6 weeks or longer); and discounting alternative reasons for treatment non-response".

A search of the Core Outcome Measures in Effectiveness Trials (COMET) database[53] for a core outcome set defining TR-AD yielded no results. Also, the International Consortium for Health Outcomes Measurement (ICHOM) Depression and Anxiety Working Group[54] did not provide an explicit definition of TR-AD. Searching clinicaltrials.gov for ongoing or terminated

studies on TR-AD revealed either no or only vague definitions of this condition. Only one terminated study on social anxiety disorder (ID: NCT00182455) used non-response or partial response – i.e., a score >4 on the Clinical Global Impression Scale - Severity (CGI-S) and >40 on the Liebowitz Social Anxiety Scale (LSAS) – to SSRI treatment (14 weeks) to define treatment resistance more precisely.

A narrative review[11] suggested to define treatment-resistant panic disorder as the failure to achieve remission – i.e., a post-treatment Hamilton Anxiety Rating Scale (HAM-A) score ≤7-10, a Sheehan Disability Scale score ≤1 on each item, and a Panic Disorder Severity Scale score ≤3, after at least 6 months of "optimal treatment" (not further specified). A systematic review[14] proposed to define treatment-resistant panic disorder as a condition which has not responded to at least two adequate 8-week treatment trials with drugs recognized as effective for that disorder in adequate doses, or to a standard course of CBT[14].

The only systematic review available to date[55] could not discern a consistent definition in 62 studies investigating treatment resistance in anxiety disorders. In 62.9% of definitions, treatment resistance was already assumed after failure of a single therapeutic trial. Most studies (93%) required pharmacological, and only 29% psychotherapeutic treatment failure. A large proportion of studies (43.5%) did not specify the type of medication, while some studies (24.2%) deemed one trial of SSRI/SNRI treatment necessary. Most studies (54.8%) required a minimal trial duration ranging from 4 weeks to 6 months, with 24.2% of studies applying an 8-week time frame. While some studies (41.9%) provided a non-response criterion (e.g., post-treatment HAM-A score improvement <50%), the definition of "treatment failure" remained unclear in 58.1% of studies. "High post-treatment anxiety severity" was identified as the most common (46.8%) criterion required to define TR-AD across studies. Having summarized these findings, the authors proposed a definition of TR-AD requiring that the severity of anxiety remains above a specified threshold after failure of at least one first-line pharmacological (SSRI, SNRI) and at least one psychological (CBT) treatment trial, delivered according to protocol for at least 8 weeks. "Treatment failure" was suggested to be defined as a pre- to post-treatment difference in HAM-A score of <50%, or a post-treatment Clinical Global Impression Scale - Improvement (CGI-I) score >2.

Against this background, a recent perspective paper[56], after identifying treatment resistance in mental health conditions as a pressing issue, stated that "for certain conditions such as mania, anxiety disorders and PTSD, consensus definitions of resistance have yet to be agreed". In the present study, we used for the first time a Delphi method-based consensus approach in order to provide internationally agreed, consistent and clinically useful operational criteria for TR-AD in adults, particularly for the clinical phenotypes of panic disorder/agoraphobia, GAD, and social anxiety disorder. This operational definition of TR-AD is expected to inform future mechanistic studies as well as clinical trials of both

pharmacotherapies and psychotherapies conducted for regulatory purposes, in an effort to develop more targeted and personalized treatment options reducing the individual and collective socioeconomic burden of anxiety disorders.

METHODS

This study was initiated by the Anxiety Disorders Research Network (ADRN), an international collaborative cross-disciplinary research group, with support from the European College of Neuropsychopharmacology (ECNP). The ADRN presently includes 28 members across 14 countries and has the principal goal of addressing currently unmet needs in anxiety and related disorders.

A subgroup of 15 ADRN members with clinical and/or basic scientific expertise in TR-AD formed the core expert team for the study. A further 18 experts (academics, clinicians, basic scientists) and three key stakeholders (two representatives of regulatory bodies, and a representative from a mutual aid advocacy organization) were selected to form the final panel (see supplementary information).

The Delphi method was considered the most appropriate tool for developing a consensus definition of TR-AD[57-60]. The method was applied according to the Guidance on Conducting and REporting DElphi studies (CREDES)[61] (see supplementary information), and following the approach recently used to develop a consensus guideline for the definition of treatment-resistant depression in clinical trials[62]. The study was registered with the Freiburger Register für Klinische Studien (FRKS) (FRKS004463) and was approved by the ethical committee of the University of Freiburg (23-1021-S1).

Twenty-nine items were identified for inclusion in an initial questionnaire on TR-AD (see supplementary information), based on a review of the literature and an in-person meeting of the ADRN core expert team in October 2022. The questionnaire, along with a narrative review of the current state of the evidence, was sent to the panel in November 2022. Anonymized responses to the questionnaire (see supplementary information) and a revised version of the narrative review were sent back to the panel and discussed in an online meeting in March 2023, using a nominal group technique to agree on the selection and wording of consensus statements. A resulting set of initially 15 draft consensus statements was subsequently sent out to the panel using the REDCap® online platform. In three *a priori* defined iterative rounds (in May, June and July 2023), all participants anonymously rated their agreement with each of the individual statements on a labelled, horizontal 9-point Likert scale (a "no answer" option was available) and could comment on or suggest changes to the phrasing or substance of the statements. After each iterative round, participants received feedback in the form of a

cumulative statistical representation of the overall panel's response, and had access to anonymized comments by their fellow panelists (see Figure 1 and supplementary information).

Where participants gave a score of 1 to 3 to a statement on the Likert scale, low agreement was assumed. A score of 4 to 6 indicated moderate agreement with a statement. When a statement was scored 7 to 9, it was considered to be agreed upon substantially[63]. Consensus regarding a statement was considered reached when ≥75% of the panel voted in substantial agreement with it, i.e. gave a score of 7 to 9. This aligns with the development of other core outcome sets[64-67], and with the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[68]. Those who had chosen the "no answer" option were removed from the denominator when ascertaining whether consensus had been reached. Statements reaching less than or only around 75% consensus in iteration rounds 1 and 2 were dropped or amended on the basis of free-text responses provided by the panel and entered as such into voting rounds 2 and 3, respectively (see supplementary information). The 14 final consensus recommendations on TR-AD as emerging from round 3 are summarized in Table 1.

RESULTS

The panel considered an operational definition of TR-AD to be useful for regulatory clinical trials probing pharmacotherapy and psychotherapy (as well as neuromodulation or virtual reality techniques, and repurposed options such as ketamine, psilocybin, or 3,4-methylendioxy-N-methylamphetamine, MDMA) (see Table 1, statement 1). This definition will allow to carry out clinical trials with good external validity, ultimately aiming at improving evidence-based treatment algorithms and guidelines in case of treatment non-response or resistance. This was seen as particularly important since patients with TR-AD have so far mostly been excluded from clinical trials conducted for regulatory purposes.

An operational definition of TR-AD was additionally considered to be essential for research on (bio)markers and (bio)mechanisms of treatment non-response or resistance (see Table 1, statement 2), and was expected to inform both individualized and innovative treatment options for patients experiencing TR-AD.

