The identification, assessment and management of difficult-to-treat depression: An international consensus statement

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Review article

The identification, assessment and management of difficult-to-treat depression: An international consensus statement

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ABSTRACT

Background: Many depressed patients are not able to achieve or sustain symptom remission despite serial treatment trials – often termed "treatment resistant depression". A broader, perhaps more empathic concept of "difficult-to-treat depression" (DTD) was considered.

Methods: A consensus group discussed the definition, clinical recognition, assessment and management implications of the DTD heuristic.

Results: The group proposed that DTD be defined as "depression that continues to cause significant burden despite usual treatment efforts". All depression management should include a thorough initial assessment. When DTD is recognized, a regular reassessment that employs a multi-dimensional framework to identify addressable barriers to successful treatment (including patient-, illness- and treatment-related factors) is advised, along with specific recommendations for addressing these factors. The emphasis of treatment, in the first instance, shifts from a goal of remission to optimal symptom control, daily psychosocial functional and quality of life, based on a patient-centred approach with shared decision-making to enhance the timely consideration of all treatment options (including pharmacotherapy, psychotherapy, neurostimulation, etc.) to optimize outcomes when sustained remission is elusive.

Limitations: The recommended definition and management of DTD is based largely on expert consensus. While DTD would seem to have clinical utility, its specificity and objectivity may be insufficient to define clinical

populations for regulatory trial purposes, though DTD could define populations for service provision or phase 4 trials.

Conclusions: DTD provides a clinically useful conceptualization that implies a search for and remediation of specific patient-, illness- and treatment obstacles to optimizing outcomes of relevance to patients.

1. Introduction

Depression is associated with a high burden of disease (GBD 2015 DALYs and HALE Collaborators 2016). Fortunately, there are many treatments, including pharmacological, psychological and neurostimulatory options that are associated with remission of symptoms and full restoration of psychosocial function (Malhi and Mann, 2018). If there is a lack of response to, or tolerability of, initial treatment, alternatives can be trialled. In other instances, acute responses may be obtained but subsequent relapses occur even on treatment. Unfortunately, a significant proportion of patients do not achieve sustained remission, despite serial treatments (Rush et al., 2006).

One way of conceptualizing the issue of non-response is as 'treatment-resistant depression' (TRD). TRD is often thought of as describing patients beyond a certain threshold in a course of serial treatment trials. While there is no universally accepted definition, it is often defined as failure to respond to at least two adequate courses of antidepressants (Brown et al., 2019). There are, however, many issues with such definitions (Rush et al., 2019). For example, it is unclear how psychotherapeutic and neurostimulatory treatments should be "counted", or how to account for differential efficacy among treatments, when assessing the degree of TRD (Brown et al., 2019; McAllister-Williams et al., 2018). There is also a semantic issue with the terminology: who or what is "resistant" – the patient or the illness? The phrase also implies a medical model (Rush et al., 2019) and can lead to social and environmental factors that might be barriers to recovery not being considered.

Inherent in all definitions of TRD is the concept that the management of depression involves serial acute treatment trials (Rush et al., 2019). In some health care settings it is clear that many patients receive suboptimal treatment, for example being continued on antidepressants to which they are not responding for long periods, without consideration of alternative or additional pharmacological options (Wiles et al., 2018). In such situations considering further serial options following a treatment algorithm may be extremely valuable (Kraus et al., 2019).

Several novel psychotherapeutic, pharmacological and neurostimulatory options have recently joined the treatment armamentarium, with more in development. This is a boon, but forces the question of when and for whom to choose these newer, often more expensive and/or invasive treatments (Conway et al., 2017; McAllister-Williams et al., 2018; Rush et al., 2019). Since some patients do not response acutely, and others do not sustain their responses despite multiple treatments (Judd et al., 1998; Rush et al., 2006), how long should clinicians go on recommending further acute treatment trials? If all available options and combinations are tried this would take more than a lifetime. Clearly, we should neither undertreat nor overtreat. When is it parsimonious to reconsider the differential diagnosis and case formulation, and to contemplate a different approach – perhaps to address psychosocial stressors or to develop ways to cope with or adjust to some of their symptoms?

Such an approach to the management of patients with depression and sub-optimal outcomes is encapsulated in the concept of "difficult to treat depression" (DTD) (Rush et al., 2019). "DTD" has advantages over "TRD" in that it is recognizes the shared responsibility between clinician and patient to manage the illness and the need to take a long-term and holistic perspective that is individualized to the patient (Rush et al., 2019). Further, DTD conceptualizes the management of depression somewhat differently to that of a TRD model. DTD views depression as treatable ("difficult" but not "impossible") while recognizing that it is

associated with challenges that may require special consideration beyond the standard treatment pathway. In such circumstances the focus is around optimization of symptom control, maximizing function and minimizing treatment burden where remission cannot be obtained (Rush et al., 2019). Such an approach is analogous to the management of chronic somatic illness such as rheumatoid arthritis (Luqmani et al., 2009) or the recovery model as applied, for example, to schizophrenia (Warner, 2009).

The DTD model has previously been described, including identifying key questions for future research (Rush et al., 2019). This paper draws on this DTD model to provide specific clinical guidance regarding the assessment and management of patients with suspected or actual DTD. Ideally guidelines are based on evidence, for example from randomized controlled trials. However, there is little evidence for selecting one treatment over another for depressions that have failed to respond to several prior treatments. Patients can have an almost infinite number of possible past treatment histories when one considers the order of treatments, their dose and duration, other treatments used in combination, and the degree of response and level of tolerability. When this is combined with the various predisposing, precipitating and perpetuating factors related to their depression and its non-response, it is apparent that a nomothetic perspective may not be possible, and an idiographic approach may be more appropriate. This paper therefore seeks to provide clinical guidance for the assessment and management of DTD based on evidence-based principles and expert consensus.

2. Methods

An international group of psychiatrists with expertise in affective disorders, comprising 15 individuals from across Europe, US, Canada and Australia convened to discuss issues relating to DTD, in the context of major depressive disorder (MDD). Objectives were agreed, and a selection of relevant literature on TRD and DTD identified (Brown et al., 2019; Conway et al., 2017; Kraus et al., 2019; Malhi et al., 2019; McAllister-Williams et al., 2018; Rush et al., 2019; Rush and Thase, 2018). A one-day consensus meeting was held in London, UK, on 1st April 2019 (attended by RHMW, CA, PB, KD, PG, AJ, SK, JCS, EV, AP and AJR). This meeting was specifically tasked with producing a consensus paper addressing: the terminology to define DTD; identification and assessment of patients with DTD; and treatment options for DTD. Treatment options were identified based on review of treatment guidelines (British Association of Psychopharmacology [BAP] [Cleare et al., 2015], Canadian Network for Mood and Anxiety Treatments [CANMAT] [Kennedy et al., 2016; Milev et al., 2016; Parikh et al., 2016], World Federation of Societies of Biological Psychiatry [WFSBP] [Bauer et al., 2013]) to ascertain those with evidence for efficacy in populations with a history of treatment failure, as well as review of literature on newer treatment options that have become available since publication of guidelines. A draft manuscript was written and circulated amongst the authors and revised iteratively based on comments received. Consensus was not possible on all issues, but this final document reflects broad agreement on principles to which all authors could subscribe.

3. Concensus

3.1. Terminology and definition of DTD

Depressive episodes may occur as part of major depressive or

bipolar disorders or secondarily to other psychiatric/neurological illness such as schizophrenia, Parkinson's disease or dementia. This consensus paper focuses on MDD, though many of the principles would equally apply to bipolar disoder. However, the differentiation between episodes of depression occurring in different contexts is an important element in the assessment of DTD (see below).

The majority of the consensus group preferred the use of DTD terminology over TRD. TRD was considered by many to lack empathy and suggest a defeatist attitude to treatment, while DTD was perceived as a more open concept that could foster a collaborative approach between physician, patient and carers/family members to overcome difficulties/challenges. Some concerns were expressed about the DTD terminology. The DTD approach is in part based upon that taken with many chronic somatic illnesses, and it was pointed out that "difficult-to-treat diabetes" or "difficult-to-treat rheumatoid arthritis" would probably be unacceptable in other areas of medicine. It was also acknowledged that "difficult" is a somewhat negative word, and that it could be asked who or what is 'difficult' – the patient or the illness. However, it was agreed that TRD was semantically not ideal and the move towards DTD was generally felt to be a significant step in the right direction, emphasising the critical role for the health care practitioner (the person who is finding treatment difficult), and with increasing recognition in the psychiatric community (Rush et al., 2019; Wilhelm, 2019). It was agreed that a fundamental principle of the concept is to convey a positive message – that depression might be "difficult" to treat but not impossible and that strategies to manage it exist, with a goal of improvement in the quality of life of people suffering with DTD.

The consensus group proposed a definition of DTD, or "suspected DTD", and described this as "*depression that continues to cause significant burden despite usual treatment efforts*". The continuing burden may be due to difficulties in: achieving response or remission acutely, sustaining the acute phase response or remission, returning to premorbid levels of function and quality of life, lack of functional restoration despite good symptomatic control, or unacceptable tolerability or non-adherence or rejection of the treatment option. It is patient defined. "Usual treatment efforts" will depend on the health care setting and environment and relate to local treatment guidelines and practice. The key to the definition is that in the circumstances in which the patient's depression is being treated it is perceived as "difficult to treat". The treatment can be of any modality (e.g. psychotherapy, pharmacotherapy, neurostimulation) and the failure of this to reduce the burden of illness might be due to non-response, intolerance, lack of acceptance or contraindication of the treatment. DTD differs from conventional descriptions of TRD that focus exclusively on acute treatment phase symptomatic response (Rush et al., 2019). It is acknowledged that the DTD 'label' will encompass a very heterogenous group of individuals.

