Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions

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Treatment-resistant depression (TRD) is common and associated with multiple serious public health implications. A consensus definition of TRD with demonstrated predictive utility in terms of clinical decision-making and health outcomes does not currently exist. Instead, a plethora of definitions have been proposed, which vary significantly in their conceptual framework. The absence of a consensus definition hampers precise estimates of the prevalence of TRD, and also belies efforts to identify risk factors, prevention opportunities, and effective interventions. In addition, it results in heterogeneity in clinical practice decision-making, adversely affecting quality of care. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have adopted the most used definition of TRD (i.e., inadequate response to a minimum of two antidepressants despite adequacy of the treatment trial and adherence to treatment). It is currently estimated that at least 30% of persons with depression meet this definition. A significant percentage of persons with TRD are actually pseudo-resistant (e.g., due to inadequacy of treatment trials or non-adherence to treatment). Although multiple sociodemographic, clinical, treatment and contextual factors are known to negatively moderate response in persons with depression, very few factors are regarded as predictive of non-response across multiple modalities of treatment. Intravenous ketamine and intranasal esketamine (co-administered with an antidepressant) are established as efficacious in the management of TRD. Some second-generation antipsychotics (e.g., aripiprazole, brexpiprazole, cariprazine, quetiapine XR) are proven effective as adjunctive treatments to antidepressants in partial responders, but only the olanzapine-fluoxetine combination has been studied in FDA-defined TRD. Repetitive transcranial magnetic stimulation (TMS) is established as effective and FDA-approved for individuals with TRD, with accelerated theta-burst TMS also recently showing efficacy. Electroconvulsive therapy is regarded as an effective acute and maintenance intervention in TRD, with preliminary evidence suggesting non-inferiority to acute intravenous ketamine. Evidence for extending antidepressant trial, medication switching and combining antidepressants is mixed. Manual-based psychotherapies are not established as efficacious on their own in TRD, but offer significant symptomatic relief when added to conventional antidepressants. Digital therapeutics are under study and represent a potential future clinical vista in this population.

Key words: Depression, treatment-resistant depression, difficult-to-treat depression, ketamine, esketamine, second-generation antipsychotics, neurostimulation, electroconvulsive therapy, precision medicine, personalized medicine, patient-reported outcomes

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It is amply documented that major depressive disorder (MDD) is highly prevalent and associated with substantial burden and economic costs[1-5]. According to the World Health Organization (WHO), MDD is the single largest contributor to loss of healthy life, and this contribution has apparently further increased during the COVID-19 pandemic[6-8].

Notwithstanding the evidence supporting the efficacy of conventional antidepressants as well as manual-based psychotherapies and specific neurostimulation modalities, the majority of individuals with MDD are inadequately responsive to first-line treatments. Moreover, a substantial proportion of them fail multiple antidepressant interventions, resulting in what is described as treatment-resistant depression (TRD)[5,9-16].

Although non-response is a common outcome of treatment with multiple conventional antidepressants, a consensus definition of TRD with predictive utility does not currently exist. Instead, a host of definitions have been proposed, differing in their conceptual framework, operational criteria and working assumptions. This heterogeneity of definitions has resulted in a wide range of estimates of the prevalence of TRD[16]. The proportion of people with TRD would be expected to be higher when multidimensional definitions are used, especially those including patient-reported outcomes[17,18].

There are multiple serious public health implications associated with TRD, which provide the impetus for a specific focus on its detection and algorithmic management. First, TRD is common in the general population: based on international epidemiological estimates, it is extrapolated that more than 100 million people globally meet one or more definitions of this condition[19]. In addition, cost of illness studies have documented staggering direct and indirect economic costs associated with MDD, of which

more than half globally are attributable to TRD[20].

The relatively higher cost of illness attributed to TRD is directly due to higher health care utilization and the need for higher intensity treatments[20-23]. Higher indirect costs are also reported in TRD as a consequence of relatively greater impairment in psychosocial function, greater need for disability benefits, higher workplace disability and absenteeism, as well as the negative impact on carers [10,21,24-35]. Moreover, the rate of suicidality, including completed suicide, is disproportionately higher in TRD populations[36].

Additional public health implications of TRD relate to the established association between MDD and multiple common and chronic non-communicable physical diseases[37-39]. For example, it is established that MDD is a risk factor for cardiovascular disease, obesity and type 2 diabetes mellitus, and this is especially apparent in individuals with more severe and/or persistent depressive syndromes, which are over-represented in TRD populations[40,41].

Notwithstanding the foregoing public health implications of TRD, relatively few interventions have been established as efficacious for persons having multiple failed trials with conventional antidepressants. Instead, the emphasis of treatment development in depressive disorders has been on non-TRD populations. In addition, prevention of TRD is not a national health policy priority in any country worldwide, nor is progress in its management a quality outcome measure in any national public health care system.