Operationalization of treatment resistance

The panel voted for the definition of response/non-response to ideally but not necessarily rest on both clinician- and self-report scales (see Table 1, statement 3). Some panelists suggested that clinician ratings are probably most apt for pharmacological trials, and self-reports for psychotherapeutic trials. Clinician ratings have been suggested to possibly increase

the effect sizes[69,70], but might at the same time be more sensitive to change and can be applied in an adequately blinded way. Self-report ratings are better able to capture the patient's core emotional experience[71,72], quality of life and symptoms affecting broader dimensions of real life, but may be more relevant for the definition of remission than treatment resistance. For an international consensus, the recommended scales should be translated, validated and available in as many languages and countries as possible.

The panel agreed on TR-AD in general to be defined as the failure to achieve a clinically significant symptom reduction from pre- to post-treatment, reflected by a <50% reduction in the HAM-A score, or a <50% reduction in the Beck Anxiety Inventory score, or a CGI-I score >2 (see Table 1, statement 4). This was the final consensus, although some panelists suggested to rather use a 25% or 30% reduction cut-off. In general, a percentage reduction to indicate non-response seemed preferable to post-treatment scores alone, since there may be considerable heterogeneity in before-treatment severity scores. It was also noted that operationalization of treatment resistance based on symptom reduction may not sufficiently portray the full picture of how well a patient does in the long term, which might be better reflected by Sheehan Disability Scale scores.

Several additional, but optional, recommendations on how to define treatment resistance in regulatory trials concerning specific anxiety disorders were agreed upon by the panel.

For social anxiety disorder, a score reduction of <28% on the LSAS-SR (self-rating) or <29% on the LSAS-CA (clinician-administered) was suggested to indicate treatment resistance (see Table 1, statement 4a). Although a LSAS total cut-off score of 30 has been reported to represent the best balance of specificity and sensitivity[73], the panel once again agreed that absolute scores do not account for initial disease severity and thus should not be included in definitions of TR-AD.

As optional operational criteria for treatment-resistant GAD, the panel agreed on a <4 point reduction on the Generalized Anxiety Disorder 7-item (GAD-7) scale score, or a <9% or <4-point reduction on the Penn State Worry Questionnaire score (see Table 1, statement 4b). GAD-7 cut-off scores ≥8 or ≥10 were also discussed, but discarded because absolute scores do not account for initial disease severity. Some panelists argued that the GAD-7 should not be used as the sole measure for treatment-resistant GAD, as some studies failed to define a cut-off score with adequately balanced sensitivity and specificity for GAD[74-76], or reported that the GAD-7 had good sensitivity and specificity for any anxiety disorders, but low specificity for GAD[77].

For treatment-resistant panic disorder and/or agoraphobia, the panel recommended optional operational criteria of a <40% score reduction on the Panic Disorder Severity Scale or a <23% score reduction on the Panic and Agoraphobia Scale (see Table 1, statement 4c). Criteria of a <50% score reduction on the Panic Disorder Severity Scale or a <50% decrease

in the number of panic attacks were discussed, but were not included in the operational definition.

Resistance to pharmacological treatment (pharmacotherapy TR-AD)

For regulatory trials, it might be useful to differentiate between resistance to pharmacotherapy and psychotherapy. The panel agreed that resistance to pharmacological treatment in anxiety disorders (pharmacotherapy TR-AD) should be defined as at least two separate failed full trials of pharmacological monotherapy with first-line agents approved for those disorders by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) or other equivalent regulatory agencies, and recommended by guidelines. These trials should involve two different classes of medications (e.g., one SSRI plus one SNRI, clomipramine or pregabalin in the case of GAD), used for at least 6-8 weeks each at a dose corresponding to at least the minimal approved one, ideally with documented treatment adherence (see Table 1, statement 5).

It was discussed whether failure of a trial with benzodiazepines should be included in the definition of pharmacotherapy TR-AD. It was argued that the majority of guidelines do not recommend benzodiazepines as first-line options for treatment of anxiety disorders. Regarding the definition of how long one trial of pharmacological treatment should last to be able to evaluate its efficacy, time frames spanning 4 to 12 weeks were considered, but the final consensus was for a treatment duration of 6-8 weeks. Monitoring plasma levels allowing for an optimized dosing and the assessment of treatment "pseudo-resistance" due to non-adherence or a rapid metabolizer status was considered desirable, but not feasible in most routine clinical settings. Treatment pseudo-resistance in general, however, should be excluded by taking into account adherence to treatment as well as additional factors such as age and renal/hepatic function.

Resistance to psychotherapy (psychotherapy TR-AD)

The panel agreed that resistance to psychotherapy in anxiety disorders (psychotherapy TR-AD) should be defined as at least one failed trial of an evidence-based, first-line, standardized, ideally manualized psychotherapy, such as CBT. Treatment should be delivered by a qualified psychotherapist with an adequate intensity and duration, ideally including a sufficient number of exposure exercises as well as monitored between-session work ("homework") and adherence (see Table 1, statement 6).

Depending on the type of anxiety disorder, a range of one session (for specific phobias) to up to 20 weeks (in GAD, panic disorder/agoraphobia or social anxiety disorder) was

proposed to constitute an adequate time frame. For the latter conditions, the consensus was for a minimal duration of 12-20 weeks, with a minimum number of 20 sessions. Individual one-to-one sessions seemed preferable, while group or online formats were discussed as potential alternatives.

Staging model and multi-modal treatment resistance (MTR-AD)

The panel additionally proposed a non-dichotomous, escalating staging model of TR-AD, in analogy to those suggested for obsessive-compulsive disorder[78] and major depressive disorder[79-81] (see Table 1, statement 7). This model – or alternatively a pseudo-linear scale of degree of resistance – would allow clinical trials for regulatory purposes or other studies to describe a particular population on a dimensional spectrum of treatment resistance, ranging from isolated resistance to pharmacological or psychotherapeutic treatment to composite resistance to several trials of multiple modalities delivered in different episodes of the anxiety disorder. This flexibility is particularly relevant for anxiety disorders, as pharmacotherapy and psychotherapy have been considered similarly effective in these disorders, and as resistance to pharmacotherapy does not preclude response to psychotherapy and *vice versa*, or to a combination of the two modalities. Also, the (bio)mechanisms of treatment resistance to pharmacotherapy and psychotherapy might be partly shared, and partly distinct.

The model proposed by the panel in order to capture the spectrum of levels of treatment resistance in anxiety disorders comprises a first stage of failure of either two adequate courses of pharmacotherapy or at least one adequate trial of psychotherapy; a second stage of failure of both two adequate courses of pharmacotherapy and at least one adequate trial of psychotherapy; and a third stage of failure of multiple adequate courses of (poly)pharmacotherapy and multiple adequate trials of psychotherapy. This last stage connotes multi-modal TR-AD (MTR-AD) (see Table 1, statement 7), which requires an intensified subsequent treatment approach, including referral to secondary or tertiary specialist care. The (bio)mechanisms underlying MTR-AD might be different from those involved in isolated pharmacotherapy TR-AD or psychotherapy TR-AD.

