Treatment-resistant and Multi-therapy resistant criteria for bipolar depression: A consensus definition

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Abstract

Background: Most people with bipolar disorder (BD) spend a significant percentage of their lifetime experiencing either sub-syndromal depressive symptoms or major depressive episodes, which contribute greatly to the high levels of disability and mortality associated with the disorder. Despite the importance of bipolar depression, there are only a small number of recognised treatment options available. Consecutive treatment failures can quickly exhaust these options leading to treatment-resistant bipolar depression (TRBD). Remarkably few studies have evaluated TRBD and those available lack a comprehensive definition of multi-therapy resistant bipolar depression (MTRBD).

Aim: To reach consensus regarding threshold definitions criterion for TRBD and MTRBD.

Method: Based on the evidence of standard treatments available in the latest BD treatment guidelines, TRBD and MTRBD criteria were agreed by a representative panel of BD experts using a modified Delphi method.

Results: TRBD criteria in bipolar depression was defined as failure to reach sustained symptomatic remission for 8 consecutive weeks after two different treatment trials, at adequate therapeutic doses, with at least two recommended monotherapy treatments or at least one monotherapy treatment and another combination treatment. MTRBD included the same initial definition as TRBD, with the addition of failure of at least one trial with an antidepressant, a psychological treatment and a course of electroconvulsive therapy.

Conclusions: The proposed TRBD and MTRBD criteria may provide an important signpost to help clinicians, researchers and stakeholders in judging how and when to consider new non-standard treatments. However, some challenging diagnostic and therapeutic issues were identified in the consensus process which need further evaluation and research.

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Background

The treatment of depressive episodes experienced by people with bipolar disorder (BD) is one of the most challenging issues faced by both clinicians and researchers. Most people with BD spend a significant percentage of their time experiencing either sub-syndromal depressive symptoms or major depressive episodes and these contribute to the high levels of distress, global disability and mortality associated with the disorder[1,2]. There are only a small number of licenced therapeutic options available for the treatment of bipolar depression, and these often fail to significantly improve patients' symptoms and functionality[3]. Consecutive treatment failures can rapidly exhaust all recommended treatment options. It has been suggested that treatment failure rates might be even higher than in major depressive disorder (MDD)[4]. Despite this, there are remarkably few studies which have specifically evaluated treatment-resistant bipolar depression (TRBD) and those available lack a common definition of TRBD which makes it difficult to generalize their results[3,5,6]. Fortunately, during the last decade, new promising non-standard treatment options have become available, but they are either not currently included in guidelines or are recommended for use only by specialist services. These emerging treatments have a limited evidence base to support their general use and some are associated with significant risks, costs and invasiveness in comparison to standard treatments. More importantly, as there is no clear consensus on the criteria defining TRBD, it is difficult to know at which point of the treatment pathway these non-standard interventions might be considered. The few TRBD definitions proposed so far vary, and most only consider pharmacological options independently of more comprehensive and standardized treatment including psychotherapy, physical therapies and lifestyle modification[7–9]. We have recently published multi-therapy resistance criteria in MDD as a guide to when clinicians could consider the use of non-standard treatments[10]. Adopting a similar approach, we first set out to reach a consensus for criteria defining TRBD mainly based on the National Institute for Health and Care Excellence (NICE) and the British Association for Psychopharmacology (BAP) BD treatment guidelines[11,12]. The main aim of this study was to reach an agreement about the

concept and definition of Multi-therapy resistant bipolar depression (MTRBD), encompassing pharmacological treatments as well as psychological and physical treatments. The purpose of developing MTRBD criteria was to define a point in the bipolar depression treatment pathway when clinicians may wish to consider the use of non-standard treatments, rather than provide specific treatment recommendations.