Currently, more than 90 clinical practice guidelines are available that aim to provide decision support to clinicians caring for adults with mood disorders, originating from 83 countries and published in 27 languages[42]. Most of them have been produced in high-income countries and integrate scientific evidence with expert opinion[42-45]. Major limitations of extant guidelines, as it specifically relates to TRD, are that they do not adopt a consensus definition of this condition, and are not consistent in their selection or sequencing of recommendations.

In addition, extant guidelines vary in how they define an adequate antidepressant regimen and frequently conflate the treatment of TRD with non-TRD populations (i.e., partial responders to antidepressants). For example, second-generation antipsychotics (SGAs), of which most have not been proven to be effective in TRD, are often recommended for this condition in combination with antidepressants, despite their evidentiary base comprised largely of populations defined as partial responders to antidepressants.

Herein, we aim to provide a synthesis of current definitions of TRD, with an emphasis on their limitations, and recommendations for the development of an improved consensus definition; to summarize best estimates of the prevalence of TRD on the basis of current definitions; to review the available evidence on risk factors for TRD; to provide recommendations concerning the detection and management of TRD, based on research evidence when available and opinions from international experts; and to review investigational interventions for TRD. We do not intend to review and/or supplant existing recommendations for depression which is not treatment-resistant[44-48].

DEFINITIONS OF TREATMENT-RESISTANT DEPRESSION

The absence of a consensus and validated definition of TRD is a major limitation from the viewpoints of translational research, treatment development, as well as clinical and policy decision-making. Indeed, the pathway towards more targeted treatments in psychiatry requires a more precise delineation of the phenotype being evaluated[49-51].

The lack of a consensus definition results in the heterogeneity of populations enrolled in clinical trials evaluating new interventions for TRD, greatly limiting the interpretability and generalizability of the results. At a clinical level, the heterogeneity of patient samples contributes to differences in recommendations on the sequencing of treatments for people not responding to conventional first-line antidepressants. Disparity in practice behavior is likely compromising optimal health outcomes amongst those living with and receiving interventions for TRD. Moreover, from a policy perspective, reimbursement and access to treatment for populations with TRD will understandably vary in the absence of a universal definition, further compromising real-world outcomes in these patients.

The definition of TRD adopted by the US Food and Drug Administration (FDA)[52] and the European Medicines Agency (EMA)[53] is failure to respond to two or more antidepressant regimens despite adequate dose and duration and adherence to treatment. These regulatory agencies recognize the lack of precision of this definition and its overlap with definitions of "partial response" to antidepressant treatment[53]. The EMA definition, contrary to the FDA one, explicitly states that the failed antidepressants can be from the same or different mechanistic classes. Limitations of the FDA and EMA definitions are that they do not explicitly operationalize non-response, and do not consider psychotherapeutic interventions, regarded as first-line treatments for mild or moderate depression by most guidelines[48].

Other definitions of TRD have tried to overcome one or more of the above drawbacks (see Table 1). A commonly cited framework for the definition of inadequate response to antidepressants is the Thase and Rush staging model[54,55]. This model does not define TRD categorically, but instead operationalizes and tacitly implies TRD along a continuum of failed antidepressant trials. Stage I is defined by failure of at least one adequate trial of one major class of antidepressants; stage II by failure of at least two adequate trials of at least two distinctly different classes of antidepressants; stage III by stage II resistance plus failure of an adequate trial of a tricyclic antidepressant (TCA); stage IV by stage III resistance plus failure of an adequate trial of a monoamine oxidase inhibitor (MAOI); and stage V by stage IV resistance plus failure of a course of bilateral electroconvulsive therapy (ECT). In the text of the reference paper, it is made clear that the first trial should be a 4-week one with a selective serotonin reuptake inhibitor (SSRI) in moderate dosages[54].

Strengths of the Thase and Rush model are its simplicity, pragmatism, and close proximity to behavior in everyday clinical practice. In addition, this model prioritizes treatments that are better tolerated, which is in line with clinical practice guidelines and treatment algorithms. A first limitation of the model is that "failure" of treatment trials is not operationalized. Furthermore, the model reflects

Table 1 Definitions of treatment-resistant depression (TRD)

	FDA	EMA	Thase & Rush	Maudsley Model	GSRD	DM-TRD	MGH-S
Categorical definition	+	+	–	+	+	+	–
Number of requested treatment failures	2	2	1	1	2	1	1
Operationalization of "failure" of treatment	–	–	–	–	+	–	–
Indication that failed antidepressants must be of different classes	–	–	+	–	+	–	–
Indication of required duration of failed treatments	+	+	+	+	+	+	+
Implication of a hierarchy of efficacy of antidepressants	–	+	+	–	–	–	–
Failure of psychotherapies included	–	–	–	–	–	+	–
Failure of ECT included	–	–	+	+	–	+	+
Failure of augmentation/combination treatments included	–	–	–	+	–	+	+
Patient-reported outcomes considered	–	–	–	–	–	–	–
Baseline severity included	–	–	–	+	+	+	–
Duration of current episode included	–	–	–	+	+	+	–
Baseline psychosocial impairment included	–	–	–	–	–	+	–
Presence of comorbidities included	–	–	–	–	–	+	+
Comorbid anxiety symptoms included	–	–	–	–	–	+	+
Comorbid personality disorder included	–	–	–	–	–	+	+
Quality of life included	–	–	–	–	–	–	–
History of psychosocial stressors included	–	–	–	–	–	+	–
History of childhood adversity included	–	–	–	–	–	–	–