The consensus group discussed whether a minimum number of treatment failures should be necessary for a patient to be considered to have DTD. Some evidence suggests that response and remission rates to third or fourth treatment steps are significantly lower than to first or second line treatments (Gaynes et al., 2018; Rush et al., 2006), which supports an argument for TRD being defined after failure to respond to two treatments (Gaynes et al., 2018; Brown et al., 2019). As a result, it was agreed that, while a strictly defined number of treatment failures may not be helpful outside of the research or regulatory settings, suspected DTD should normally be considered after at least two treatment trials. However, some patients with a single treatment failure might be considered to have DTD e.g., where comorbidities and concomitant medications are contraindications for many standard treatment options.

What constitutes "significant burden" in the definition of DTD is subjective and likely to vary between patients. It was generally agreed that burden relates more to impairments in daily function, quality of life, and/or symptoms rather than resting exclusively on depressive symptomatology, though it was argued by some that symptoms are the driver of the burden. Adverse effects of treatment also contribute to the overall burden experienced by the patient.

If depression continues to cause significant burden despite standard first- and second-line treatment efforts, then it may be considered "suspected DTD". Simply adjusting, switching or augmenting the current treatment may lead to a sustained full remission of symptoms with restoration of function. As such, the depression may not be "difficult to treat". At what point suspected DTD becomes DTD is a clinical decision, based on a thorough assessment of the patient and illness characteristics, and treatment history (see Section 3.2). Essentially a patient's depression might be viewed as DTD if the depression continues to cause significant burden despite adequate standard treatment trials and attempts at addressing all easily tractable maintaining issues identified in the assessment and/or there being ongoing less tractable factors helping to maintain a sub-optimal outcome. Whether a clinician views the depression as difficult to treat will depend on their own expertise and the nature of the health care setting in which they are working. This may include the responsiveness of the system and what constraints are placed on the clinician (e.g., limited time for consultations or restrictions on access to treatments). If a clinician feels that a specific factor or factors are leading to the depression being difficult to treat, then this should be a precipitant to seeking advice from a colleague or referring the patient to a more specialist centre if available. This may lead to an adjusted assessment and an altered clinical decision as to whether the patient is or is not suffering from DTD.

DTD and TRD are related, overlapping, concepts but with key differences. Firstly, TRD is defined by a failure to respond to treatment, while DTD is defined by lack of acute phase response/remission or not sustaining the acute response/remission. Secondly, TRD is unidimensional resting solely on depressive symptom outcomes. In addition to symptoms, DTD considers psychosocial functioning and quality of life from a patient perspective. Thirdly, the action implied by the TRD concept is further acute treatment trials, while the consensus group argues that the DTD concept calls for re-evaluation of the depression, a search for treatable biomedical and psychosocial causes of poor outcome, and consideration of a shift in treatment goals from remission to optimal management. The proposed concept and definition of DTD is intended for clinical practice (as described above) rather than research or regulatory affairs, in large part because of its idiographic approach. TRD, as conventionally defined, is likely to remain of relevance for drug approval and commissioning of services since these necessarily require a nomothetic approach.

Just as in TRD (Malhi et al., 2019), this broad umbrella definition of DTD encompasses a large and heterogeneous group of patients, with different characteristics, different treatment histories, and different levels of ongoing burden. Identifying a depression that meets the broad description of suspected DTD is a starting point for a thorough assessment (see next section) to identify a treatment paradigm that will be best place to remedy, or at least reduce, the multiple obstacles that prevent full resolution of the symptomatic and dysfunctional state. It was considered impractical to define clearly delineated subcategories of DTD due to the large number of possible permutations of illness and treatment history variables. Rather, it was agreed that it is more clinically useful to consider specific aspects of DTD at an individual level for patients meeting the broad description of DTD, i.e., taking an idiographic approach.

Several numerical staging models have been proposed for TRD, and these have some predictive utility (Fava, 2003; Fekadu et al., 2018; Kraus et al., 2019; Ruhé et al., 2012). While the patient's treatment history is an important prognostic indicator, other factors are also critical in the understanding and management of DTD. These multi-dimensional factors do not easily lend themselves to a simplistic quantitative staging system. Consequently, the consensus group does not propose staging or numerical scoring to indicate the "degree" of difficulty of treatment for the depression an individual is suffering, at this time. Further research is required to explore the optimal way of objectively assessing DTD. This may involve a combination of assessments

Table 1
Depression prognostic factors.

Factor	Approx. OR	Strength of evidence	References	Comments
Patient-related factors				
Older age		1	De Carlo et al., 2016; Kraus et al., 2019; Perlman et al., 2019	
Family history of affective disorders		1	Kornstein and Schneider, 2001; Perlman et al., 2019	Risk for early onset, chronicity and non-response. Positive response to a medication by a family member may predict a response in the patient and vice versa
Personality traits	3.4	3	Perlman et al., 2019; Takahashi et al., 2013a, 2013b	High neuroticism; other associated personality traits (low extraversion, openness and conscientiousness)
History of abuse		1	Perlman et al., 2019	History of physical, emotional and/or sexual abuse at any stage in life
Any childhood maltreatment	2.5	1	Kraus et al., 2019; Nelson et al., 2017; Perlman et al., 2019; Tunnard et al., 2014	Any form of childhood maltreatment
Multiple childhood maltreatment	4.1	2	Nelson et al., 2017	
Illness-related factors				
Duration of illness	2.0	1	Balestri et al., 2016; De Carlo et al., 2016; Kautzky et al., 2017; Perlman et al., 2019	A long duration of illness
Early onset <18	2.3	1	Balestri et al., 2016; Dudek et al., 2010; Perlman et al., 2019	
Late onset >60		1	Kornstein and Schneider, 2001; Perlman et al., 2019	
Recurrent episodes	1.5	1	Balestri et al., 2016; Dudek et al., 2010; Perlman et al., 2019	Risk compared with single MDE
Severity	1.7	1	Balestri et al., 2016; Kornstein and Schneider, 2001; Perlman et al., 2019; Souery et al., 2007	Greater severity
No. of hospitalizations	1.6	1	De Carlo et al., 2016; Perlman et al., 2019	If more than 1 psychiatric admission
Suicide risk	2.2	1	Balestri et al., 2016; Dold et al., 2018; Dudek et al., 2010; Kautzky et al., 2018; Kornstein and Schneider, 2001; Souery et al., 2007	Current elevated suicidal risk as indicated by ideations
Quality of remission	10.4	2	Dudek et al., 2010; Kornstein and Schneider, 2001	Lack of full remission
Anhedonia		2	McMakin et al., 2012; Perlman et al., 2019; Uher et al., 2012	Persistent anhedonia a risk for chronicity, lack of remission and relapse
Dysthymia	1.5	1	Balestri et al., 2016; Keller et al., 1983; Kraus et al., 2019; McCullough et al., 2000; Rhebergen et al., 2009	Increased risk of relapse and lack of full remission
Comorbid anxiety disorder	2.6	1	Balestri et al., 2016; De Carlo et al., 2016; Dudek et al., 2010; Kautzky et al., 2018; Kornstein and Schneider, 2001; Kraus et al., 2019; Perlman et al., 2019; Souery et al., 2007	
Comorbid panic disorder	3.2	1	Balestri et al., 2016; Dudek et al., 2010; Kautzky et al., 2018; Kornstein and Schneider, 2001; Souery et al., 2007	
Comorbid social phobia	2.1	1	Balestri et al., 2016; Dudek et al., 2010; Kautzky et al., 2018; Kornstein and Schneider, 2001; Souery et al., 2007	
Comorbid personality disorder	1.7	1	Balestri et al., 2016; Dudek et al., 2010; Kornstein and Schneider, 2001; Kraus et al., 2019; Papakostas et al., 2003; Perlman et al., 2019	
Comorbid PTSD		2	Angstman et al., 2016; Hegel et al., 2005	
Comorbid medical illness		1	Fugger et al., 2019; Gardner et al., 2004; Howland, 1993; Kornstein and Schneider, 2001; Kraus et al., 2019; Perlman et al., 2019	Includes endocrine disorders, diabetes (poor glycaemic control), neurological disorders, pancreatic carcinoma, connective tissue disorders, vitamin deficiency, viral infections, obesity, and coronary heart disease
Substance abuse		1	Kornstein and Schneider, 2001; Kraus et al., 2019; Perlman et al., 2019	Bidirectional effects – both exacerbate and maintain the other
Treatment-related factors				
First antidepressant	1.6	1	Balestri et al., 2016; Kautzky et al., 2017; Kraus et al., 2019	Non- or delayed- response to the first antidepressant
Dosage		1	Berlim and Turecki, 2007; Kornstein and Schneider, 2001	Sub-optimal dosing
Duration of treatment		1	Berlim and Turecki, 2007; Kornstein and Schneider, 2001	Early discontinuation
Tolerance/side effects	0.04	2	Balestri et al., 2016; Kornstein and Schneider, 2001; Souery et al., 2007	Through discontinuation or sub-optimal dosing
Non-adherence		2	Kornstein and Schneider, 2001	
Pharmacokinetics		2	Kornstein and Schneider, 2001	Rapid metabolism, malabsorption etc leading to sub-therapeutic serum levels

This table has been compiled based on a selective review of key references exploring risk factors for non-response to treatment and does not represent an exhaustive list of factors that could influence outcomes in DTD. The factors have been grouped according to the three-dimensional model discussed in the paper. Approximate odds ratios (OR) are provided relating to the increased risk associated with the specific risk factor (where available or able to be calculated based on the strongest evidence available for that factor). The strength of the evidence supporting the factor and OR is graded 1–3 with 1 being strong evidence based on meta-analyses and/or high-quality replicated data, 2 being replicated data and 3 being small and/or non-replicated data.
DTD, difficult-to-treat depression; OR, odds ratio; PTSD, post-traumatic stress disorder.

of depressive symptoms, psychosocial function, quality of life, treatment response and course of illness.