Method

The development of the criteria definitions followed five successive phases (Figure 1). Initially, a group of UK experts representing all major specialists' centres and relevant domains of expertise were approached and all consented to participate. The initial consensus panel was composed of 18 bipolar disorder experts from primary, secondary and tertiary care. Two members of the panel (AHY, PRAS) and a facilitator (DHM) developed a first set of TRBD and MTRBD criteria based on the latest NICE and BAP treatment guidelines for bipolar disorder which were among the most updated treatment guidelines at the time this project started [11,12]. These criteria were reviewed and discussed during an initial face-to-face and online meeting sponsored by the Royal College of Psychiatrists (London, March 2018), and challenging issues highlighted were noted while drawing up the initial draft criteria. The meeting participants decided that both TRBD and MTRBD criteria were needed to cover the whole trajectory and range of possibilities in the course of treating bipolar depression. To ensure that the criteria were as consistent and practical as possible, it was agreed that TRBD criteria should be embedded as the initial pharmacological treatment stage of the more comprehensive MTRBD criteria as a natural continuum of clinical practice.

Feedback and discussion from the initial meeting was incorporated into a new second version of the draft criteria. This, and unresolved diagnostic and therapeutic issues, were then rated for their

relevance to be included in the criteria and this manuscript through a modified Delphi method[13,14]. To ensure criteria generalizability, during the Delphi process, seven non-UK bipolar disorder experts from key representative international societies ((Canadian Network for Mood and Anxiety Treatments (CANMAT), International College of Neuropsychopharmacology (CINP), European College of Neuropsychopharmacology (ECNP), International Society for Affective Disorders (ISAD), International Society for Bipolar Disorders (ISBD), World Federation of the Societies of Biological Psychiatry (WFSBP) and the Royal Australian and New Zealand College of Psychiatrists (RANZCP)) were invited to be part of the consensus panel. The international representatives invited were previously or currently involved in the development of treatment guidelines in their respective societies, which are amongst the leading evidence-based international treatment guidelines for BD. Additionally, in order to include the patient's perspective in the consensus, an expert patient was also invited to anonymously join the Delphi process. An expert patient is a person who has the knowledge needed to play an active role in making shared decisions about their own health care and management of their chronic condition[15]. All the international representatives and the expert patient contacted accepted the invitation to be involved in the process.

[Figure 1 goes here]

The modified Delphi method was conducted using an online survey collecting anonymous responses in three rounds. The items included in the surveys were organized in three sections: (1) statements about unresolved elements of the second draft TRBD and (2) MTRBD criteria as well as (3) statements about challenging diagnostic and treatment issues identified throughout the process. The participants rated the surveys items ranging from "Essential", "Important", "Don't know/Depends", to "Unimportant" or "Should not be included". The first survey round also allowed participants to add comments after rating each item, which could include suggestions about other pertinent references, studies or treatment guidelines. In each round, the expert patient was offered additional information and support to understand and respond appropriately to each item according to their own judgement.

After reading and analysing the comments provided by the participants, three of the authors (AHY, PRAS, DHM), determined if they contained new information which merited the addition of a new item in subsequent Delphi rounds. Survey items were classified as endorsed, re-rated or rejected. Endorsement cut-off was set to at least 80% of answers rating an item as essential or important. Items rated as essential or important by 65% to 79.9% of the participants were included in the subsequent rounds for re-rating. These cut-off criteria have been also used by similar expert consensus using the Delphi method in the field[14,16]. Participants could decide whether they wanted to maintain or change their previous rating on these re-rated items only once; if items did not achieve the threshold for endorsement or re-rate, they were rejected. After each round, all the aggregated results were sent to the participants. Items requiring re-rating after the third round are outlined in the discussion section.

Results

The initial survey included 33 items (Supplementary material 1), and the second survey included 17 items of which 3 were items needing re-rating and 14 were new items extracted from the comments left by the experts in the first round. All the participants completed the first round of the Delphi survey whereas the second and third round were completed by 92.3% (24/26) and 88.5% (23/26) of the panel, respectively. In the second round, 7 items were endorsed by the experts, 6 items were excluded and 4 remained unresolved diagnostic and therapeutic issues which required re-rating. In the final round, 3 out of the 4 items were endorsed while 1 item remained unresolved. In total, 15 out of the original 33 items were endorsed and included in the final criteria (Figure 2).