FDA – US Food and Drug Administration, EMA – European Medicines Agency, GSRD – European Group for the Study of Resistant Depression, DM-TRD – Dutch Measure for quantification of Treatment Resistant Depression, MGH-S – Massachusetts General Hospital Staging, ECT – electroconvulsive therapy

some non-validated assumptions: for instance that, in a patient initially not responding to an SSRI, a non-classmate antidepressant is more likely to be efficacious as a next-step treatment strategy; or that MAOI exposure should be limited to populations with treatment resistance. In addition, there is no explicit consideration of depression features such as duration and severity of the index episode, and no mention of psychotherapeutic interventions. Finally, although augmentation or combination strategies are mentioned in the text of the reference paper[54], they are not explicitly included in the staging model.

The Maudsley Staging Model (MSM) was developed to improve upon the limitations of the Thase and Rush model[56]. It defines treatment resistance as failure to attain significant level of improvement (i.e., clinical remission) from an accurately diagnosed depressive episode following treatment with an antidepressant given at an adequate dose for a minimum of six weeks. Three dimensions of resistance are included: treatment failure, duration of the depressive episode, and severity of depression[56].

A maximum of seven points can be assigned for the treatment dimension: one point for failure on 1-2 medications; two points for failure on 3-4 medications; three points for failure on 5-6 medications; four points for failure on 7-10 medications; five points for failure on more than 10 medications. One further point is assigned if augmentation treatment has failed, and one further point if ECT has not been effective. A maximum of three points can be assigned for the duration of the depressive episode: one if the episode is acute (up to 12 months); two if it is subacute (from 13 to 24 months); three if it is chronic (more than 24 months). A maximum of five points can be assigned for the severity of depression: one if it is subsyndromal; two if it is mild; three if it is moderate; four if it is severe without psychosis; and five if it is severe with psychosis. The overall staging of TRD is defined as mild (total score between 3 and 6), moderate (total score between 7 and 10) or severe (total score between 11 and 15).

Thus, in the MSM, resistance is assessed on the basis not only of treatment but also of illness variables, which has been reported to be useful in predicting short- and intermediate-term outcomes in TRD populations[57,58]. Overall, the threshold for the definition of TRD is low, requiring failure of just one adequate treatment. Failure of treatment is not operationalized, although a discussion of the complexity of defining clinical remission is provided in the text of the main paper presenting the model[56]. The assignment of scorings is in some respects arbitrary: for instance, a differential weighting is assigned to populations who fail at least five vs. less than five treatments, in the absence of validation. Failure of manual-based psychotherapies is not considered.

The European Group for the Study of Resistant Depression (GSRD)[14] separately defined non-response (failure to respond to one trial of 6-8 week duration of any antidepressant treatment); TRD (failure to respond to two or more adequate trials of different classes of antidepressants, with five different levels

of resistance depending on the overall duration of trials); and chronic resistant depression (failure to respond to several antidepressant trials, including augmentation strategies, of the overall duration of at least 12 months) [14].

Strengths of the GSRD staging method are the explicit definition of treatment non-response as a reduction of less than 50% in the total score on the Hamilton Depression Rating Scale (HAM-D)[59] or the Montgomery-Åsberg Depression Rating Scale (MADRS)[60], and the lack of any implicit hierarchy of efficacy of antidepressants. Limitations are the lack of validation of any of the provided time-based subcategories, including the definition of chronic depression based on a duration of at least one year, which is considerably briefer than what is generally accepted (i.e., longer than two years).

The Dutch Measure for quantification of Treatment Resistant Depression Model (DM-TRD) was developed to improve upon the point system proposed in the MSM[61]. To the variables considered in that system, this model adds functional impairment (with a score from 0, no impairment, to 3, severe impairment); comorbid anxiety symptoms (with a score from 0, not present, to 1, fulfilling criteria for at least one DSM-IV anxiety disorder); comorbid personality disorder (with a score from 0, not present, to 1, present based on formal interview); psychosocial stressors (with a score of 0, no psychosocial stressor, or 1, at least one psychosocial stressor); several categories of augmentation/combination regimens (with a score from 0, not used, to 3, five or six medications); use of psychotherapy (with a score from 0, not used, to 2, at least two empirically supported psychotherapies); and intensified treatment (with a score from 0, not used, to 2, inpatient treatment). The maximum total score becomes 27.