3.2. Assessment of DTD or suspected DTD

Diagnosis and (regular) assessment of patients with DTD or suspected DTD is critical for the effective management of the depression (Malhi et al., 2019).

The starting point for assessment is consideration of the differential diagnosis of the presenting major depressive episode (MDE). Is the episode occurring secondary to some organic pathology, for example dementia or a cerebrovascular accident, or in the context of a non-affective psychotic illness? In either case, the depression is very likely to be difficult to treat and the management paradigm for DTD is appropriate alongside management of the primary pathology where possible. In terms of affective disorders, an important differential diagnosis is between MDD and bipolar disorder. There is evidence of higher rates of undiagnosed bipolar disorder in treatment resistant versus non-resistant depression (Perugi et al., 2019; Sharma et al., 2005). This may relate to the observation that bipolar depression does not tend to respond to standard antidepressant medications (McGirr et al., 2016; Pacchiarotti et al., 2013; Sidor and MacQueen, 2012) and alternative treatment strategies are required (Goodwin et al., 2016; Grunze et al., 2018; Yatham et al., 2018).

In terms of diagnostic assessment, the presence of comorbid illness or symptoms is of profound importance in terms of the distinction between suspected and actual DTD. The rule of thumb is that all comorbidities increase the risk of non-response to treatment. A core, but not exhaustive, list of comorbidities to specifically assess for include anxiety (Fava et al., 2008), substance misuse (Howland et al., 2009), psychotic symptoms (Jääskeläinen et al., 2018) and pain (DeVeaugh-Geiss et al., 2010). Assessment for dysthymia is also important. The situation becomes complex when considering "double depression" (the comorbidity of dysthymia and an MDE) and differentiating between residual depressive symptoms following treatment of an MDE versus a return from double depression to a dysthymic state. The goal of full and sustained remission may be more achievable in the former compared with the latter situation (Rhebergen et al., 2009). Other diagnostic issues such as depression secondary to general medical disorders or iatrogenic causes are discussed further below.

Beyond issues of the primary diagnosis, the consensus group proposes a three-dimensional model for the assessment of suspected DTD, with dimensions of patient characteristics, illness characteristics and treatment history. This model is based upon the evidence regarding outcome and prognosis of patients with depression. Table 1 lists some of the many potential factors to consider under each dimension, based on a selective review of some key references exploring risk factors for non-response to treatment. It is important to note that the various factors in the model are not necessarily independent. One strength of the proposed model is that it promotes thinking in terms of patient*-disease*treatment interactions, providing a framework for consideration of multiple factors that could impact treatment outcomes. This contrasts with a treatment-focussed approach, as suggested by TRD terminology, which can lead to continuing along the treatment pathway without pausing to address other factors. Table 1 highlights many factors that could be relevant to DTD overall, as heterogeneous patient group. Only a few factors may be applicable to any particular patient. In addition to factors shown in Table 1, the nature of health care delivery and the degree of patient engagement with their treatment also impacts the outcomes of patients with depression (Rush and Thase, 2018). This is discussed further in Sections 3.3 and 3.4.

3.2.1. Patient characteristics

Numerous patient characteristics are associated with poorer treatment outcomes (see Table 1). Characteristics with the greatest effect include childhood trauma, stressful life events and marital status of being divorced or separated. Some of these (e.g., childhood trauma and family history of mood disorders) are not amenable to direct intervention (though may be important foci for prevention of mental ill health), but they may influence how a patient's depression may be managed. For example, various psychotherapeutic options may be considered when there is a history of past trauma, a history of successful medical treatment of a family member may influence medication choice for the patient. Other factors may be more directly targetable by psychosocial interventions (such as social isolation and lack of employment).

While there is surprisingly relatively little data regarding the role of personality traits on treatment outcome and likelihood of non-response, undoubtedly, they can play an important role in the risk of developing depression and the likelihood of treatment response or relapse. For example, optimistic, but not pessimistic, personality traits influence the risk of becoming depressed while both influence outcome and likelihood of returning to work (Kronström et al., 2011). Dependency traits may also affect help-seeking and outcome to treatment of depression (Rost et al., 2019). Patients' perspectives on their situations are of paramount importance and may be a focus for self-management (see Section 3.4.6).

3.2.2. Illness characteristics

Again, there are numerous illness characteristics that impact on the ease and difficulty of managing depression and influence management strategies (see Table 1). The characteristic associated with by far the highest risk of a poor outcome compared with all others (patient, illness or treatment) is the lack of full remission and presence of residual symptoms after appropriate treatment. This highlights the importance of striving for depressive symptom remission if at all possible. Other than this, comorbidity of any nature is associated with a poorer outcome, as discussed above. While some post-hoc analyses suggest that patients with atypicality respond to monoamine oxidase inhibitors (Pae et al., 2014), the importance of symptom profile to treatment choice is contentious, with some data finding no clear relationship symptom profile and response to different treatments (Arnow et al., 2015; Rush et al., 2008). However, there is clear importance of identification of serious symptoms associated with risk (e.g. suicidality) or the need for additional treatment (e.g. psychosis). Some comorbid mental illnesses, such as obsessive-compulsive disorder, may influence treatment choice (Hoehn-Saric et al., 2000). Similarly, comorbid physical illness, for example a recent myocardial infarction, may influence treatment choice from a safety perspective (Glassman et al., 2002).

3.2.3. Treatment history

The adequacy of past treatment trials, whether psychological, pharmacological or neurostimulatory in nature, should be assessed. Treatment failures throughout the disease course (not just the current episode) are relevant. The types of medication previously used may inform subsequent treatment choices and inform the degree of difficulty that might be expected. For example, has the patient just had multiple trials of selective serotonin reuptake inhibitors (SSRIs) as opposed to a variety of drugs with at least slightly different mechanisms of action? The latter would suggest a greater degree of difficulty of treatment. Failure to respond to particular treatments may be especially relevant when considering degree of difficulty of treatment. For example, five-year longitudinal data suggests that the outcome of patients who have failed to respond to electroconvulsive therapy (ECT) is worse than those that have (Aaronson et al., 2017). Whether the treatment failed to generate an acute response or remission, or failed to sustain an acute benefit, may inform the next treatment strategies. The consensus group identified a change in brand of a drug as a possible reason why relapse

can occur in patients with DTD. Given the importance of remission for maximising functional outcomes and minimising risk of relapse, partial but inadequate response should also be considered a treatment failure. The place of pharmacogenetic testing and therapeutic blood level monitoring is unclear in the work up of patients with DTD (Rush et al., 2019). Medication plasma levels may be helpful in identifying non- or partial-adherence and as pharmacogenetic evidence grows, this may become increasingly relevant to consider (Hicks et al., 2019).

The proposed heuristic, like any other, has limitations. It does not take into account other factors that may affect outcome, including the patient's psychosocial environment and health care setting. Psychotherapies that address interpersonal environmental factors that contribute to DTD should be considered when such factors are deemed important (which would be identified under the 'patient' or 'treatment' element of the model proposed above). The health care setting may well affect outcome and needs to be addressed on a patient by patient basis, considered under the 'treatment' section above.

A thorough assessment is essential to identify any aspect of a patient's depression that if properly addressed could make the depression more manageable. For example, a patient's poor adherence, if identified, may benefit from psychoeducation or formal psychotherapy; a patient with a substance use disorder could be referred to appropriate services to manage that aspect of their illness; a patient in whom investigations reveal hypothyroidism can be treated with thyroxine. These examples illustrate that straightforward interventions can facilitate management of depression that otherwise appeared quite challenging before these factors were identified and addressed. They highlight the importance of identifying potentially modifiable factors, underlying causes, and comorbidities. A summary of investigations recommended as part of the thorough assessment of patients presenting with apparent DTD in primary or specialist care settings is presented in Table 2.

3.3. Goals and principles of the management of DTD

The group identified several goals of treatment and principles as to how to manage DTD (Fig. 1).