Additional aspects

The panel agreed that comorbidity with other mental disorders – particularly depression, substance use disorders and personality disorders – should not influence the operational definition of TR-AD, but should be recorded and considered *post hoc* (see Table 1, statement 8). Furthermore, the identification of sex and age subgroups was not considered necessary for the operational definition of TR-AD, but relevant for *post hoc* analyses as well as for differential

treatment. For instance, women in the peri- and post-menopausal or in the peri-partum period, children/adolescents, as well as elderly patients with declining renal or hepatic function, might warrant particular attention (see Table 1, statement 9).

Biographical factors such as socioeconomic status, social support, specific life events (e.g., childhood trauma, acute or chronic stress), as well as exposure to novel anxiogenic stimuli or situations during treatment, were considered to possibly influence treatment resistance[19,82,83]. However, for the sake of simplicity and to reflect a naturalistic setting, those factors were suggested by the panel not to be included in the operational definition of TR-AD, but to be recorded, possibly as "specifiers", monitored and taken into consideration in *post hoc* analyses to reduce the study population variability and, in a clinical setting, to be targeted specifically (see Table 1, statement 10).

The panel agreed that duration of (untreated) illness and number of episodes or relapses, while influencing treatment resistance in several patients[84-86], should not be included in the definition of TR-AD, but recorded and considered *post hoc* (see Table 1, statement 11). It has to be noted that TR-AD usually involves a longer duration of illness, entailing a potential tautology. Additionally, it might be difficult to delineate distinct episodes. While for TR-AD regulatory trials it might be useful to restrict the number of previous failed treatments, in order to increase the likelihood of improvement, the panel agreed not to propose a statement on the maximum number of failed previous treatments. However, it suggested that they should be routinely recorded and considered *post hoc*.

TR-AD vs. difficult-to-treat AD

The panel agreed to use the term "treatment-resistant" anxiety disorders (TR-AD), since it is routinely adopted and widely understood in the present regulatory context, and is already established for other disorders in the international nomenclature. However, it acknowledged that "difficult-to-treat" AD could be considered as a potentially more comprehensive term, which might be more useful in a clinical context (see Table 1, statement 14).

The term TR-AD was considered to clearly refer to the disorder and not to the patient as being treatment-resistant, to the existing treatment options being inadequate, to relate to the patient's history and not the future, to be respectful of the patient-clinician relationship, and to allow a precise definition relevant for drug approval and commissioning of services. The alternative term "difficult-to-treat" AD – in analogy to "difficult-to-treat" depression[87] – has been suggested to represent a more comprehensive and multi-dimensional concept, to potentially be more apt to inform clinical practice rather than research or regulatory affairs, and to seem less stigmatizing, pessimistic, discouraging or defamatory from a patient's perspective[88].

The concept of "difficult-to-treat" AD might furthermore allow for considering intolerance

or refusal or contraindication of treatment, and the impact of living conditions, comorbidities and other factors on treatment outcome, rather than just non-response, and does not relate simply to one point in time when TR-AD criteria are met. Some panelists, however, raised concerns that the term "difficult" could inadvertently be taken to refer to the patient, and even reduce hope for future treatments. Also, it could imply that successful treatments should be "easy" and straightforward, while treatment can still be highly effective despite a very complex, atypical or "difficult" clinical presentation or a "difficult" therapeutic process.

In sum, both terms might be needed, with TR-AD constituting a pragmatic nomothetic construct for clinical trials conducted for regulatory purposes, as well as for other research projects, while "difficult-to-treat" AD could represent a more holistic, idiographic concept as well as a "roadmap" for clinicians relevant for effectiveness trials as well as clinical care. However, the boundaries of "difficult-to-treat" AD are uncertain, and an evidence-based taxonomy as well as reliable assessment tools beyond traditional outcome metrics remain to be established for this condition[89]. Research into this topic has been deemed to be of importance.

Preferences and attitudes of persons with anxiety disorders

In general, labelling a condition as either TR-AD, MTR-AD, "treatment-refractory" AD or "difficult-to-treat" AD might be regarded as stigmatizing. Consequently, it is essential to be sensitive and not judgmental towards persons experiencing treatment resistance, and to ensure respectful language awareness and use (e.g., "patient with TR-AD", not "TR patient" or "difficult-to-treat patient"). On the other hand, providing an operational definition of TR-AD might in fact relieve patients from the feeling of having failed themselves, and aid in destigmatizing the condition.

It is imperative that persons with anxiety disorders are fully informed about the comparative efficacy of the various treatment modalities based on current official guidelines, and that their preferences are respected. It is to be taken into consideration that certain classes of medication or psychotherapy might be unacceptable or untimely from a patient's point of view, or that certain treatment options might simply not be available or delivered optimally. Additionally, given that many patients with TR-AD have already gone through numerous pharmacological and/or psychotherapeutic treatment trials, the definition of TR-AD should not be limited to a relatively short duration of disease or to a maximum number of failed previous trials, as this would discriminate against those patients by excluding them from regulatory trials that may potentially offer more efficacious treatment options.

In future attempts to further refine the definition of TR-AD, the inclusion of questionnaires focusing on self-reported quality of life and level of functioning – for instance, the Sheehan

Disability Scale or the Psychosocial fActors Relevant to BrAin DISorders in Europe (PARADISE 24) metric[90] – should be considered. Furthermore, "minimal important differences" for patient reported outcomes (i.e., the smallest changes in outcome measures that patients perceive as an important improvement or deterioration) should increasingly be defined and taken into account[91]. In general, it is essential to engage with patients, to include patients' social environment in the diagnostic and therapeutic process where appropriate, to be transparent, to promote inclusivity, to ensure continuity of care, and to convey hope and perspective (see Table 1, statement 13).

Research directions

Research into clinical, (epi)genetic, proteomic, metabolomic, microbiome, physiological and neuroimaging biomarkers as predictors of treatment resistance in anxiety disorders, allowing for a more personalized and precise care in this field, was welcomed by the panel (see Table 1, statement 12). However, the very limited currently available evidence was acknowledged[92-95].

Real-world data such as gait analysis or time/event-contingent actigraphy data using ecological momentary assessment might provide additional markers predicting TR-AD[96-99]. Machine-learning approaches could aid in integrating biological, biographical and ecological momentary assessment markers[82].

DISCUSSION

The present Delphi method-based consensus on operational criteria for TR-AD (see Table 2) is hoped to serve as a systematic, consistent and practical guideline to define this condition and thereby aid in designing future clinical trials for regulatory purposes as well as other research projects. This effort could ultimately lead to the development of more effective evidence-based stepped-care treatment algorithms for patients with TR-AD.

The Delphi method-based process is considered "state-of-the art" to achieve international consensus on a given research or clinical issue. The selected international experts and stakeholders represent a broad range of expertise in the field. Response rates in the three separate voting rounds did not reach 100% (first round: 80.6%; second round: 94.4%; third round: 86.1%), but this corresponds to the upper part of the range of other published Delphi method-based studies, where response rates between 45% and 93% have been reported across three rounds of voting[100].

The coverage of both pharmacological interventions and psychotherapies in the proposed

operational criteria for TR-AD is not a common feature in currently available definitions for other treatment-resistant mental disorders, although frequently regarded as appropriate or even necessary[101-103]. This represents in itself an important development.