This model is the most comprehensive in terms of variables included, although physical comorbidities and childhood adversities are not considered. As in the MSM, the threshold for the definition of TRD is low, requiring failure of just one adequate treatment, and non-response is not operationalized. The predictive validity of the model has been supported to some extent[61].

The Massachusetts General Hospital Staging Model (MGH-S) definition of TRD integrates the number of failed trials with the intensity/optimization of each trial, without assumptions on the hierarchy of antidepressant classes[62]. One point is assigned for non-response to each adequate trial of a marketed antidepressant (duration of at least six weeks and adequate dosage). Half a point is assigned for each trial based on optimization of dose, optimization of duration, or an augmentation/combination strategy. Three points are assigned for non- response to ECT.

Limitations of the MGH-S include the lack of operationalization of "failure" of trials; the arbitrary scores attributed to treatments; the fact that optimization of dose or duration of treatment is weighted equally as augmentation/combination strategies (which is not empirically supported); and the assignment of one point for each failed antidepressant, which may generate a very high total score[63].

None of the extant TRD definitions are universally accepted and/or implemented at point-of-care in clinical practice[11,32,64-68]. In addition, no existing TRD definition is supported by an external validator and/or biomarker. Most TRD definitions do not explicitly consider failure of manual-based psychotherapies in their hierarchical characterization of treatment resistance. As psychotherapeutic interventions are recommended as first-line treatments in persons presenting with depression of mild or moderate severity, any working definition of TRD with clinical utility will need to explicitly include non-response to these interventions.

Also, common across most definitions of TRD is the absence of a quantifiable and consensus endpoint defining response versus non-response to antidepressants. An additional limitation is that the definition of outcome is based on a clinician assessment, while patient-reported outcomes are not considered. Indeed, even amongst patients classified as "responders", many continue to manifest debilitating residual symptoms[69,70]. This was highlighted in the STAR*D trial, in which it was observed that only 10% of persons "in remission" were fully asymptomatic[71]. If, for example, a person is classified as "responder" to treatment but continues to experience cognitive deficits that are impairing, it would be incorrect to consider this an adequate antidepressant response[72].

None of the extant definitions of TRD includes reference to quality of life. This is a major limitation, given the importance assigned to this variable by persons with lived experience[73]. The predictive utility of quality of life as a critical outcome measure when defining TRD is underscored by the observation that persons remitting with antidepressants who continue to report decreased quality of life are at greater risk of relapse and recurrence[74,75].

Further drawbacks of existing TRD definitions are that they fail to take into consideration the social, economic, anamnestic (e.g., adverse childhood experiences) and interpersonal factors which, alone or in combinations, are known to moderate antidepressant response[1,44,47,71,75-81]. Furthermore, an unintended consequence of a TRD framework that is hierarchical is encouraging multiple unproven treatment strategies, with polypharmacy and the possibility of associated safety and tolerability concerns[70,75].

Moreover, results of a recent analysis in the WHO World Mental Health Surveys underscores that persistence with next-step treatments is uncommon in persons with MDD[82]. Also, in those who do switch to next-step treatments, a considerable treatment delay (i.e., 6-9 months) elapses before switching occurs[82,83].

An example of a patient-centric framework describing persons with multiple antidepressant failures is the construct of difficult-to-treat depression (DTD)[84]. This construct relies on a biopsychosocial approach when considering causal, perpetuating and treatment factors of poor outcomes in depression[70]. The therapeutic emphasis in DTD pivots away from symptomatic remission towards symptomatic control, functional recovery and quality of life improvement as part of chronic disease management[70].

For several patients, despite non-remission status, more modest improvement in overall depressive symptom severity may result in significant self-assessed improvement in well-being[85-87]. For example, an approximate 35% improvement from baseline in total MADRS score may be associated with significant improvement of quality of life in persons with TRD[87]. These data support the notion that more modest improvements in symptom severity in persons with TRD may be clinically meaningful, and invite the need for multidimensional definitions that are not solely dependent on threshold symptomatic improvement[86,88,89].

Surveys of persons with lived depression experience have highlighted the importance of dimensional symptomatic outcomes in addition to categorical ones[90,91]. For example, alleviation of emotional blunting, anhedonia, anxiety and rumination are often prioritized by persons living with depression over full symptomatic remission[92]. Shared-decision making, patient-centered care focusing on specific symptoms of concern, and integrating treatment modalities become paramount in DTD, in keeping with the guiding principles of chronic disease management[84,93-96]. Although DTD is not currently recognized by regulators as a pathway for treatment approval and marketing authorization, it more closely approximates real-world presentations and outcomes among persons with TRD, and could serve as a clinical heuristic or even a framework informing the further characterization of TRD.