The first goal is to '**strive for optimal symptom control**'. While the concept of DTD encompasses the notion that it is not always possible to achieve symptomatic remission (Rush et al., 2019), its potential importance in reducing risk of relapse (Judd et al., 1998; Rush et al., 2006) and optimizing psychosocial functioning (Fried and Nesse, 2014; Kennedy and Paykel, 2004; Romera et al., 2010) means that identifying a patient's depression as difficult to treat does not mean that such a goal should be abandoned. Indeed, this should be the default goal of treatment. However, in patients with DTD it is also important to consider the burden of treatment that can come with increased doses of medication and polypharmacy. This calls for optimization of symptom control balanced against burden of treatment. Even in patients suffering from a chronic episode of depression, there is a degree of waxing and waning of symptoms (Judd et al., 1998). As a result, the second goal is to take steps to '**reduce risks and impact of relapse**'. Whatever the situation with regards the level depressive symptomatology, the most important consideration, and third goal, is '**optimization of psychosocial functioning**' and return to a "meaningful life" (Zimmerman et al., 2006).

The first principle in the management of DTD is identification of treatment goals based upon '**shared decision making**' with the patient. This is a critical step in the broad principle of treatment '**enhance engagement and retention in services**' (Rush and Thase, 2018). What is clear is that a higher concordance between physician and patient expectations from treatment results in better outcomes (Demyttenaere et al., 2015). In addition to the utilization of a broad range of psychological, pharmacological and neurostimulatory treatments, it is important to empower patients through '**supporting self-management strategies**', a key principle aimed at preparing patients, and where appropriate their families or support systems, to effectively

manage DTD over the longer term.

A principle strongly endorsed by the consensus group was the importance of measurement, which has important parallels with the management of chronic somatic illnesses. Clinicians would not dream of treating hypertension and not measuring it. There is evidence that simply '**implementing measurement-based care**' by measuring the severity and different domains of patient's depression can significantly improve outcomes (Guo et al., 2015).

An overarching principle in the model is having '**integrated service pathways**'. There is evidence that, in some health care settings, patients with DTD 'fall between the cracks' between primary and secondary care (Wiles et al., 2018). This may in part relate to symptoms of hopelessness that patients with DTD may experience, leading them to not actively seek the care they need. Finally, it is essential that the management of DTD includes '**frequent re-assessment and consideration of treatment direction**'. Aside from standard clinical reviews, from time to time it is important to review the comprehensive assessment of the patient described above. Have any of the identified factors resolved or become more problematic? Are there new factors to consider? This then leads onto reviewing what direction treatment might progress over the next period of time. Is there a case for one or more acute treatment trials, for example with a newly available option (in other words following a more traditional TRD model of treatment (e.g. Kraus et al., 2019)? Alternatively, is there a case for considering a longer-term treatment such as vagus nerve stimulation (VNS), or a psychotherapeutic approach to address some underlying factor, alongside current medication? The guiding principle here is avoiding both under- and over-treatment.

Table 2

Investigations of patients with DTD: recommendations for primary and specialist care.

Primary care	Specialist care (additionally to primary care)
Blood tests	Blood tests
-Complete blood count	-Magnesium, calcium
-Thyroid function tests (including TSH)	-Vitamin D
-Ferritin	Hormonal status
-Vitamin B$_{12}$	-Further investigation of menopausal markers
-HbA1c	-Mood fluctuation around menstrual cycle
-CRP	Cognitive tests
-Liver function tests (including GGT)	-DSST – provides a quick assessment of multiple cognitive domains
-Menopausal markers (FSH, LH) in women	-MoCA
-Testosterone in men	Symptom questionnaires/scales e.g.
Vital signs	-MADRS, HDRS and/or IDS/QIDS (self-rated or clinician)
-Blood pressure	-MDQ (to screen for bipolar disorder)
-Heart rate	-AUDIT (to screen for alcohol misuse)
-Weight/BMI	-SDS (to assess the key issue of psychosocial function)
Symptom questionnaires/scales	Objective sleep assessment (if indicated to exclude a sleep disorder)
-PHQ-9	-Polysomnography/actigraphy
-GAD-7	Neuroimaging
Cognitive tests	-CT/MRI/SPECT – e.g. to identify organicity such as a dementia
-MMSE (to exclude dementia)	

AUDIT, Alcohol Use Disorders Identification Test; BMI, body mass index; CRP, C-reactive protein; CT, computerized tomography; DSST, digit symbol substitution test; FSH, follicle stimulating hormone; GAD-7, generalized anxiety disorder 7-item scale; GGT, gamma glutamyl transpeptidase; HbA1c, glycated haemoglobin; HDRS, Hamilton Depression Rating Scale; IDS, Inventory of Depressive Symptomatology; LH, luteinizing hormone; MADRS, Montgomery–Åsberg Depression Rating Scale; MDQ, Mood Disorder Questionnaire; MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; PHQ-9, patient health questionnaire (9-items); QIDS, Quick Inventory of Depressive Symptomatology; SPECT, single photon emission computed tomography; SDS, Sheehan Disability Scale; TSH, thyroid stimulating hormone.
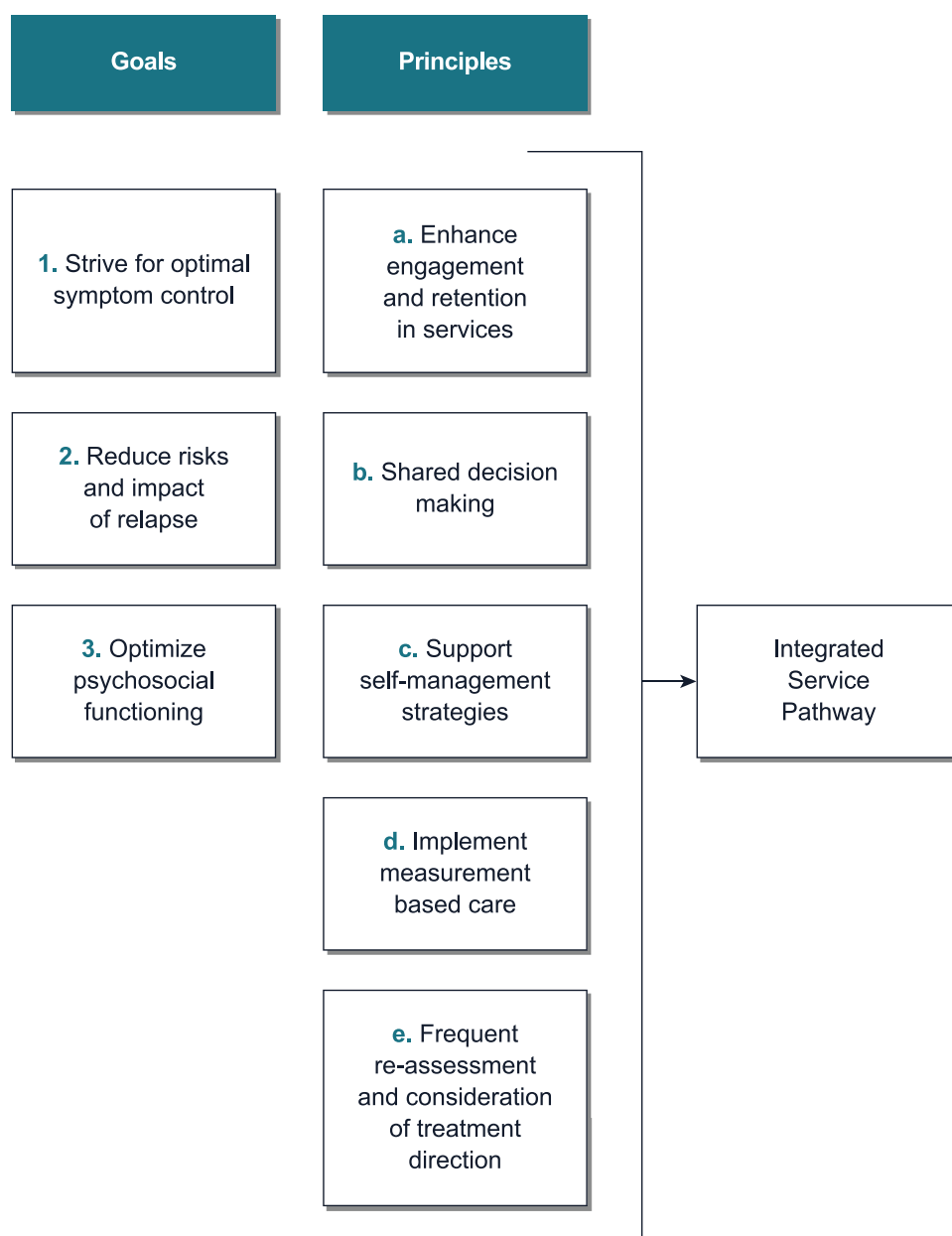
Fig. 1. Goals and principles in the management of DTD.

3.4. Managing DTD: putting principles into practice

Fig. 2 provides an overview of practical approaches that can be employed to help achieve the goals set out in Fig. 1 and put the key principles in the management of DTD into practice.

3.4.1. Achieve optimal symptom control using measurement-based treatment

It is not possible to provide a treatment algorithm, as there is no standard treatment pathway given the considerable variability among patients and their illness and treatment histories, all of which might influence treatment choices alongside patient preference. Some barriers to treatment may remain. For example, access to resources, local treatment approval status or access to treatment centres may limit treatment options.