We acknowledge that experts or stakeholders outside the present panel might have differing views on how TR-AD should be conceptualized, which may limit the generalizability of the proposed criteria. Therefore, in a next step, the conceptualization of TR-AD presented here should be empirically investigated and validated. In the future, a more fine-grained and potentially dimensional definition of TR-AD, comprising multiple modalities (e.g., self-report and clinician ratings, biological/physiological recordings), covering a variety of factors (e.g., life events, treatment intolerance, psychosocial functioning, comorbidities), and incorporating a lifespan perspective, might increase construct validity and better reflect the complex and multifaceted nature of anxiety, including its waxing and waning course[17,20,104,105]. The definition of such core outcome sets could follow the Core Outcome Set-STAndards for Development (COS-STAD)[106] and Core Outcome Set-STAndards for Reporting (COS-STAR)[107].

It has to be noted that the presently proposed consensus criteria for TR-AD are limited to the population of adult patients, while criteria for TR-AD in childhood and adolescence and in elderly patients remain to be established in future studies[108-111]. Along this line, the diagnostic entities "separation anxiety disorder" and "selective mutism", previously classified in the DSM-IV section "Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence" and now listed in the DSM-5 chapter on Anxiety Disorders[112-114], warrant investigation with regard to treatment resistance in adulthood.

It is desirable to identify factors predicting and mechanistically underlying treatment resistance in anxiety disorders. Some studies of limited quality and highly heterogeneous in design suggest a number of potential risk factors – such as high expressed emotions within the family, higher severity and longer duration of the disorder, age of onset, or comorbid conditions – which however have not been consistently replicated[13,19,81,82]. In a similar vein, the identification of reliable and valid biomarkers indicating an increased risk of treatment resistance would be helpful to inform algorithms for individually tailoring an intensified treatment for those patients[22,23,93,94,115].

To date, no internationally endorsed evidence-based guidelines exist for the treatment of patients with TR-AD. Clinical recommendations[13,18,19,26,116-119] comprise switching medication within one class or to a different class; augmentation strategies with other antidepressants, antipsychotics or anticonvulsants; combining pharmacotherapy and psychotherapy, as well as treating comorbid mental and/or somatic disorders complicating the treatment course. The present Delphi method-based consensus operational criteria for TR-AD may help to foster clinical trials probing innovative pharmacological, psychotherapeutic and non-invasive brain stimulation approaches in order to establish more effective treatment options for this condition.

For instance, "third-wave" psychotherapeutic interventions such as acceptance and commitment therapy, mindfulness-based stress reduction, meta-cognitive therapy and compassion-focused therapy[120-124], as well as novel pharmacological compounds targeting monoamines (including psychedelics), GABA, glutamate, cannabinoid, cholinergic and neuropeptide systems[25,125,126] might prove useful in treating TR-AD.

In sum, the presently proposed Delphi method-based consensus operational criteria for TR-AD are expected to inform both pharmacological and psychotherapeutic clinical trials for regulatory purposes towards more targeted and personalized treatment options for persons with TR-AD, thus reducing the individual and collective socioeconomic burden of anxiety disorders. If they are empirically validated, a dissemination plan could include their endorsement by professional associations and health care authorities to facilitate their implementation in practice.

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed. Washington: American Psychiatric Association, 2013.
2. Wittchen HU, Jacobi F, Rehm J et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 2011;21:655-79.
3. Kessler RC, Petukhova M, Sampson NA et al. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J Methods Psychiatr Res 2012;21:169-84.
4. Kessler RC, Angermeyer M, Anthony JC et al. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry 2007;6:168-76.
5. Craske MG, Stein MB, Eley TC et al. Anxiety disorders. Nat Rev Dis Primers 2017;3:17024.
6. Olesen J, Gustavsson A, Svensson M et al. The economic cost of brain disorders in Europe. Eur J Neurol 2012;19:155-62.

7. Penninx BW, Pine DS, Holmes EA et al. Anxiety disorders. Lancet 2021;397:914-27.

8. Solis EC, van Hemert AM, Carlier IVE et al. The 9-year clinical course of depressive and anxiety disorders: new NESDA findings. J Affect Disord 2021;295:1269-79.

9. Baxter AJ, Vos T, Scott KM et al. The global burden of anxiety disorders in 2010. Psychol Med 2014;44:2363-74.

10. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry 2022;9:137-50.

11. Chen MH, Tsai SJ. Treatment-resistant panic disorder: clinical significance, concept and management. Prog Neuropsychopharmacol Biol Psychiatry 2016;70:219-26.

12. Roy-Byrne P. Treatment-refractory anxiety; definition, risk factors, and treatment challenges. Dialogues Clin Neurosci 2015;17:191-206.

13. Van Ameringen M, Mancini C, Pipe B et al. Optimizing treatment in social phobia: a review of treatment resistance. CNS Spectr 2004;9:753-62.

14. Freire RC, Zugliani MM, Garcia RF et al. Treatment-resistant panic disorder: a systematic review. Expert Opin Pharmacother 2016;17:159-68.

15. Bandelow B, Allgulander C, Baldwin DS et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders – Version 3. Part I: Anxiety disorders. World J Biol Psychiatry 2023;24:79-117.

16. Bystritsky A. Treatment-resistant anxiety disorders. Mol Psychiatry 2006;11:805-14.

17. Loerinc AG, Meuret AE, Twohig MP et al. Response rates for CBT for anxiety disorders: need for standardized criteria. Clin Psychol Rev 2015;42:72-82.

18. Sanderson WC, Bruce TJ. Causes and management of treatment-resistant panic disorder and agoraphobia: a survey of expert therapists. Cogn Behav Pract 2007;14:26-35.

19. Taylor S, Abramowitz JS, McKay D. Non-adherence and non-response in the treatment of anxiety disorders. J Anxiety Disord 2012;26:583-9.

20. Yonkers KA, Bruce SE, Dyck IR et al. Chronicity, relapse, and illness-course of panic disorder, social phobia, and generalized anxiety disorder: findings in men and women from 8 years of follow-up. Depress Anxiety 2003;17:173-9.

21. Springer KS, Levy HC, Tolin DF. Remission in CBT for adult anxiety disorders: a meta-analysis. Clin Psychol Rev 2018;61:1-8.

22. Sartori SB, Singewald N. Novel pharmacological targets in drug development for the treatment of anxiety and anxiety-related disorders. Pharmacol Ther 2019;204:107402.

23. Bandelow B, Baldwin D, Abelli M et al. Biological markers for anxiety disorders, OCD and PTSD – a consensus statement. Part I: Neuroimaging and genetics. World J Biol Psychiatry 2016;17:321-65.

24. Bandelow B, Baldwin D, Abelli M et al. Biological markers for anxiety disorders, OCD and PTSD: a consensus statement. Part II: Neurochemistry, neurophysiology and neurocognition. World J Biol Psychiatry 2017;18:162-214.

25. Vismara M, Girone N, Cirnigliaro G et al. Peripheral biomarkers in DSM-5 anxiety disorders: an updated overview. Brain Sci 2020;10:564.

26. Perna G, Caldirola D. Management of treatment-resistant panic disorder. Curr Treat Options

Psychiatry 2017;4:371-86.

27. Bandelow B, Zohar J, Hollander E et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders. World J Biol Psychiatry 2002;3:171-99.

28. Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Panic Disorder and Agoraphobia. Australian and New Zealand clinical practice guidelines for the treatment of panic disorder and agoraphobia. Aust N Z J Psychiatry 2003;37:641-56.

29. European Medicines Agency. Guideline on clinical investigation of medicinal products indicated for the treatment of panic disorder. Amsterdam: European Medicines Agency, 2005.

30. Baldwin DS, Anderson IM, Nutt DJ et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2005;19:567-96.

31. Canadian Psychiatric Association. Clinical practice guidelines. Management of anxiety disorders. Can J Psychiatry 2006;51:9s-91s.

32. Connolly SD, Bernstein GA. Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. J Am Acad Child Adolesc Psychiatry 2007;46:267-83.

33. Bandelow B, Zohar J, Hollander E et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders – first revision. World J Biol Psychiatry 2008;9:248-312.

34. Ministry of Health and Consumer Affairs. Clinical practice guideline for treatment of patients with anxiety disorders in primary care. Madrid: Ministry of Health and Consumer Affairs, 2008.

35. American Psychiatric Association. Practice guideline for the treatment of patients with panic disorder, 2nd ed. Washington: American Psychiatric Association, 2009.

36. Levitan MN, Chagas MH, Crippa JA et al. Guidelines of the Brazilian Medical Association for the treatment of social anxiety disorder. Rev Brasil Psiquiatr 2011;33:292-302.

37. National Institute for Health and Care Excellence. Generalised anxiety disorder and panic disorder in adults: management. London: National Institute for Health and Care Excellence, 2011.

38. Levitan MN, Chagas MH, Linares IM et al. Brazilian Medical Association guidelines for the diagnosis and differential diagnosis of panic disorder. Rev Brasil Psiquiatr 2013;35:406-15.

39. National Collaborating Centre for Mental Health. Social anxiety disorder: recognition, assessment and treatment. Leicester: British Psychological Society, 2013.

40. Seedat S. Social anxiety disorder (social phobia). S Afr J Psychiatr 2013;19:192-6.

41. Stein DJ. Generalised anxiety disorder. S Afr J Psychiatr 2013;19:175-9.

42. Baldwin DS, Anderson IM, Nutt DJ et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol 2014;28:403-39.

43. Bandelow B, Wiltink J, Alpers GW et al. S3-Leitlinie Behandlung von Angststörungen. Zurich: Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, 2014.

44. Lim L, Chan HN, Chew PH et al. Ministry of Health clinical practice guidelines: anxiety disorders. Singapore Med J 2015;56:310-5.

45. Gautam S, Jain A, Gautam M et al. Clinical practice guidelines for the management of generalised anxiety disorder (GAD) and panic disorder (PD). Indian J Psychiatry 2017;59:S67-73.

46. Andrews G, Bell C, Boyce P et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. Aust N Z J Psychiatry 2018;52:1109-72.

47. Yoon H, Oh DJ, Suh HS et al. Korean guidelines for the pharmacological treatment of social anxiety disorder: initial treatment strategies. Psychiatry Investig 2018;15:147-55.

48. Walter HJ, Bukstein OG, Abright AR et al. Clinical practice guideline for the assessment and treatment of children and adolescents with anxiety disorders. J Am Acad Child Adolesc Psychiatry 2020;59:1107-24.

49. Bandelow B, Aden I, Alpers GW et al. S3-Leitlinie Behandlung von Angststörungen – Version 2. Zurich: Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, 2021.

50. Bandelow B, Allgulander C, Baldwin DS et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders – Version 3. Part II: OCD and PTSD. World J Biol Psychiatry 2023;24:118-34.

51. Katzman MA, Bleau P, Blier P et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry 2014;14(Suppl. 1):S1.

52. Australian Therapeutic Guidelines. https://tgldcdp.tg.org.au.

53. COMET Initiative. Core outcome measures in effectiveness trials. www.comet-initiative.org.

54. Obbarius A, van Maasakkers L, Baer L et al. Standardization of health outcomes assessment for depression and anxiety: recommendations from the ICHOM Depression and Anxiety Working Group. Qual Life Res 2017;26:3211-25.

55. Bokma WA, Wetzer G, Gehrels JB et al. Aligning the many definitions of treatment resistance in anxiety disorders: a systematic review. Depress Anxiety 2019;36:801-12.

56. Howes OD, Thase ME, Pillinger T. Treatment resistance in psychiatry: state of the art and new directions. Mol Psychiatry 2022;27:58-72.

57. Cantrill JA, Sibbald B, Buetow S. The Delphi and nominal group techniques in health services research. Int J Pharm Pract 1996;4:67-74.

58. Dalkey NC. The Delphi method: an experimental study of group opinion. Santa Monica: RAND Corporation, 1969.

59. Moher D, Schulz KF, Simera I et al. Guidance for developers of health research reporting guidelines. PLoS Med 2010;7:e1000217.

60. Trevelyan EG, Robinson PN. Delphi methodology in health research: how to do it? Eur J Integr Med 2015;7:423-8.

61. Jünger S, Payne SA, Brine J et al. Guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care: recommendations based on a methodological systematic review. Palliat Med 2017;31:684-706.

62. Sforzini L, Worrell C, Kose M et al. A Delphi-method-based consensus guideline for definition of treatment-resistant depression for clinical trials. Mol Psychiatry 2022;27:1286-99.

63. Fackrell K, Smith H, Colley V et al. Core Outcome Domains for early phase clinical trials of sound-,

psychology-, and pharmacology-based interventions to manage chronic subjective tinnitus in adults: the COMIT'ID study protocol for using a Delphi process and face-to-face meetings to establish consensus. Trials 2017;18:388.

64. Vogel C, Zwolinsky S, Griffiths C et al. A Delphi study to build consensus on the definition and use of big data in obesity research. Int J Obes 2019;43:2573-86.

65. Knaapen M, Hall NJ, van der Lee JH et al. Establishing a core outcome set for treatment of uncomplicated appendicitis in children: study protocol for an international Delphi survey. BMJ Open 2019;9:e028861.

66. Santaguida P, Dolovich L, Oliver D et al. Protocol for a Delphi consensus exercise to identify a core set of criteria for selecting health related outcome measures (HROM) to be used in primary health care. BMC Fam Pract 2018;19:152.

67. Blade J, Calleja M, Lahuerta JJ et al. Defining a set of standardised outcome measures for newly diagnosed patients with multiple myeloma using the Delphi consensus method: the IMPORTA project. BMJ Open 2018;8:e018850.

68. Guyatt GH, Oxman AD, Vist GE et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.

69. Cuijpers P, Li J, Hofmann SG et al. Self-reported versus clinician-rated symptoms of depression as outcome measures in psychotherapy research on depression: a meta-analysis. Clin Psychol Rev 2010;30:768-78.

70. Ahmadzad-Asl M, Davoudi F, Mohamadi S et al. Systematic review and meta-analysis of the placebo effect in panic disorder: implications for research and clinical practice. Aust N Z J Psychiatry 2022;56:1130-41.

71. LeDoux JE, Hofmann SG. The subjective experience of emotion: a fearful view. Curr Opin Behav Sci 2018;19:67-72.

72. Taschereau-Dumouchel V, Michel M, Lau H et al. Putting the "mental" back in "mental disorders": a perspective from research on fear and anxiety. Mol Psychiatry 2022;27:1322-30.