[Figure 2 goes here]

The final consensus reached on the criteria for TRBD and MTRBD are detailed in Table 1 and Table 2.

[Table 1 goes here]

[Table 2 goes here]

Discussion

In this study, we reached consensus definitions for both treatment resistant bipolar depression and multi-therapy resistant bipolar depression. We hope that these criteria will be a useful guide for clinicians when they are considering the use of non-standard treatment options and for researchers as a framework to guide future studies.

It is important to note that these are not the first proposed definitions for treatment resistance in bipolar depression. Many previous definitions are based on commonalities in the clinical presentation and treatment of bipolar depression and major depressive disorder (MDD)[3,5,7,9]. Most of these criteria include one or two failures to respond to treatments or reach remission to either mood stabilizers and/or antidepressants at adequate doses after between 6 and 8 weeks. However, over the last ten years, a growing body of evidence has demonstrated marked differences in treatment efficacy of a range of treatments, for example SSRI antidepressants, between BD and MDD[17], and several studies have shown the useful role of quetiapine and lurasidone for the treatment of bipolar depression[18].

In this context, Pacchiarotti et al. previously provided a stepwise series of definitions for treatment refractoriness in bipolar depression ranging from treatment-resistant to involutional bipolar[7]. The first step of this definition for bipolar I depression defined treatment resistance as a failure to reach remission with adequate plasma levels of lithium (0.8 mEq/l) or to other adequate ongoing mood-stabilizing treatment, plus lamotrigine (50–200 mg/day) or with full dose (≥600 mg/day) of quetiapine as monotherapy (300-600 mg /day allowed for bipolar II depression)[7]. An adequate trial period to reach remission was defined as 8 weeks as in our criteria. Our criteria contain similar options to those of Pacchiarotti, but more explicitly allow for combination therapy and do not require a minimum dose of 600mg Quetiapine for bipolar I depression. Since the Pacchiarotti et al criteria, new emerging evidence and consensus have been published, especially regarding the use of antidepressants, as well

as other standard treatments (i.e. lurasidone)[5,16]. As a result, guidelines have been updated accordingly and these changes have been reflected in our version of the TRBD definition criteria. In comparison to previous proposed criteria, our MTRBD criteria were developed with a more pragmatic approach but within the initial evidence framework of the latest NICE and BAP guidelines[11,12].

TRBD criteria

The agreed TRBD criteria includes failure to reach sustained remission or tolerate at least two different adequate treatment trials, for at least 8 weeks at therapeutic doses with acceptable adherence, of monotherapy (quetiapine, lurasidone, lamotrigine or olanzapine/fluoxetine combination), or at least one of these as monotherapy and one of these in combination with lamotrigine, valproate or lithium. These criteria were mostly based on NICE and BAP bipolar depression guidelines. The number of required failed trials was a matter of discussion which required a Delphi round to reach agreement. There were concerns that only two trials were a low threshold to consider further treatments, whilst on the other hand increasing the number of required treatment trials would extend the time that the patient remains symptomatic and inhibit access to other potential beneficial treatments. Treatment refractoriness was set as intolerance to treatment or failure to reach symptomatic sustained remission after at least eight consecutive weeks with each trial[19]. For lamotrigine monotherapy, this could be considered as eight consecutive weeks at a stable therapeutic dose after an initial dose titration of about 6 to 8 weeks. However, the length of this particular trial alongside the controversial evidence around its efficacy as monotherapy requires a thoughtful consideration before starting it, balancing patients´ symptoms severity and preferences[20].