Patients suffering from chronic DTD that has not responded to multiple treatments frequently feel hopeless, which can negatively impact their engagement with services and adherence with

management strategies. This presents a significant challenge to clinicians. The reader is directed to Rush and Thase (2018) who present a set of comprehensive strategies to enhance engagement and adherence using a patient-centred approach. An element of this is the use of 'shared decision making' around treatment selection and implementation. This is advocated to take account of patients' preferences and promote a positive attitude towards their treatment. Engaging supportive partners (e.g., spouse, parent, etc.) in treatment decisions is desirable too, where possible. Managing patients' expectations is also important, particularly in DTD where restoring function to the best level possible for the individual patient is often a more realistic goal than a full return to pre-morbid functionality or complete remission. Understanding that some level of 'scarring' is likely to remain (just as it would from a physical wound) should help combat pessimism about residual deficits and allow a shift in focus to positive and meaningful improvements in functioning and quality of life.

It is always important to consider a goal of symptomatic remission though this is not always practical, at least in the first instance. In
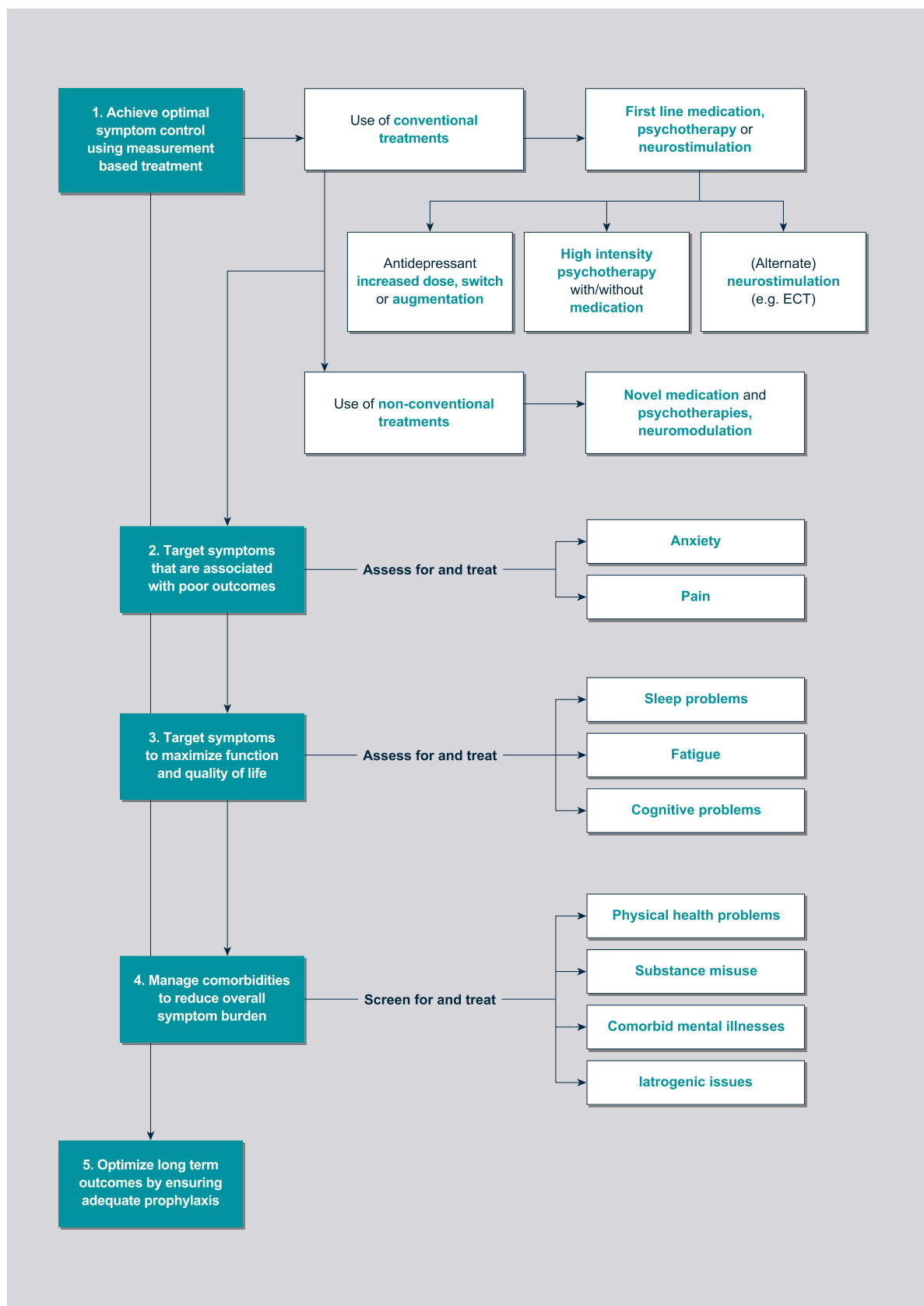
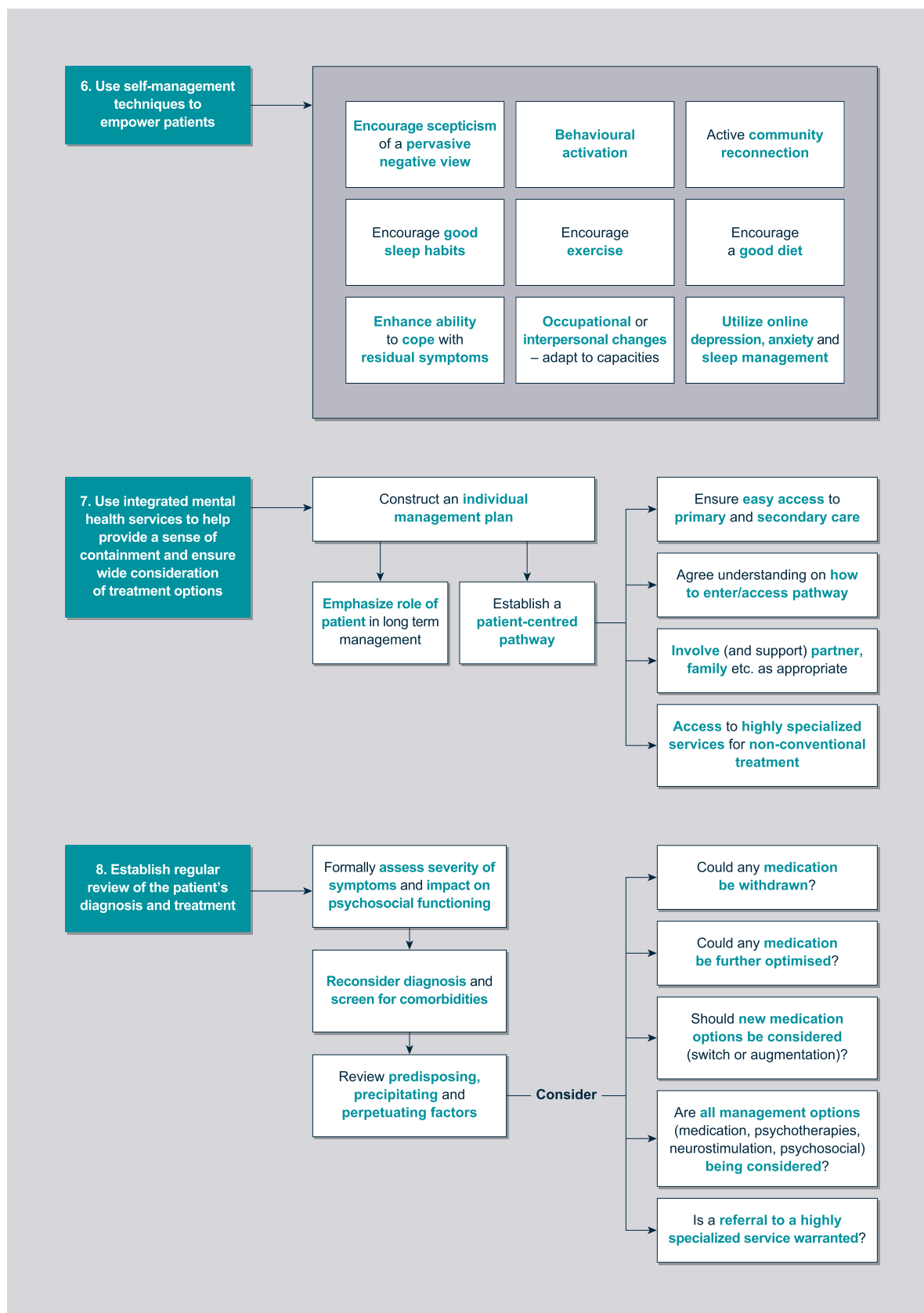**Fig. 2.** Managing DTD: Putting principles into practice.

6. Use self-management techniques to empower patients

Encourage scepticism of a **pervasive negative view**

Behavioural activation

Active **community reconnection**

Encourage **good sleep habits**

Encourage **exercise**

Encourage a **good diet**

Enhance ability to **cope** with **residual symptoms**

Occupational or **interpersonal changes** – adapt to capacities

Utilize online depression, anxiety and **sleep management**

7. Use integrated mental health services to help provide a sense of containment and ensure wide consideration of treatment options

Construct an **individual management plan**

Ensure **easy access** to **primary** and **secondary care**

Agree understanding on **how to enter/access pathway**

Emphasize role of patient in long term management

Establish a **patient-centred pathway**

Involve (and support) **partner, family** etc. as appropriate

Access to **highly specialized services** for **non-conventional treatment**

8. Establish regular review of the patient's diagnosis and treatment

Formally **assess severity of symptoms** and **impact on psychosocial functioning**

Could any **medication be withdrawn**?