73. Mennin DS, Fresco DM, Heimberg RG et al. Screening for social anxiety disorder in the clinical setting: using the Liebowitz Social Anxiety Scale. J Anxiety Disord 2002;16:661-73.

74. Pranckeviciene A, Saudargiene A, Gecaite-Stonciene J et al. Validation of the Patient Health Questionnaire-9 and the Generalized Anxiety Disorder-7 in Lithuanian student sample. PLoS One 2022;17:e0263027.

75. Rutter LA, Brown TA. Psychometric properties of the Generalized Anxiety Disorder scale-7 (GAD-7) in outpatients with anxiety and mood disorders. J Psychopathol Behav Assess 2017;39:140-6.

76. Stanyte A, Fineberg NA, Podlipskyte A et al. Validation of the Patient Health Questionnaire-9 and the Generalized Anxiety Disorder-7 in Lithuanian individuals with anxiety and mood disorders. J Psychiatr Res 2023;164:221-8.

77. Delgadillo J, Payne S, Gilbody S et al. Brief case finding tools for anxiety disorders: validation of GAD-7 and GAD-2 in addictions treatment. Drug Alcohol Depend 2012;125:37-42.

78. Pallanti S, Hollander E, Bienstock C et al. Treatment non-response in OCD: methodological issues and operational definitions. Int J Neuropsychopharmacol 2002;5:181-91.

79. Fava M. Diagnosis and definition of treatment-resistant depression. Biol Psychiatry 2003;53:649-59.

80. Fekadu A, Wooderson S, Donaldson C et al. A multidimensional tool to quantify treatment resistance in depression: the Maudsley staging method. J Clin Psychiatry 2009;70:177-84.

81. McIntyre RS, Alsuwaidan M, Baune BT et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry 2023;22:394-412.

82. Bokma WA, Zhutovsky P, Giltay EJ et al. Predicting the naturalistic course in anxiety disorders using clinical and biological markers: a machine learning approach. Psychol Med 2022;52:57-67.

83. Alboni S, van Dijk RM, Poggini S et al. Fluoxetine effects on molecular, cellular and behavioral endophenotypes of depression are driven by the living environment. Mol Psychiatry 2017;22:552-61.

84. Bokma WA, Batelaan NM, Hoogendoorn AW et al. A clinical staging approach to improving diagnostics in anxiety disorders: is it the way to go? Aust N Z J Psychiatry 2020;54:173-84.

85. Bokma WA, Batelaan NM, Penninx BWJH et al. Evaluating a dimensional approach to treatment resistance in anxiety disorders: a two-year follow-up study. J Affect Disord Rep 2021;4:100139.

86. Altamura AC, Dell'Osso B, D'Urso N et al. Duration of untreated illness as a predictor of treatment response and clinical course in generalized anxiety disorder. CNS Spectr 2008;13:415-22.

87. McAllister-Williams RH, Arango C, Blier P et al. The identification, assessment and management of difficult-to-treat depression: an international consensus statement. J Affect Disord 2020;267:264-82.

88. Demyttenaere K. What is treatment resistance in psychiatry? A "difficult to treat" concept. World Psychiatry 2019;18:354-5.

89. Rush AJ, Sackeim HA, Conway CR et al. Clinical research challenges posed by difficult-to-treat depression. Psychol Med 2022;52:419-32.

90. Cieza A, Sabariego C, Anczewska M et al. PARADISE 24: a measure to assess the impact of brain disorders on people's lives. PLoS One 2015;10:e0132410.

91. Devji T, Carrasco-Labra A, Qasim A et al. Evaluating the credibility of anchor based estimates of minimal important differences for patient reported outcomes: instrument development and reliability study. BMJ 2020;369:m1714.

92. Bosman RC, van Balkom A, Rhebergen D et al. Predicting the course of anxiety disorders: the role of biological parameters. Prog Neuropsychopharmacol Biol Psychiatry 2020;101:109924.

93. Roseberry K, Le-Niculescu H, Levey DF et al. Towards precision medicine for anxiety disorders: objective assessment, risk prediction, pharmacogenomics, and repurposed drugs. Mol Psychiatry 2023; doi: 10.1038/s41380-023-01998-0.

94. Abi-Dargham A, Moeller SJ, Ali F et al. Candidate biomarkers in psychiatric disorders: state of the field. World Psychiatry 2023;22:236-62.

95. Stein DJ, Craske MG, Rothbaum BO et al. The clinical characterization of the adult patient with an anxiety or related disorder aimed at personalization of management. World Psychiatry 2021;20:336-56.

96. Merikangas KR, Swendsen J, Hickie IB et al. Real-time mobile monitoring of the dynamic associations among motor activity, energy, mood, and sleep in adults with bipolar disorder. JAMA Psychiatry 2019;76:190-8.

97. Zhao N, Zhang Z, Wang Y et al. See your mental state from your walk: recognizing anxiety and depression through Kinect-recorded gait data. PLoS One 2019;14:e0216591.

98. Moore RC, Depp CA, Wetherell JL et al. Ecological momentary assessment versus standard

assessment instruments for measuring mindfulness, depressed mood, and anxiety among older adults. J Psychiatr Res 2016;75:116-23.

99. McGinnis EW, Lunna S, Berman I et al. Discovering digital biomarkers of panic attack risk in consumer wearables data. medRxiv 2023:2023.03.01.23286647.

100. Gargon E, Crew R, Burnside G et al. Higher number of items associated with significantly lower response rates in COS Delphi surveys. J Clin Epidemiol 2019;108:110-20.

101. Maj M. Understanding depression beyond the "mind-body" dichotomy. World Psychiatry 2023;22:34-50.

102. Weissman MM. Does treatment-resistant depression need psychotherapy? World Psychiatry 2023;22:417-8.

103. Cuijpers P. From treatment resistance to sequential treatments of depression. World Psychiatry 2023;22:418-9.

104. Lenze EJ, Wetherell JL. A lifespan view of anxiety disorders. Dialogues Clin Neurosci 2011;13:381-99.

105. Wittchen HU, Lieb R, Pfister H et al. The waxing and waning of mental disorders: evaluating the stability of syndromes of mental disorders in the population. Compr Psychiatry 2000;41:122-32.

106. Kirkham JJ, Davis K, Altman DG et al. Core Outcome Set-STAndards for Development: The COS-STAD recommendations. PLoS Med 2017;14:e1002447.

107. Kirkham JJ, Gorst S, Altman DG et al. Core Outcome Set-STAndards for Reporting: The COS-STAR Statement. PLoS Med 2016;13:e1002148.

108. Barton S, Karner C, Salih F et al. Clinical effectiveness of interventions for treatment-resistant anxiety in older people: a systematic review. Health Technol Assess 2014;18:1-59.

109. Chiu A, Falk A, Walkup JT. Anxiety disorders among children and adolescents. Focus 2016;14:26-33.

110. Lydiard RB, Brawman-Mintzer O. Panic disorder across the life span: a differential diagnostic approach to treatment resistance. Bull Menninger Clin 1997;61:A66-94.

111. Reinblatt SP, Walkup JT. Psychopharmacologic treatment of pediatric anxiety disorders. Child Adolesc Psychiatr Clin N Am 2005;14:877-908.