The possibility of patient´s refusal of at least one of the trials was considered in the Delphi process, but was ultimately rejected due to the very low threshold for the definition and operational uncertainty of standardizing valid reasons for refusal. Other aspects confirmed by the first Delphi round included the minimum dose of quetiapine and minimum lithium plasma levels. In both cases,

the panel endorsed the minimum effective dose of 300mg/day for quetiapine and plasma levels of 0.8 mEQ/L for lithium. In the second round, despite some debate around the issue, the panel decided to keep the combination of olanzapine and fluoxetine (OFC) as a treatment option, rather than a more generic second generation antipsychotic and antidepressant combination. This takes into account that OFC is a licensed combination in the USA for this indication. Although only OFC is included in our criteria, we have no reason to believe that other second generation antipsychotic and selective-serotonin reuptake inhibitors (SSRIs) combinations would not be effective for the treatment of bipolar depression; nevertheless, it should be noted that such other combinations have not yet been examined in clinical trials. These points are also consistent with other recent international BD treatment guidelines[21]. An additional point which was endorsed by the panel was the safety and inefficacy warning about lamotrigine and valproate combination. This combination is not supported by the guidelines and, if used, plasma levels and side effects should be closely monitored.

There were some suggestions for adding other agents among the initial pharmacological options which, after reviewing the body of evidence provide by the treatment guidelines adopted for this study[11,12], as well as experts opinions during the Delphi process, were ultimately rejected. They are listed in Supplementary Table 1. Finally, the panel agreed that these criteria should apply to both working age and older adults diagnosed with bipolar I or II disorder.

MTRBD criteria

The MTRBD criteria extends the TRBD criteria by specifying: a trial of bupropion, or a selective SSRI, or a serotonin–norepinephrine reuptake inhibitor (SNRI) for at least 8 weeks at therapeutic doses, in combination with an anti-manic drug in bipolar I patients , and carefully monitored in both bipolar I and II patients; a course of cognitive behavioural therapy (CBT); and a trial of electro-convulsive therapy (ECT) (except in the case of contraindications, intolerance or patient refusal). The main points

of controversy during the initial discussion and the Delphi process were the types of antidepressants and psychological treatments to include in the MTRBD criteria.

Even though prior consensus statements about the use of antidepressant monotherapy for bipolar depression discouraged their use, antidepressants are still widely used for the treatment of bipolar depression worldwide[16,22]. It has been suggested that the risk of switch to mania should be balanced and considered on a case-by-case basis rather than recommending a broad restriction, especially in the particular circumstances of TRBD in which options are limited[23]. In this context, it was initially proposed that antidepressants should be avoided in patients with either a previous history of rapid cycling, mixed episodes or manic/hypomanic switches or current mixed symptoms and agitation. However, the panel did not endorse this as a general rule, but the evidence available in guidelines and several comments of the panel emphasised that special care should be taken when antidepressants are used for the treatment of bipolar depression[11,12]. In line with this, the panel agreed that if antidepressants are prescribed in bipolar I depression, they should only be used adjunctively with an antimanic drug[24], whereas in bipolar II depression, monotherapy with antidepressants is acceptable. All patients with bipolar depression treated with antidepressants should be warned about risk of switch to hypomanic or manic symptoms and should be careful monitored for the emergence of such symptoms. The other area where consensus proved harder concerned which classes of antidepressants should be considered for the treatment of bipolar depression. The general agreement among panel members was to be as pragmatic as possible and not to limit the already few options available while balancing the benefit and risks. As a result, SSRIs, SNRIs and bupropion were endorsed by the panel in the final Delphi round.

The other widely debated area for the MTRBD criteria was the inclusion of psychological interventions in the treatment process. This is mainly due to the limited evidence on which guidelines recommend these interventions for bipolar depression[25]. The panel agreed that psychological treatments, in general, should be included in the criteria, but due to the lack of evidence of efficacy for bipolar

depression, only Cognitive Behavioural Therapy (CBT) was endorsed in the last round as a potentially useful approach, in particular its behavioural activation component. The inclusion of a structured psychoeducation program among the psychological treatments was the only unresolved item not reaching endorsement or rejection rates after the three rounds in the Delphi process. Although the effectiveness of a psychoeducational intervention to prevent relapses has been extensively demonstrated, the evidence is not robust enough for the treatment of acute episodes[25]. Nonetheless, and depending on the functional and cognitive status of each individual patient who has not received this intervention previously, general or brief psychoeducational interventions might be considered as an option, especially taking into account the long time required to complete the whole treatment trajectory proposed in MTRBD criteria and long-term relapse prevention after the episode has been resolved.