Could any **medication be further optimised**?

Reconsider diagnosis and **screen for comorbidities**

Should **new medication options be considered** (switch or augmentation)?

Review **predisposing, precipitating** and **perpetuating factors** — **Consider** —

Are **all management options** (medication, psychotherapies, neurostimulation, psychosocial) **being considered**?

Is a **referral to a highly specialized service warranted**?

Fig. 2. (*continued*)

considering recommendations for managing DTD, the group have used the term 'controlling illness' drawing from the parallel of managing chronic somatic illness. To achieve this, when managing a patient's DTD there may be different phases of treatment. Early on, for example after just two failed antidepressant medication trials, it is likely that a more traditional approach of a series of acute treatment trials of different medications, neurostimulatory techniques, psychotherapies and treatment combinations may be very appropriate. The conceptualization of DTD (Rush et al., 2019) suggests that at some point that a broader perspective, ideally guided by the assessment of the patient and their depression, and the context of the care delivery system, be considered wherein the goal of treatment may be revised from symptom remission to optimal symptom control. This revised treatment focus should not preclude regular reconsideration of further acute treatment trials in the future.

3.4.1.1 Treatment options. An expanding armamentarium of treatment options is available to clinicians. Importantly these include biological options with mechanisms of action going beyond medications with direct action on monoamine transmission (e.g., esketamine [Daly et al., 2019; Popova et al., 2019], transcranial magnetic stimulation [Chen et al., 2017], VNS [Aaronson et al., 2017] and deep brain stimulation [Kisely et al., 2018]). How treatments might be sequenced is well described in the review by Kraus et al. (2019).

A key question is when the clinician should depart from more conventional treatments to ones that are more expensive, more invasive, associated with a higher side effect burden and/or supported by less robust data. This is discussed in the review by McAllister-Williams et al. (2018), which concluded that 'non-standard' interventions are often not considered until later in the treatment pathway than may be appropriate. A full range of treatment options, beyond pharmacotherapy, should be considered. If significant psychosocial stressors are identified it may be appropriate to consider social interventions or psychotherapy to help the patient cope with those stressors, before prescribing other increasingly invasive, expensive or less well tolerated treatments.

Unfortunately, presently, only a limited number of treatment options have evidence of efficacy in patients who would meet the proposed criteria for DTD. Table 3 lists treatment options set out in guidelines for the treatment of MDD/unipolar depression (BAP [Cleare et al., 2015], CANMAT [Kennedy et al., 2016; Milev et al., 2016; Parikh et al., 2016], and WFSBP [Bauer et al., 2013]), with updates to include treatment options that have become available since publication of the guidelines, highlighting evidence for efficacy in patients with a history of treatment failure (based on various definitions of treatment resistance). Our aim is not to make specific treatment recommendations, but rather to provide a comprehensive (though not exhaustive) overview of potential treatment options and summarize the available evidence to facilitate treatment decisions, to be tailored based on patient, illness- and treatment-related factors as described above.

3.4.1.2 Treatment strategies. It is important to consider how the selected treatment(s) will be used in relation to existing treatments (or in relation to each other in the event of further treatment failure or suboptimal response), i.e. augmenting existing treatments versus switching to a new treatment approach. For patients with a partial response (that is evidence of improvement in symptoms but short of a substantial improvement or full remission – using a rating scale, improvement in symptoms that is less than 50% improvement from the baseline value) to their prior treatment, the consensus group concurred that there is clearly a rationale for continuing that treatment, assuming acceptable tolerability, and adding an adjunctive treatment to enhance response. For patients with non-response to prior treatment, there appears to be little difference in outcomes between switch and augmentation strategies (Connolly and Thase, 2011). Factors to consider, when contemplating treatment switching versus

augmentation, include how well the existing treatment is tolerated, risk of withdrawal symptoms on discontinuation, and risk of drug-drug interactions or non-compliance with a more complicated/burdensome medication regimen if new treatment is added to existing treatment (Kennedy et al., 2016; Nelson, 1998; Papakostas, 2009).

For patients with DTD who experience multiple pharmacological treatment failures, it is important to recognize when to explore other options, including neurostimulation. There may be little value in prolonging trial-and-error of different pharmacological treatments, especially those employing similar mechanisms of action; this may simply delay potential treatment success with a different approach. Neurostimulation is not reserved for patients only after all standard pharmacological treatment options have been exhausted. Indeed, it is not a stepwise progression from pharmacotherapy to neurostimulation; pharmacological options may be revisited in case of failure of a non-pharmacological approach. For example, esketamine or intravenous ketamine may be considered before or after failure of ECT. Furthermore, initiating neurostimulatory treatment does not mean switching away from pharmacotherapy altogether. Antidepressant maintenance therapy reduces relapse rates in patients undergoing ECT (Cleare et al., 2015), and VNS is approved as an adjunctive treatment to ongoing antidepressant treatment (Milev et al., 2016). Similarly, psychotherapy may reduce relapse rates when added to medication, and may work when drugs fail and vice versa (Schatzberg et al., 2005).

3.4.1.3 Measuring treatment success. When a new treatment strategy has been initiated, its success may be judged largely from the patient's perspective. However, a quantifiable outcome helps to gauge whether treatment is producing measurable improvement and has been shown to be associated with improved outcomes (Guo et al., 2015). Many scales covering a range of domains are available (Baer and Blais, 2010). Which exact scale is probably of little relevance – rather that scales are used longitudinally to aid clinical decision making while managing the patient's depression. The consensus group recommends the use of both symptom rating scales (e.g., Patient Health Questionnaire [PHQ-9] or Quick Inventory of Depressive Symptomatology [QIDS]) and measures of psychosocial function (e.g., the Sheehan Disability Scale [SDS; Sheehan and Sheehan, 2008] or the Functioning Assessment Short Test [FAST; Rosa et al., 2007]). Alongside clinical assessment, the patient's perspective is crucial to determine whether any improvement in functionality is meaningful, and whether residual deficits have been reduced to a manageable level. The patient therefore shares in the decision making regarding next steps in the treatment pathway, and what point to stop escalating treatment and accept the level of symptom relief/functionality that has been achieved, considering their preferences for what level of invasiveness or side effects they are prepared to accept in pursuit of greater efficacy.

3.4.2. Target symptoms that are associated with poor outcomes

Symptoms such as anxiety and pain are associated with worse outcomes in patients with depression (DeVeaugh-Geiss et al., 2010; Fava et al., 2008). While there has been limited research exploring the impact of targeting such symptoms, there was consensus among the group that targeting them can potentially be a valuable strategy. This might be utilizing antidepressant treatments that have demonstrable efficacy for the associated symptoms (e.g., a SSRI for depression and anxiety [Baldwin et al., 2006] or duloxetine for depression and pain [Detke et al., 2002]). Alternatively, it may be utilizing treatments that can specifically target the associated symptom (e.g., quetiapine or pregabalin for anxiety [Bandelow et al., 2010; Montgomery et al., 2006] or various analgesics for pain). Care needs to exercised that such treatments are not associated with a burden of adverse effects that contribute to a worse quality of life or lead to iatrogenic problems.

3.4.3. Target symptoms to maximize function and quality of life

A key goal in the management of DTD is maximizing functional

Table 3
Evidence-based treatment options for patients with non-response to first line treatments.