Overall, there is a confluence of research, clinical, policy, and public health reasons to have a validated and universal TRD definition. Existing definitions would be best characterized as frameworks that vary in their constituent variables and working assumptions. The existing TRD frameworks reviewed herein have not provided any substantive insight into the pathogenesis, treatment discovery and development, or clinical care of persons with TRD.

Moreover, there is no compelling evidence that any of the foregoing TRD frameworks have been implemented at large scale by the clinical or research community. A consensus definition of TRD at the very least will need to provide a quantifiable endpoint defining response, integrate manual-based psychotherapies, empirically validate assumptions surrounding differential treatment weighting, and integrate multiple factors known to influence antidepressant response. A TRD definition that is consistent across disparate clinical care ecosystems, and fulfills both research and clinical needs, is badly needed.

PREVALENCE OF TREATMENT-RESISTANT DEPRESSION

Differences in the definition of TRD have resulted in highly variable estimates of its prevalence rate[99]. TRD is often stated to affect approximately 30% of persons receiving antidepressant treatment in research settings, while its prevalence in real world practice is estimated to range between 6 and 55% [32,98-101].

Most individuals with MDD access mental health care initially through the primary care system, where measurement-based care is rarely implemented[102-104]. A tentative estimate of the prevalence of TRD in primary care can be made only indirectly by using a "depression treatment cascade" approach[105]. Approximately 10-15% of patients in primary care present with clinically significant depressive symptoms, and only about half of these cases are diagnosed, of which an estimated 25% are prescribed an antidepressant[106]. Replicated evidence indicates that, of those prescribed antidepressants, the majority discontinue treatment prematurely. Hence, only about 5-7% of persons with depression treated in primary care settings would be expected to achieve remission[106]. The foregoing cascade approach – which integrates aspects of misdiagnosis, non-adherence, inadequate treatment trials, as well as implementation gaps – underscores the high prevalence of poor outcomes of depression in primary care, of which a significant percentage would be expected to meet criteria for TRD[10,30,64,71,107,108].

A more precise estimate of the prevalence of TRD can be done by referring to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, a National Institute of Mental Health (NIMH)-sponsored multisite study (18 primary care and 23 psychiatric care settings) carried out in the US[33]. All eligible subjects enrolled in the STAR*D trial initiated treatment with citalopram. After a 12-week trial (level 1 treatment), those persons not in remission were randomly assigned to one of seven switch/combination approaches (level 2). Non-response to a switch/combination level 2 treatment resulted in randomization to further treatments (levels 3 and 4). The FDA and EMA definitions of TRD would align with failure to level 1 and 2 treatments in the STAR*D trial. On this basis, it can be estimated that approximately 55% of persons with MDD would meet the FDA/EMA criteria for TRD (i.e., inadequate response to two or more antidepressants despite adequate treatment intensity and duration)[33].

In summary, while it is often stated that TRD is affecting approximately 30% of persons receiving antidepressant treatment, a more stringent and multidimensional definition of this condition emphasizing symptomatic remission increases this estimate to about 55%.

RISK FACTORS FOR TREATMENT-RESISTANT DEPRESSION

Many factors have been identified as being associated with reduced antidepressant response, but relatively few are established as risk factors specifically for TRD. In addition, most factors identified as negatively affecting antidepressant outcomes are reported in small studies and are described with a particular antidepressant intervention. Amongst the relatively few studies that have sought to identify factors associated with TRD, most are limited by the inconsistent definition of this condition, and primarily evaluate outcomes with monoamine-based antidepressants.

Herein, we endeavour to identify factors that are associated with TRD. As most studies have evaluated factors associated with reduced response to conventional antidepressants rather than TRD, we provide clarity and attempt to separate these two aspects.

Sociodemographic factors

It is established that older persons more frequently fail multiple monoamine-based antidepressant treatments, which may be taken as evidence that TRD is more common in this subpopulation[109,110]. However, there is no evidence of an attenuated response in older adults with depression receiving manual-based psychotherapeutic treatments[111], and the efficacy of ECT does not seem to be reduced as a function of age[112]. It is also reported that repetitive transcranial magnetic stimulation (rTMS) may have similar (or potentially greater with increased pulse dose) efficacy in older adults with MDD[113].

It is not established whether female sex is a risk factor for TRD[114]. Whether depression during reproductive life events (e.g., peripartum onset depression) is more likely to be treatment-resistant is also not sufficiently established[115]. It is, however, well known

that females are affected by depression at twice the rate of males, and are more likely to be prescribed antidepressants[116]. Consequently, females would be expected to represent the majority within a TRD population, although it remains uncertain whether their relative risk is higher.

Socioeconomic position is a risk factor for TRD in persons receiving monoamine-based antidepressants. For example, in the STAR*D trial, persons meeting level 2 criteria (i.e., inadequate response to two sequential antidepressant regimens) were more likely to report lower income and dependence on the public health system[117]. In addition, persons of lower educational attainment or unemployed are found to be more often resistant to multiple sequential antidepressant strategies[17,118].