112. Baldwin DS, Gordon R, Abelli M et al. The separation of adult separation anxiety disorder. CNS Spectr 2016;21:289-94.

113. Muris P, Ollendick TH. Children who are anxious in silence: a review on selective mutism, the new anxiety disorder in DSM-5. Clin Child Fam Psychol Rev 2015;18:151-69.

114. Schiele MA, Bandelow B, Baldwin DS et al. A neurobiological framework of separation anxiety and related phenotypes. Eur Neuropsychopharmacol 2020;33:45-57.

115. Lueken U, Zierhut KC, Hahn T et al. Neurobiological markers predicting treatment response in anxiety disorders: a systematic review and implications for clinical application. Neurosci Biobehav Rev 2016;66:143-62.

116. Bandelow B, Michaelis S, Wedekind D. Treatment of anxiety disorders. Dialogues Clin Neurosci 2017;19:93-107.

117. Reinhold JA, Mandos LA, Rickels K et al. Pharmacological treatment of generalized anxiety disorder. Expert Opin Pharmacother 2011;12:2457-67.

118. Ipser JC, Carey P, Dhansay Y et al. Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders. Cochrane Database Syst Rev 2006;4:CD005473.

119. Diemer J, Vennewald N, Domschke K et al. Therapy-refractory panic: current research areas as possible perspectives in the treatment of anxiety. Eur Arch Psychiatry Clin Neurosci 2010;260(Suppl. 2):S127-31.

120. Caletti E, Massimo C, Magliocca S et al. The role of the acceptance and commitment therapy in the treatment of social anxiety: an updated scoping review. J Affect Disord 2022;310:174-82.

121. Gloster AT, Rinner MTB, Ioannou M et al. Treating treatment non-responders: a meta-analysis of randomized controlled psychotherapy trials. Clin Psychol Rev 2020;75:101810.

122. Hoge EA, Bui E, Mete M et al. Mindfulness-based stress reduction vs escitalopram for the treatment of adults with anxiety disorders: a randomized clinical trial. JAMA Psychiatry 2023;80:13-21.

123. Solem S, Wells A, Kennair LEO et al. Metacognitive therapy versus cognitive-behavioral therapy in adults with generalized anxiety disorder: a 9-year follow-up study. Brain Behav 2021;11:e2358.

124. Millard LA, Wan MW, Smith DM et al. The effectiveness of compassion focused therapy with clinical populations: a systematic review and meta-analysis. J Affect Disord 2023;326:168-92.

125. Singewald N, Sartori SB, Reif A et al. Alleviating anxiety and taming trauma: novel pharmacotherapeutics for anxiety disorders and posttraumatic stress disorder. Neuropharmacology 2023;226:109418.

126. Correll CU, Solmi M, Cortese S et al. The future of psychopharmacology: a critical appraisal of ongoing phase 2/3 trials, and of some current trends aiming to de-risk trial programmes of novel agents. World Psychiatry 2023;22:48-74.
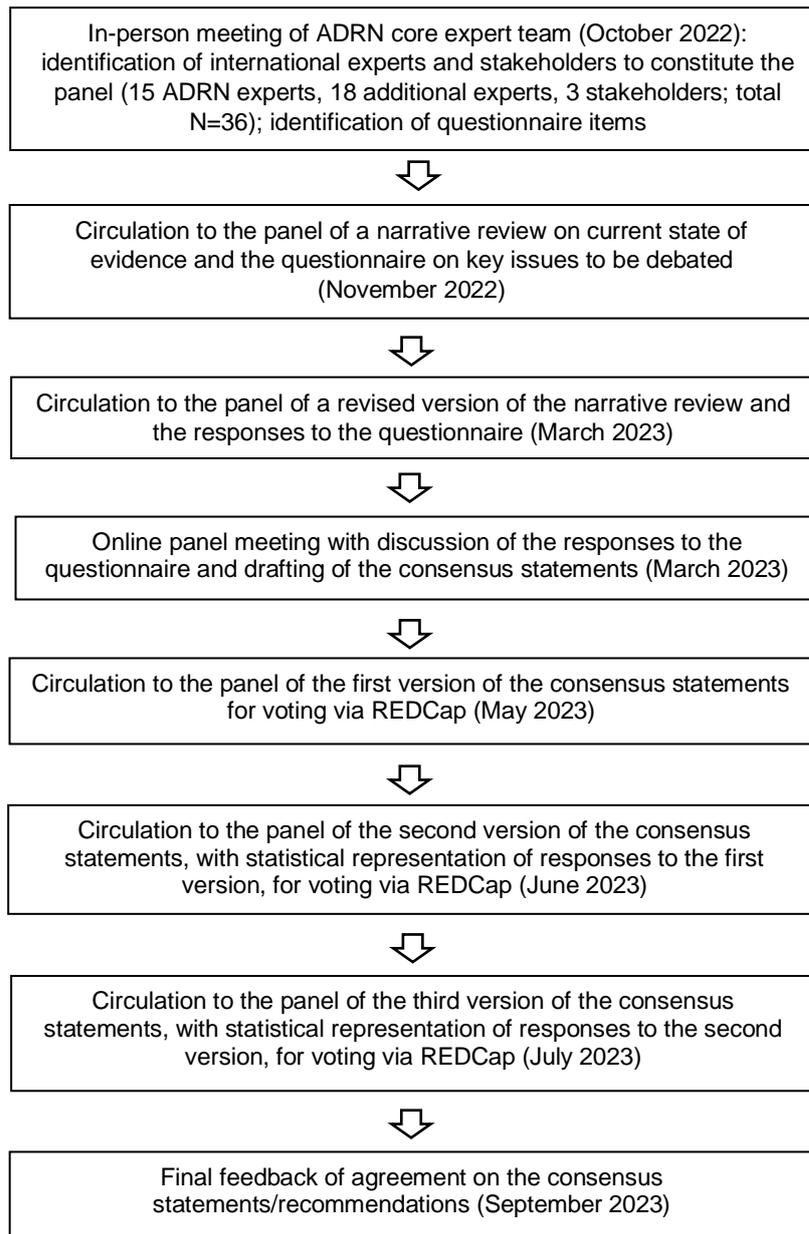
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┌─────────────────────────────────────────────────────────────┐
│ In-person meeting of ADRN core expert team (October 2022):    │
│ identification of international experts and stakeholders to    │
│ constitute the panel (15 ADRN experts, 18 additional experts, │
│ 3 stakeholders; total N=36); identification of                │
│ questionnaire items                                           │
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┌─────────────────────────────────────────────────────────────┐
│ Circulation to the panel of a narrative review on current     │
│ state of evidence and the questionnaire on key issues to be   │
│ debated (November 2022)                                       │
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┌─────────────────────────────────────────────────────────────┐
│ Circulation to the panel of a revised version of the narrative│
│ review and the responses to the questionnaire (March 2023)    │
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│ Online panel meeting with discussion of the responses to the  │
│ questionnaire and drafting of the consensus statements        │
│ (March 2023)                                                  │
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┌─────────────────────────────────────────────────────────────┐
│ Circulation to the panel of the first version of the          │
│ consensus statements for voting via REDCap (May 2023)         │
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┌─────────────────────────────────────────────────────────────┐
│ Circulation to the panel of the second version of the         │
│ consensus statements, with statistical representation of      │
│ responses to the first version, for voting via REDCap         │
│ (June 2023)                                                   │
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│ Circulation to the panel of the third version of the          │
│ consensus statements, with statistical representation of      │
│ responses to the second version, for voting via REDCap        │
│ (July 2023)                                                   │
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┌─────────────────────────────────────────────────────────────┐
│ Final feedback of agreement on the consensus                  │
│ statements/recommendations (September 2023)                   │
└─────────────────────────────────────────────────────────────┘
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Figure 1 Flow diagram of the Delphi method-based process. ADRN – Anxiety Disorders Research Network