Treatment	Use	Evidence base in treatment-resistant patient populations*
Pharmacological		
Aripriprazole[a,b,c] Olanzapine[a,b,c] Quetiapine[a,b,c] Risperidone[a,b,c]	Adjunctive therapy	- Meta-analyses (10–16 trials; N = 1500–3549 patients with TRD [various definitions]) (Nelson and Papakostas, 2009; Papakostas et al., 2007; Spielmans et al., 2013) - Network meta-analysis (18 trials; N = 4422 patients with a current episode of MDD and inadequate response to ≥1 course of conventional antidepressant therapy) found that all agents listed, used at standard doses, showed superior efficacy to placebo, when added to SSRIs/SNRIs (Zhou et al., 2015)
Brexpiprazole[a]	Adjunctive therapy	- Three Phase 3 RCTs in patients with inadequate response to 1–3 antidepressants (n = 379–677; total N = 1559) (Hobart et al., 2018; Thase et al., 2015a, 2015b) - One RCT in patients with inadequate response after 6 weeks' antidepressant treatment (Bauer et al., 2019); this trial did not meet the primary endpoint of increased rate of full remission vs. placebo
Ziprasidone[a]	Adjunctive therapy	- One RCT in patients with MDD whose symptoms persisted after 8 weeks' treatment with escitalopram (n = 139; patients who had failed >3 antidepressant trials of adequate dose and duration prior to enrolment were excluded) (Papakostas et al., 2015)
Lithium[a,b,c]	Adjunctive therapy	- Two meta-analyses (9–10 small trials; n = 7–62); lithium added to various antidepressants including TCAs, second generation antidepressants, SSRIs, tetracyclics, MAOIs (Bauer et al., 2010; Crossley and Bauer, 2007; Nelson et al., 2014)
Thyroid hormones (tri-iodothyronine)[a,b,c]	Adjunct to TCA Adjunct to SSRI	- Meta-analysis (8 studies, including 4 RCTs; n = 292 patients with TRD) (Aronson et al., 1996) - Three small open-label studies (n = 11–25 [Abraham et al., 2006; Agid and Lerer, 2003; Iosifescu et al., 2005]), one single-blind RCT (n = 142 [Nierenberg et al., 2006]), one small double-blind RCT (n = 36 [Joffe et al., 2006]) (reviewed in Cooper-Kazaz and Lerer, 2008)
S-adenosyl-L-methionine (SAMe)[b]	Adjunctive therapy	- One RCT (n = 73 patients with non-response to an SSRI at adequate dose and duration) (Papakostas et al., 2010)
Esketamine (nasal spray)	Adjunct to SSRI/SNRI	- Two Phase 3 RCTs in patients with non-response to ≥2 antidepressants (total N = 932) (Daly et al., 2019; Popova et al., 2019)
Ketamine (i.v. infusion)[a,b]	Experimental; monotherapy or adjunctive therapy	- Systematic review (25 studies including single- and multiple dose, open label studies and double-blind RCTs; N = 399 patients with TRD [Serafini et al., 2014]) and additional more recent studies (e.g., Fava et al., 2018; Phillips et al., 2019; Singh et al., 2016 [n = 41–99]) generally support rapid antidepressant effects - Meta-analysis (9 studies, including 5 specifically in treatment-resistant patients; n = 15–73) supported efficacy of ketamine in treatment-resistant subgroup (Fond et al., 2014) - Data on long-term efficacy and safety are limited (Kennedy et al., 2016)
Ketamine (oral)	Experimental; adjunct to usual treatment	- One proof-of-concept RCT (n = 41 patients with TRD) (Domany et al., 2019) - Case series (n = 22 patients with non-response to ≥3 adequate trials of pharmacological treatments and ≥1 adequate trial of rTMS; open-label treatment); modest efficacy reported (Al Shirawi et al., 2017) - Systematic review (13 studies including patients with unipolar and bipolar depression) (Rosenblat et al., 2019)
Pramipexole[a]	Off-label; adjunctive therapy	- One RCT (n = 60 patients with TRD [continued depression despite treatment with ≥1 prior antidepressant in the current depressive episode]) (Cusin et al., 2013) - Case series (n = 42, including 24 with MDD and 18 with bipolar depression); patients had failure of ≥4 adequate antidepressant trials (including non-response to ECT in 8 patients) (Fawcett et al., 2016)
Buproprion[a,b,c] Buspirone[b,c]	Combination	- One RCT (n = 565 patients with no remission after ~12 weeks citalopram monotherapy) (Trivedi et al., 2006)
Modafinil[a,b]	Adjunctive therapy	- Two RCTs (N = 348 patients with partial response to SSRIs, and persisting fatigue/sleepiness) (Fava et al., 2007)
Tetracyclic medications[b,c] (mirtazapine, mianserin)	Combination therapy (with SSRI or TCA)	Rationale based on complementary MoAs; empirical data from RCTs specifically in TRD populations are limited (Bauer et al., 2013; Cleare et al., 2015) - Principle of combination therapy supported in general MDD population (e.g., RCT in patients with MDD; n = 105 [Blier et al., 2010]) - RCT (n = 480 patients with TRD) did not find convincing evidence of a clinically important benefit for mirtazapine in addition to a SSRI or a SNRI (Kessler et al., 2018 [MIR study])
MAOIs[b,c]	Switch or combination with non-serotonergic medications	Recognized in treatment guidelines as a possible approach following inadequate/non-response to first-line treatment (Bauer et al., 2013; Cleare et al., 2015) although empirical data from RCTs, particularly in TRD populations, is lacking
Psychotherapy		
CBT[a,b]	Adjunct to usual care	- Open label RCT (n = 469 patients with TRD [BDI score ≥14 after 6 weeks' adequate antidepressant treatment]) with CBT administered as adjunct to usual care (Wiles et al., 2013)
CBASP[a,c]	Adjunct to pharmacotherapy	- Uncontrolled pilot study (n = 70 inpatients with chronic depression and history of treatment resistance) (Brakemeier et al., 2015) - Open-label RCT (n = 491 partial- or non-responders to pharmacotherapy) (Kocsis et al., 2009) 　- Augmentation of continued pharmacotherapy with CBASP did not produce significantly different outcomes vs. optimized pharmacotherapy

Table 3 (*continued*)

Treatment	Use	Evidence base in treatment-resistant patient populations*
Neurostimulation		
rTMS[a,b]	Usually used as adjunct to pharmacotherapy	- >30 systematic reviews and meta-analyses; most studies involved patients who with ≥1 or ≥2 failed antidepressant trials (Milev et al., 2016) - Meta-analysis of studies specifically in patients with TRD defined as ≥2 antidepressant treatment failures (18 studies using rTMS in augmentation or switch settings; *n* = 12–74) (Gaynes et al., 2014) - Meta-analysis of studies comparing rTMS vs sham (23 studies) or ECT (6 studies) (*n* = ~15–300; various definitions for TRD) (Health Quality Ontario, 2016) - Statistically significant but small effect size vs. sham (smaller than pre-specified clinically important treatment effect); ECT superior to rTMS in active comparator studies
ECT[ab,c,]	Most effective when used in combination with pharmacotherapy	- Meta-analysis (7 studies; *N* = 585 patients with previous pharmacotherapy failure) (Heijnen et al., 2010) - ECT was effective in TRD patients, although response rate was lower than that for patients without a history of pharmacotherapy failure (48% vs. 65%)

tDCS[a]	Efficacy enhanced when used in combination with pharmacotherapy or psychotherapy	- Four meta-analyses (6–10 trials; *N* = 200–393 patients) (Berlim et al., 2013; Brunoni et al., 2016; Meron et al., 2015; Shiozawa, 2014)
		  - Three meta-analyses found modest superiority over sham with small effect sizes (Brunoni et al., 2016; Meron et al., 2015; Shiozawa et al., 2014), one found no superiority over sham (Berlim et al., 2013)
		  - History of treatment resistance was associated with poorer response to tDCS (Brunoni et al., 2016; Meron et al., 2015)

VNS[a,b,c]	Adjunct to usual treatment	- RCT (*n* = 235 patients with 2–6 treatment failures) (Rush et al., 2005a, 2005b)
		  - Open-label follow up (12 months) suggested growing long-term benefit
		- Open, uncontrolled study (*n* = 74 patients with TRD) (Bajbouj et al., 2010; Schlaepfer et al., 2008)
		  - Outcomes reported at 3, 12 and 24 months, showing increasing efficacy over time
		- Meta-analysis (6 studies [including the studies described above]; *n* = 60–636) supports overall benefits of VNS (adjunct to usual treatment) over usual treatment alone (Berry et al., 2013)
		- 5-year observational study (*n* = 795 patients with ≥4 failed treatments [including ECT in approximately 50% of patients]) showed adjunctive VNS enhanced antidepressant effects compared with treatment as usual in a severely ill patient population (Aaronson et al., 2017)

DBS[a,b]	Experimental	- Two meta-analysis (9–14 small studies; *N* ≥ 190) (Kisely et al., 2018; Zhou et al., 2018)
MST[a]	Experimental	- Two RCTs (*n* = 20–37 patients with TRD) (Fitzgerald et al., 2018; Kayser et al., 2011) - Both studies showed equivalent efficacy of MST to ECT

The list of options included in this table was arrived at via review of the options set out in guidelines for MDD/unipolar depression (CANMAT, BAP, WSFBP), and selecting those with evidence in patient populations with TRD (based primarily on literature cited in the guidelines). Related literature published since the guidelines, and new treatment options that have become available since guidelines were published (2016), e.g. esketamine, have been added.

Treatments listed in: [a]CANMAT guidelines; [b]BAP guidelines; [c]WFSBP guidelines; *Definitions for TRD/degree of treatment resistance noted where available

BAP, British Association of Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Treatments; CBASP, cognitive behavioral analysis system of psychotherapy; CBT, cognitive behavioral therapy; DBS, deep brain stimulation; ECT, electroconvulsive therapy; i.v., intravenous; MAOI; monoamine oxidase inhibitor; MDD, major depressive disorder; MST, magnetic seizure therapy; n, number of patients in trial; N, total number of patients in pooled trials/meta-analysis; RCT, randomized controlled trial; rTMS, repetitive transcranial magnetic stimulation; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; tDCS, transcranial direct current stimulation; TRD, treatment-resistant depression; VNS, vagus nerve stimulation; WFSBP, World Federation of Societies of Biological Psychiatry.

outcomes. Poorer function and quality of life have been shown to be associated with poorer symptom control (IsHak et al., 2015); hence optimizing symptom control as described above is important. However, it is also important to assess which symptoms are identified by patients as being associated with impairment in function and quality of life. A frequently cited residual symptom is insomnia (Conradi et al., 2011). Addressing this either pharmacologically using a hypnotic or sedative medication (e.g. trazodone or mirtazapine), or psychotherapeutically using, for example, cognitive behavioral therapy (CBT) for insomnia (Cunningham and Shapiro, 2018), can lead to significant reductions in distress caused by the symptoms as well as improvement in the depression itself. Daytime fatigue and cognitive impairment are frequently reported symptoms by patients with DTD (Conradi et al., 2011) and these are associated with impairment in functioning (Fried and Nesse, 2014). There are few evidence-based treatments to address these problems (Salagre et al., 2017). However, some evidence supports the use of modafinil augmentation for daytime fatigue (Goss et al., 2013) and modafinil and vortioxetine for cognitive dysfunction (Kaser et al., 2017; Mahableshwarkar et al., 2015; Vieta et al., 2018).