Finally, at least twelve bilateral sessions of ECT was the last therapeutic option included in the MTRBD criteria, provided there were no contraindications and it was accepted and tolerated by the patient. Otherwise, it was agreed during the panel discussions that this should be considered a failed trial, and thus, the criteria for MTRBD would have been fulfilled.

During the panel discussions a number of diagnostic and therapeutic considerations emerged, which are outlined below.

Diagnostic considerations

Although most treatment guidelines provide recommendations for the management of bipolar depression, they provide less clarity about how to address treatment resistance. In reflecting on this, the panel provided some theoretical and practical considerations which could be drawn from standard clinical practice and guidelines.

The first of these is the need to ensure that for people with TRBD or MTRBD a comprehensive medical evaluation is conducted. It is important that clinicians exclude primary organic or pharmacologic causes for a depressive episode in BD. This should include a medical screening comprising a complete physical examination, blood screening and imaging tests when appropriate. Additionally, any already existing organic comorbidities and treatment side-effects should be re-assessed to exclude triggering or contributing factors. Abnormal test results or co-morbid conditions should be evaluated and if necessary treated by a specialist as appropriate[26] .

Secondly, given the high prevalence of comorbid psychiatric conditions in BD, the assessment of psychiatric comorbidities, particularly substance use, personality and anxiety disorders, is critical in the treatment of TRBD and MTRBD as they have been shown to have a negative impact on treatment outcomes[27–29]. In this context, even if the patient is already well known and to the clinician, semi-structured interviews may be helpful to assist diagnostic co-morbidity assessments[30]. The co-occurrence of one or more psychiatric co-morbidities requires a full assessment of its severity and specific evidence-based pharmacological and psychological treatments in coordination with professionals with expertise in these conditions, if available. Potential depressogenic agents should be avoided in the treatment of comorbid conditions, if possible[31]. However, since co-morbid conditions are exclusion criteria in most BD clinical trials, there is little evidence regarding the efficacy of commonly used treatments for these patients.

Finally, the panel considered that it was important to emphasise the need to employ a systematic and consistent method to assess the severity of the depressive symptoms, quality of life and functionality with standardized scales used throughout the treatment pathway, particularly before and after starting new treatments[32]. This should include continuous and rigorous medication adherence and risk assessment, including for psychotic symptoms and suicidality, as standards of clinical practice [11,12].

Therapeutic considerations

General health and exercise

Current guidelines recommend a healthy diet, smoking cessation and regular exercise alongside pharmacological and non-pharmacological therapies, with appropriate interventions where possible [11,12,33,34]. Diet, smoking cessation and exercise may benefit physical co-morbidities, the metabolic risk factors associated with the use of some pharmacotherapies, and may augment other therapies. However, we could not define diet or exercise 'treatment resistance' in TRBD or MTRBD because of the limited and heterogeneous evidence base.

Mixed-states, psychotic and suicidal symptoms

Even though controversies still exist around the DSM-5 criteria for BD with mixed features, the prevalence of mixed features utilizing these criteria has been reported to be as high as one-third of bipolar patients suffering a depressive episode[35]. Hence, we would suggest that screening for mixed features should be a priority during the evaluation of depressive symptoms. However, the evidence base for the treatment of mixed states is even more limited than for bipolar depression and there are no treatments currently approved by the EMA (European Medicines Agency) or FDA (Food and Drug Administration) for the treatment of bipolar depression with mixed features. In general terms, BAP and NICE as well as other international guidelines such as CANMAT[21] and WFSBP[36] discourage the use of antidepressant treatments in these circumstances. Second-generation antipsychotics, lithium, valproate and lamotrigine have been evaluated for the treatment of depression with mixed features but not all have demonstrated efficacy in bipolar depression and most evidence is extrapolated from unipolar depression. Among them, a recent review of international guidelines reported that lurasidone and ziprasidone may be useful in treating acute mixed depression, valproate may be useful in the prevention of new mixed episodes, and lithium and quetiapine may be useful in preventing affective episodes of all polarities[37]. ECT might also deserve a special consideration when mixed features are present[11].