Future research should evaluate whether racial and/or ethnic factors contribute to the occurrence of TRD, and also endeavour to explore whether sexual orientation and/or gender identity, marital status, interpersonal connectedness, and measures of loneliness are risk factors for TRD.

Adverse experiences and trauma

It is well established that childhood maltreatment is associated with greater severity of depression, earlier age at onset, cognitive dysfunction, presence of psychotic symptoms, and physical/psychiatric comorbidities, each of which is also associated with attenuated response to antidepressants and manual-based psychological interventions[119-123].

There are also studies providing evidence that a reported history of childhood emotional abuse is associated with recurrent depression, persistent depression, as well as treatment resistance to antidepressants[124]. The international Study to Predict Optimized Treatment for Depression (iSPOT-D) reported that, amongst adults with MDD and a history of trauma between the ages of 4 and 7 years, only 15.9% achieved remission after 8 weeks of treatment with escitalopram, sertraline or venlafaxine, compared to 84.1% in individuals with no history of childhood trauma[125].

The attenuated response to antidepressants in persons with a history of childhood maltreatment may not, however, occur with all antidepressants. For example, preliminary evidence suggests that response to vortioxetine or ketamine treatment in depression is not reduced in persons with trauma, suggesting different outcomes as a function of the putative mechanism of action of medications[126,127].

More in general, life stress events have been directly associated with a poorer response to commonly prescribed antidepressants, as well as with a greater occurrence of suicidal behavior and comorbidities and a greater severity of symptoms, which are variables that could mediate the association with an attenuated response to antidepressants and possibly to TRD[128].

Clinical factors

Greater baseline severity is a highly replicated risk factor for TRD, and is indeed included in some frameworks as a variable in the hierarchical characterization of the condition. Illness duration is also highly associated with TRD, with replicated evidence indicating that the length of a depressive episode is inversely proportional to the probability of treatment response[129].

Evidence also suggests that some phenomenological characteristics of depression may be associated with treatment resistance. Psychotic symptoms affect approximately 20% of adults with MDD and are highly associated with TRD[130]. Mixed features are reported to be present in approximately 25% of persons with MDD and are associated with attenuated antidepressant response, although it remains to be determined whether they are a risk factor specifically for TRD[47,131].

Anhedonia is a core component of depression endorsed by 35-75% of patients, and may be a risk factor for TRD in persons whose treatment history is delimited to SSRIs [132,133]. Cognitive deficits in MDD are prevalent, persistent, and often progressively increase as a function of illness severity and duration; they are associated with attenuated response to select antidepressants, and may represent a risk factor for TRD[72,134-136].

Anxiety symptoms are frequently reported in TRD populations, and their presence in MDD is associated with a more severe illness presentation, lower probability of remission, comorbidities and suicidality[137-140]. Results from the STAR*D trial indicate that persons presenting with anxious depression exhibit attenuated antidepressant response and are more likely to develop TRD[141]. The GSRD study also reported that anxiety disorders were over-represented in persons meeting criteria for TRD[142].

It is well established that TRD populations have a higher rate of psychiatric and physical comorbidities as compared to non-TRD populations[143]. In addition, TRD is a risk factor for incident physical comorbidities, such as cardiovascular disease, type 2 diabetes mellitus, osteoporosis, and metabolic syndrome[40,144-146]. Evidence indicates that the foregoing physical diseases are in their turn risk factors for TRD[145,147-152].

DETECTION OF TREATMENT-RESISTANT DEPRESSION

The assessment of an individual with MDD towards personalization of treatment selection and sequencing has been previously reviewed in this journal[13]. Herein, we specifically focus on the assessment process aimed to confirm that TRD is present, and to rule out the possibility of pseudo-resistance.

Reviewed herein are the most common modifiable contributors to pseudo-resistance, including inaccuracy of the MDD diagnosis, inadequacy of current and past treatment trials, inaccurate assessment of response, and individual differences in the metabolism of antidepressants[153,154].

Accurate diagnosis of MDD

Inaccuracy of the MDD diagnosis is a common reason for pseudo-resistance. It is estimated that approximately half of individuals with MDD are not correctly diagnosed[155]. A not uncommon scenario in clinical practice is the depressed patient presenting with resistance to multiple sequential antidepressants whose correct diagnosis should be bipolar disorder instead of MDD[156].

For most individuals with bipolar disorder, depression is the index presentation, which warrants reconsideration of the MDD diagnosis in any person presenting with TRD. Indeed, it is reported that individuals prescribed multiple failed antidepressant trials

(i.e., TRD) have a much greater likelihood of an underlying diagnosis of bipolar disorder as compared to persons prescribed a single antidepressant trial[157]. Furthermore, it is reported that the transition from a diagnosis of MDD to one of bipolar disorder occurs at a rate of approximately 1-3% per year, indicating that diagnostic assessment must be reconsidered in all TRD presentations[130,158,159].