Table 1 Consensus results on the definition of treatment-resistant anxiety disorders (TR-AD)

No.	Statement	Mean score ±SD on 9-point Likert scale	% of agreement
General remarks			
1	A definition of TR-AD is useful for both pharmacological and psychotherapeutic clinical trials conducted for regulatory purposes.	8.74 ±0.58	100
2	A definition of TR-AD is useful for research, e.g. in the search for disease or treatment response mechanisms and biomarkers.	8.68 ±0.60	100
Operational definition			
3	The definition of TR-AD should ideally, but not necessarily, rest on both observer-rated and self-report scales.	8.23 ±0.99	90.3
4	Treatment resistance in anxiety disorders can be operationally defined by the failure to achieve clinically significant reduction in symptom severity from pre- to post-treatment. This can be reflected by a <50% reduction in Hamilton Anxiety Scale score or a <50% reduction in Beck Anxiety Inventory score or a Clinical Global Impression Scale - Improvement >2.	8.35 ±0.75	96.8
4a	Optional specific criteria for treatment-resistant social anxiety disorder: Liebowitz Social Anxiety Scale (LSAS)-SR (self-rating) score reduction <28% or LSAS-CA (clinician-administered) score reduction <29%.	8.21 ±1.11	89.7
4b	Optional specific criteria for treatment-resistant GAD: Generalized Anxiety Disorder 7-item (GAD-7) scale score <4-point reduction, or Penn State Worry Questionnaire score <9% or <4-point reduction.	8.03 ±1.09	89.7
4c	Optional specific criteria for treatment-resistant panic disorder/agoraphobia: Panic Disorder Severity Scale score reduction <40% or Panic Agoraphobia Scale score reduction <23%.	8.03 ±1.09	89.7
5	The definition of pharmacological treatment resistance in anxiety disorders should rest on at least two unsuccessful trials of pharmacological monotherapy with first-line agents approved for the treatment of anxiety disorders and recommended by guidelines (two different classes, e.g. one SSRI plus one SNRI, clomipramine or pregabalin, in the case of GAD) using at least the minimal approved dose, for the duration of at least 6-8 weeks each, ideally with documented therapy adherence.	8.50 ±0.73	100
6	The definition of psychotherapeutic treatment resistance in anxiety disorders should rest on at least one unsuccessful trial of adequately delivered (e.g., qualified therapist) first-line psychotherapy such as cognitive behavioral therapy (CBT) with adequate intensity (e.g., a sufficient number of exposure exercises, homework, adherence) and duration (depending on the type of anxiety disorders, e.g., 12-20 weeks in GAD, panic disorder/agoraphobia or social anxiety disorder).	8.07 ±1.55	96.7
Staging model			
7	A staging model might capture the spectrum of TR-AD with various levels of treatment resistance, comprising: i) failure of either two adequate courses of pharmacotherapy or ≥1 adequate trial of psychotherapy ii) failure of both two adequate course of pharmacotherapy and ≥1 adequate trial of psychotherapy	8.29 ±0.82	100

	iii) failure of multiple adequate courses of (poly)pharmacotherapy and multiple adequate trials of psychotherapy (connoting multiple TR-AD, MTR-AD).		
Additional aspects			
8	Comorbidities with depression, substance abuse or personality disorders should not influence the operational definition of TR-AD, but their presence should be recorded and considered *post hoc*.	8.65 ±0.61	100
9	Subgroups of AD (e.g., by sex, age, menopause, peri-partum period) should not influence the operational definition of TR-AD, but should be recorded and considered *post hoc*.	8.61 ±0.62	100
10	Specific biographical factors (e.g., life events, history of trauma) should not influence the operational definition of TR-AD, but their presence should be recorded and considered *post hoc*.	8.58 ±0.67	100
11	Duration of illness and number of episodes should not influence the operational definition of TR-AD, but they should be recorded *post hoc*, considering that TR-AD by definition might entail a longer duration of illness and that delineation of distinct episodes might be difficult.	8.65 ±0.61	100
12	Research into biomarkers and other predictors and mechanisms of TR-AD might be useful in the future.	8.71 ±0.59	100
13	It is essential to be sensitive and not judgmental towards patients suffering from TR-AD, to include their social environment in the diagnostic and therapeutic process where appropriate, and to respect patients' preferences after they are fully informed about the comparative efficacy of the various treatment modalities based on current official guidelines.	8.68 ±0.60	100
14	In the future, the merits of the term TR-AD in a regulatory context are to be discussed against potential drawbacks, with consideration of a potentially more comprehensive term such as "difficult-to-treat" anxiety disorders, which might be more useful in a clinical context.	8.32 ±0.79	100

GAD – generalized anxiety disorder

Table 2 Definition of treatment-resistant anxiety disorders (TR-AD): main consensus recommendations

Treatment resistance

<50% reduction in HAM-A score
         OR   <50% reduction in BAI score
         OR   - CGI-I score >2

Pharmacological treatment resistance
- At least two unsuccessful separate full trials of pharmacological monotherapy   - First-line agents approved for the treatment of anxiety disorders and recommended by guidelines (two different classes, e.g. one SSRI plus one SNRI, clomipramine or pregabalin, in the case of GAD)   - At least at the minimal approved dose   - Duration of at least 6-8 weeks each   - Ideally with documented therapy adherence
Psychotherapeutic treatment resistance
- At least one unsuccessful trial of adequately delivered (e.g., qualified therapist) first-line psychotherapy (e.g., CBT)   - Adequate intensity (e.g., a sufficient number of exposure exercises, homework, adherence)   - Adequate duration (e.g., 12-20 weeks in GAD, PD/AG or SAD)
Staging model
i. Failure of *EITHER* two adequate courses of pharmacotherapy *OR* ≥1 adequate trial of psychotherapy ii. Failure of *BOTH* two adequate courses of pharmacotherapy *AND* ≥1 adequate trial of psychotherapy iii. Failure of multiple adequate courses of (poly)pharmacotherapy *AND* multiple adequate trials of psychotherapy (MTR-AD)

BAI – Beck Anxiety Inventory, CBT – cognitive behavioral therapy, CGI-I – Clinical Global Impression Scale - Improvement, GAD – generalized anxiety disorder, HAM-A – Hamilton Anxiety Scale, MTR-AD – multi-modal treatment-resistant anxiety disorder, PD/AG – panic disorder/agoraphobia, SAD – social anxiety disorder, SSRI – selective serotonin reuptake inhibitor, SNRI – serotonin and norepinephrine reuptake inhibitor