Suicide and self-harm

Following recommendations of existing guidelines and practice standards, the presence of suicidal symptoms mandates an ongoing risk evaluation to determine the most appropriate setting in which to continue the treatment. In these cases, a written risk assessment, safety plan and coping strategies must be discussed with the patient. Lithium should be considered as one of the first treatment options in these situations given its evidence in preventing suicide in the long-term treatment of people with BD[38]. When psychotic or suicidal symptoms are present and persistent, a re-evaluation of treatment needs to consider the option of more invasive approaches such as ECT[39].

Treatment across the lifespan

The available literature for the treatment for bipolar depression in the perinatal period is generally limited, which is reflected in the limited information provided in treatment guidelines. Most of the recommendations available come from retrospective reports and/or case studies[40,41]. However, in women of childbearing age with a potential mental health condition, general principles should be considered in those fulfilling criteria for TRBD-MTRBD according to existing guidelines. In this group, we would like to highlight that the use of sodium valproate is contraindicated in all females of childbearing potential unless conditions of a pregnancy prevention programme are met as is detailed in the TRBD-MTRBD criteria[42,43].

The panel agreed in the second round of the consensus process that TRBD-MTRBD criteria should only be applied to working age and older adults and should not be applied to children and adolescents. The main reason for this decision was that there is insufficient evidence in these age groups about the response to standard and non-standard treatments for bipolar depression and sometimes uncertainty about the bipolar diagnosis and its potential overlap with the symptoms of other conditions. However, NICE guidelines recommend following a similar pharmacological approach as for adults, stressing the importance of modifying drug treatments according to age and not routinely continuing antipsychotic treatment for longer than 12 weeks[12]. Additionally, these guidelines recommend providing to these

groups, either individual CBT or interpersonal psychotherapy for at least 3 months. Similarly, BAP guidelines recommend following the same pharmacological interventions as in working age adults but also suggest considering and balancing dosing and potential harms. Nonetheless, BAP treatment guidelines emphasize the scarce empirical evidence available to assume a direct extrapolation from adult treatments in these age groups and encourages an integrated treatment approach[11].

There is also a dearth of studies and evidence-based clinical guidelines in older adults. Due to the increased rates of organic comorbidities in this population as well as the reduced hepatic and renal clearance, to avoid adverse effects, special caution should be taken titrating and adjusting doses as is recommended in existing guidelines[11,12,44].

Strengths and limitations

This is the first study in which both TRBD and the new concept of MTRBD criteria were agreed by a diverse but highly qualified group of international experts, including a patient expert, using a systematic Delphi consensus process. Our initial TRBD and MTRBD criteria were also based on two of the most updated and highest quality ones among BD treatment guidelines at the time this project started (November 2017). In comparison to previous definition proposals, our MTRBD consensus criteria were developed with a pragmatic approach considering the whole bipolar depression illness trajectory within the existing evidence-based pharmacological treatments while also taking into account non-pharmacological options. As a result, the criteria are well supported by standardized guidelines and are highly applicable to real-world clinical practice. However, for the same reasons, the criteria may be affected by the limitations and biases of the evidence contained within current guidelines. This also limits the generalization of these criteria to other regions of the world where treatments included in the criteria might not be available. However, although the initial starting criteria were limited to the British guidelines, all panel members could suggest other evidence-based treatment options from different treatment guidelines or studies throughout the consensus process.