Multiple screening tools for bipolar disorder have been validated, including the Rapid Mood Screener (RMS)[160], the Patient Mania Questionnaire (PMQ)[161], the Mood Disorder Questionnaire (MDQ)[162], and the Hypomania Checklist-32[163]. Although screening tools are not sufficient to diagnose bipolar disorder, they can be used routinely in clinical practice and, if positive, warrant a more comprehensive assessment of the possible presence of bipolar disorder.

In addition to screening for bipolar disorder, relevant comorbid conditions should be diagnosed and managed if present. They include substance and alcohol use disorders, anxiety disorders, personality disorders, and some physical diseases such as hypothyroidism.

Determining the adequacy of treatment trials

The adequacy of an antidepressant treatment refers to the choice of medication, its dose, the duration of treatment, and the patient's adherence. A comprehensive and precise characterization of current and past medication regimens is required in order to confirm the presence of TRD, and can be captured by several instruments.

The Antidepressant Treatment History Form (ATHF) is a data capture instrument suitable for implementation at point-of-care. It was originally developed in studies of ECT and has subsequently undergone a broader clinical and research application[164]. It has explicit criteria for evaluating response to pharmacological and neurostimulation treatments, and is also available in a shorter version (the ATHF-Short Form, ATHF-SF)[165]. Other instruments that capture and record current and prior antidepressant regimens are the self-rated Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ)[166] and the Maudsley Treatment Inventory[56].

First of all, the appropriateness of the antidepressant regimen needs to be confirmed. It is well established that a knowledge-implementation gap exists between what are proven treatment strategies in MDD and what are actually implemented[42]. The adequacy of the dose of the medication has then to be considered: dosing recommendations are established for all approved antidepressants and are described in their respective product monographs.

The adequate duration of an antidepressant trial is generally considered to be 4-6 weeks at optimal dosing, although 60% of persons who achieved remission in the STAR*D trial with level 1 treatment did so after week 6 of treatment, indicating that a subpopulation of adults with MDD may require longer treatment trials[167,168].

Adherence to treatment has also to be assessed. A replicated observation is the high rate of non-adherence to antidepressants in persons with MDD. Persons with less than 80% adherence to antidepressant regimen recommendations are commonly defined as non-adherent[169]. Using this definition, about 30-50% of persons prescribed with antidepressants are non-adherent in acute phase treatment[169]. Assessing adherence to therapy includes pill counts and patient self-report. Digital sensor systems have been used in academic studies to document adherence, but are not readily available for clinical implementation.

Assessing outcome of previous antidepressant trials

Defining TRD implies quantification of therapeutic outcome with previous antidepressant treatments. However, as already stated, most definitions of TRD do not provide a quantifiable and consensus endpoint defining response versus non-response to antidepressants. An exception is the GSRD staging method[14], which explicitly defines treatment non-response as a reduction of less than 50% in the total score on the HAM-D or the MADRS. This may represent a useful reference in ordinary clinical practice.

However, it is noticed that, in some patients, a reduction of total MADRS score of about 35% may be associated with significant improvement of quality of life[87], supporting the need for multidimensional definitions that are not solely dependent on threshold symptomatic improvement[86,88,89]. The use of measures such as the World Health Organization-Five Well-Being Index (WHO-5) may be suggested for this purpose[170]. More in general, therapeutic endpoints that integrate patient-reported outcomes along with symptomatic measures may provide a more precise characterization of response to treatment[82].

Although "failure" of one or more antidepressant trials is an integral part of all definitions of TRD, it must be acknowledged that there is no consensus in the field about how this "failure" should be defined and ascertained. Overcoming this major limitation is an obvious priority for future research on TRD.

Pharmacogenomic testing and evaluating antidepressant blood levels

Evidence indicates that a subset of MDD patients presenting with TRD may exhibit a failed antidepressant response as a consequence of a suboptimal bioavailability of the administered antidepressant, due to rapid metabolizer status[171-174]. Available evidence indicates that allelic variations of cytochromes P450-2D6 (CYP2D6) and P450-2C19 (CYP2C19) are especially associated with antidepressant outcome. In particular, CYP2D6 phenotypes may be important in some patients taking TCAs and venlafaxine, and CYP2C19 phenotypes in some individuals receiving TCAs, citalopram, escitalopram and sertraline[171]. Although pharmacogenetic testing cannot be recommended as a routine assessment in TRD, some preliminary evidence does suggest that, in select circumstances, it may be warranted.

Furthermore, blood levels should be monitored in non-responding persons receiving some TCAs (i.e., imipramine, desipramine, nortriptyline), as therapeutic levels/windows have been established for these agents[175-177].