3.4.4. Manage comorbidities to reduce overall symptom burden

The importance of the identification of comorbidities of any type has been emphasized above. There is little evidence to guide the management of DTD in patients with comorbid disorders. However, there was consensus around the principle that in such circumstances the depression cannot be targeted alone, the comorbidity also needs to be actively addressed. This may necessitate referral of the patient to an appropriate specialist.

When considering comorbidities, the consensus group highlighted the importance of assessing and addressing iatrogenic issues, such as depression exacerbated by treatment utilized for a comorbid condition (e.g., beta blockers or calcium channel antagonists for hypertension) or drug-drug interactions either reducing the effectiveness of medications targeting depression (e.g., concurrent administration with carbamazepine) or leading to problematic adverse effects (e.g., the combination of an SSRI for depression and amitriptyline used for pain control).

3.4.5. Optimize long term outcomes by ensuring adequate prophylaxis

Depression is a highly recurrent condition. Many patients with DTD

have a waxing and waning course to their depressions. The harder it is to treat in the acutely, the higher the risk of relapse (Rush et al., 2006). Adequate prophylaxis is important to minimize the likelihood of and severity of symptom exacerbations as well as full-blown relapses for patients who have made a full or partial response to treatment. The burden of adverse effects of ongoing treatment, and importance of maintaining adequate dosing, needs to be addressed in shared decision making around long term treatment. Patients should be counselled that discontinuation of treatment may well be associated with a relapse of illness and hence in such circumstances there needs to be careful monitoring of adherence. It is also important to consider the time scale of effects and response to neurostimulatory treatment. For example, ECT can be highly effective acutely in patients who have not responded to a number of medications (Heijnen et al., 2010), but has a high relapse rate in the months after an acute course (Itagaki et al., 2017; Jelovac et al., 2013). Conversely, antidepressant effects of VNS can take around 6 months to become evident and two years or more to plateau (Aaronson et al., 2017; Berry et al., 2013), but durable responses have been reported (Kumar et al., 2019). It should be noted that rates and duration of response to VNS and ECT have not been compared directly. The effectiveness and durability of any medication, psychosocial therapy or neurostimulatory treatment is likely to be enhanced by a patient reducing their use of recreational drugs and alcohol and learning to manage stressors. The success of longer-term treatments depends substantially on active patient engagement and collaboration in their own treatment, as described below.

3.4.6. Use self-management techniques to empower patients

Hopelessness can lead patients to not only feel that treatment alternatives are unlikely to work and there is no chance that they will ever feel better, but also to feel powerless to do anything about the depression themselves. Encouraging self-management strategies can be very empowering for many patients. There are potentially many elements to this and these need to be tailored to the individual patient (Rush and Thase, 2018). Perhaps most importantly, as described by Rush et al. (2019), is encouraging scepticism of the pervasive hopelessness that patients feel. In addition, encouraging a healthy lifestyle through good diet and sleep habits and exercise can be helpful; the latter have significant antidepressant effects (Morres et al., 2019). Behavioral activation, with activity scheduling and supporting active community reconnection possibly by utilising "social prescribing", can be beneficial for many patients alongside psychological, pharmacological and neurostimulatory treatments, especially for patients unable to engage with more formal psychotherapies. Similarly, enhancing a patient's ability to cope with residual depressive symptoms and making occupational or interpersonal changes to allow them to function as optimally as possible within their capacities, can be vital for patients with DTD of any chronicity. An additional self-management option is the burgeoning number of on-line resources to manage depression, anxiety and sleep problems. Some patients also find great benefit in using on-line symptom rating tools to monitor their progress.

3.4.7. Use integrated mental health services to help provide a sense of containment and ensure wide consideration of treatment options

A key principle in the management of DTD is shared decision making as described above. However, this is only part of a patient-centred approach, which ideally includes having care pathways that are responsive to the needs of the patient. The consensus group recognizes that this is not always the reality in many healthcare systems. Nevertheless, it was felt important to emphasize the importance for patients with DTD to have easy access into primary and secondary care, with clear guidance as to when and how to achieve this. DTD is associated with a vast economic burden to health care systems and wider society. It is likely that improved access to care would decrease this burden and prove to be cost effective. It also helps provide a sense of containment to the patient.

Taking a patient-centred approach also entails considering the patient's partner, family and/or other significant individuals in their life. Living with, and supporting, a patient with DTD can place a great strain on a carer; such individuals need support in their own right. Additionally, close family and friends can be excellent therapeutic allies or saboteurs; it is well worth clinicians trying to ensure they are the former rather than the latter (with the consent of the patient).

Finally, an important principle in the management of DTD is not to give up on finding a treatment strategy that will work for the patient; this could instil feelings of hopelessness in the patient, which is a risk for suicidality. If the treating physician reaches a point where it is not clear what approach to try next, we advocate seeking a second opinion, or consulting a colleague who may have clinical experience with different options (e.g., a physician who has not used neuromodulation themselves may wish to refer a patient to a specialist who has experience in that area).

3.4.8. Establish regular review of the patient's diagnosis and treatment

Following an initial detailed assessment, regular re-assessment is a critical part of long-term patient care. The consensus group recommends that, in addition to routine clinical reviews, patients with DTD should have a formal case review/overview conducted at least annually. The diagnosis of the patient should be reviewed, and the patient should be screened for comorbidities. Central to an annual formal review is assessing symptom control, level of functioning and quality of life using rating scales.

At the review a range of questions should be considered:

- Has there been a meaningful improvement regarding clinical symptoms, cognition or psychosocial functioning, constituting a successful treatment response in relation to the patient's own treatment goals?
- Have there been new episodes of depression since the last review, and if so, can precipitating factors/triggers, including possibly medication changes, be identified?
- Are there any new/current psychosocial stressors that need to be addressed?
- Has there been adherence to treatment and how has this been tolerated?
- How well is the patient engaging in behavioral activation?
- Is there an opportunity to 'clean up' medication and eliminate irrational polypharmacy – discontinuing medications that are not producing positive effects, or medications with redundancy between modes of action?
- Is switch or augmentation of current medication warranted, if response is sub-optimal?
- Are all options being considered (beyond pharmacotherapy)?
- Have any new treatments become available, and are they worth considering for this patient?
- Is a second opinion or referral warranted (e.g., to a centre that offers interventions that are not universally available, such as VNS)?

There should be a clear decision as to the direction of treatment. Any residual symptoms should be addressed where possible. Therapeutic drug monitoring may be useful, if available, to confirm that all medications are reaching therapeutic doses adequate for target engagement. The group do not recommend making unnecessary changes to a treatment that is producing benefits. Dosing should be maintained; whatever dose was needed to achieve acute improvement is the dose needed to maintain the improvement, at least for SSRIs (Fava et al., 1995; Franchini et al., 1998). If a patient is responding to a branded medication, it is recommended continuing that specific product rather than switching to a generic equivalent, as such a switch can be associated with a range of issues including reductions in efficacy, reduced medication adherence and increased health care cost (Blier et al., 2019). Similarly, if a generic product is working, it is preferable to

continue with the same one. In contrast, if a patient has not responded to a generic drug, a switch to the branded medication may be worthwhile, especially if further investigation is necessary before selecting the next therapeutic step. Consideration should be given to whether all avenues have been explored regarding prophylaxis and mitigation of exacerbations of symptoms. This might include a review of personalized relapse signatures, resilience training and stress management, and increasing protective factors and reducing risk factors (Rush and Thase, 2018).

4. Limitations

This consensus document is not based on a formal process, such as using the Delphi technique. The reasons for this are that at the initial meeting of the authors a very broad range of questions were considered for which there was a strong consensus such that a Delphi process was not felt to be warranted. During the iterative process of producing the manuscript little disagreement between authors was identified. Where there was a lack of consensus, this is stated. Otherwise, the iterative process of producing the manuscript was considered complete when all contributors were happy to be identified as authors.

A potential limitation of this consensus in clinical practice is that the recommendations are based on a view of best practice. The health care environment in which an individual clinician may significantly limit what is possible.

5. Conclusions

An inclusive definition of DTD as "depression that continues to cause significant burden despite usual treatment efforts" is proposed, along with principles for the management of DTD. The broad perspective encompassed by DTD has advantages over applying the label 'treatment resistant' and focussing on next steps on the treatment pathway, providing greater scope for addressing other factors that could influence outcomes. Recommended key principles in the management of DTD including a thorough assessment, both initially after identifying a patient as having suspected DTD and at regular intervals during long-term follow up; the use of a three-dimensional framework to facilitate identification of barriers to successful treatment; a patient-centred approach based on shared decision making around all aspects of treatment; and optimizing medication choices and doses for each person as well as selecting and implementing specific psychosocial interventions in order to achieve optimal symptom control, while recognizing that full resolution of symptoms may not be achievable for the individual patient. DTD may provide a more clinically useful conceptualization of patients with TRD as it implies a search for the obstacles that prevent the achievement of a sustained symptom free state with a return to premorbid function. When that ideal goal is not met, the goal of the intervention changes to optimizing symptom control, function and quality of life over the longer term.

Disclosures

Acknowledgments

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.02.023.

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