Currently, there is very limited evidence to guide the management of TRBD. The evidence that does exist comes from remarkably few randomised controlled trials and also open studies, case series and reports. Furthermore, the lack of a common TRBD definition used in this research limits the generalizability of their results. This is potentially one reason why treatment assumptions based on data extrapolated from the treatment of unipolar depressive episodes continue to exist[3,5,9].

There are some obvious limitations inherent to the Delphi method and how we implemented it. First, the initial set of TRBD and MTRBD criteria were previously developed and discussed in a panel of experts comprising three-quarters of the whole final Delphi participants, leaving the remaining members of the panel with fewer possibilities to modify the initial criteria or raise further points. However, the first round of the Delphi survey included the possibility to add further comments to each item to be considered during subsequent rounds. Secondly, there is also a potential lack of heterogeneity in an expert panel from a specific field which could lead to shared bias in the area. To balance for this, the initial panel was not limited to secondary and tertiary care participants but also included a primary care expert. Additionally, to minimize regional biases and increase the chances of generalizability, the participation in the process of international representatives from leading professional societies and an expert patient could be considered strengths of this study to overcome the above-mentioned issues.

Finally, it is important to emphasise that the proposed TRBD and MTRBD criteria does not imply treatment recommendations that clinicians should follow for therapeutic refractoriness in BD. The rationale for our suggested criteria is to help clinicians, researchers and other stakeholders in determining when non-standards treatment options could be considered. An overview of the current non-standard treatments available for MDD, which might also be extrapolated to bipolar depression, is available in our recently published work about the definition of multiple-therapy-resistant MDD[10].

Conclusion

This consensus criteria should be considered as a complement to clinical expertise, as well as to the resources available and the particular clinical characteristics and preferences of every single person experiencing bipolar depression. We hope the MTRBD criteria will guide clinicians, researchers and stakeholders in deciding when to consider the use of novel pharmacological and non-pharmacological treatments for resistant bipolar depression in the treatment pathway. Among the unresolved diagnostic and therapeutic issues, the utility of different antidepressants classes and psychological interventions for the treatment of bipolar depression remain as pressing questions urgently needing further research.

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D.H.M. developed the initial criteria, acted as a facilitator in the Delphi process, conducted the analyses and wrote the first draft of the manuscript. D.D. participated as an expert of the panel and collaborated in the first draft of the manuscript writing the General health section as well as subsequent reviews of the whole manuscript. J.C.S. participated as an expert of the panel as part of the International society for affective disorders (ISAD) and collaborated in the subsequent reviews of the manuscript. T.S. participated as an expert of the panel as part of the International Society of Bipolar Disorders (ISBD) and collaborated in the subsequent reviews of the manuscript. S.K. participated as an expert of the panel as part of The International College of Neuropsychopharmacology (CINP) and collaborated in the subsequent reviews of the manuscript. E.V. participated as an expert of the panel as part of the European College of Neuropsychopharmacology (ECNP) and collaborated in the subsequent reviews of the manuscript. L.N.Y. participated as an expert of the panel as part of the Canadian Network for Mood and Anxiety Treatments (CANMAT) and collaborated in the subsequent reviews of the manuscript. H.G. participated as an expert of the panel as part of the World Federation of Societies of Biological Psychiatry (WFSBP) and collaborated in the subsequent reviews of the manuscript. M.B. participated as an expert of the panel as part of the Royal Australian and New Zealand College of Psychiatrists (RANZCP) and collaborated in the subsequent reviews of the manuscript. A.C., A.J.C., A.D., J.G., G.G., J.F.H., I.J., K.M., R.H.M.W., R.M., S.N, S.P., J.C.S., D.J.S., P.S.T., S.W. participated as experts of the panel and collaborated in the subsequent reviews of the manuscript. A.H.Y. developed the initial criteria, participated as an expert of the panel, and collaborated in the first draft and subsequent reviews of the manuscript. P.R.A.S. obtained grant funding and developed the initial criteria, chaired the first meeting of the project, supervised the whole project, participated as an expert of the panel, and supervised and edited the first and subsequent drafts of the manuscript.

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