MANAGEMENT OF TREATMENT-RESISTANT DEPRESSION

Herein, we review tactics which can be considered for managing TRD once the presence of this condition is confirmed. These

tactics include extending the current antidepressant trial, switching antidepressants, combining antidepressants, use of esketamine/ketamine, and neurostimulation (see Table 2).

Although manual-based psychotherapies are not proven to be efficacious as a standalone intervention in TRD, their efficacy in combination with antidepressants is briefly reviewed. Also, we briefly review the evidence for other strategies (e.g., lithium, thyroid hormone) that are better established in patients with partial response to TCAs and MAOIs rather than principally studied in TRD.

We also review data for SGAs, despite the fact that – with the exception of the olanzapine-fluoxetine combination – these medications are not approved for TRD, but only for

Table 2 Options for management of treatment-resistant depression (TRD)

Option	Rationale	Limitations
Extending antidepressant trial	Delayed time to response amongst subpopulations with TRD.	Modest evidence base supporting the strategy. Unlikely to be acceptable to most patients living with TRD. Alternative strategies for TRD better established (e.g., ECT, esketamine).
Switching antidepressants	Mechanistically dissimilar antidepressants from different classes may offer improved health outcomes in TRD in some cases. Especially appropriate when index antidepressant class is poorly tolerated.	Modest evidence base supporting the strategy. Newly initiated antidepressant will require at least 4 weeks before outcome can be assessed.
Combining antidepressants	May target symptoms not responding to index antidepressant (e.g., fatigue, cognitive impairment, sleep problems). May improve tolerability via antidote of emergent adverse events (e.g., bupropion for antidepressant-induced sexual dysfunction).	Limited evidence base in TRD. Potential for drug-drug interactions. Decreased adherence with polypharmacy regimens. Greater cost of treatment.
Ketamine	Acute efficacy established in TRD. Beneficial effects on suicidality. Rapid onset of symptomatic improvement.	Insufficient long-term efficacy, tolerability and safety data. Access to treatment limited in many jurisdictions. Specialized personnel required for safe administration. Long-term safety profile in TRD not established (e.g., abuse liability, gateway activity).
Esketamine	Acute and maintenance efficacy established in TRD. Beneficial effects on suicidality. Rapid onset of symptomatic improvement. Superiority to SGA (i.e., quetiapine XR) in acute and maintenance treatment of TRD.	Access to treatment limited in many jurisdictions. Acquisition cost. Recommendation to co-prescribe with underlying antidepressant in TRD.
Second-generation antipsychotics (SGAs)	Scalable and accessible treatments. Evidence established for olanzapine-fluoxetine combination.	With exception of olanzapine-fluoxetine combination, studied in partial responders rather than TRD. Short- and long-term tolerability concerns.
Electroconvulsive therapy (ECT)	Highly effective in acute and maintenance treatment of TRD. Non-inferiority to IV ketamine suggested by available evidence. Efficacy in TRD across the age span.	Relative lack of availability in many contexts. Stigma and lack of acceptability to many patients with TRD. Tolerability concerns (e.g., memory deficits).
Repetitive transcranial magnetic stimulation	Shown to be effective in TRD. More acceptable to patients than ECT. Accelerated protocol demonstrates significant remission rates within one week. Tolerability advantages compared to ECT (i.e., persisting cognitive deficits not observed).	Relative lack of availability in many jurisdictions. Inferiority to ECT in TRD with non-accelerated protocols. Insufficient long-term data in TRD.
Vagus nerve stimulation	Proven efficacy in TRD in persons with extensive antidepressant failure histories. Treatment does not need to be administered on a daily basis.	Not available in most countries globally. Complexity of procedure limits scalability. Complications of implant. Cost of treatment.
Psychotherapies	Evidence supports efficacy when used adjunctively in TRD. Opportunity to target comorbidities. Facilitate coping strategies with improved effects on patient-reported outcomes. Highly acceptable to persons with lived experience of TRD. Opportunity to tailor treatment targeting specific therapeutic outcomes.	Lack of availability of treatment or adequately trained providers. Low adherence to therapy. Lack of evidence as standalone treatment in TRD.

individuals with MDD exhibiting partial response to an index antidepressant.

Extending the antidepressant trial

As mentioned earlier, results from the STAR*D trial indicated that a proportion of individuals who responded to level 1 treatment did so after week 6. A systematic review of available studies sought to evaluate the likelihood of response during weeks 5-8 and 9-12 in individuals with MDD not responding after four weeks[178]. It was concluded that approximately 20% of patients with MDD not responding in the first four weeks responded during weeks 5-8, while approximately 10% responded during weeks 9-12[178].

However, it is not established that extending an antidepressant trial in patients defined as having TRD results in any considerable likelihood of treatment success. In addition, persons with lived depression experience prioritize rapidity of antidepressant action, so that prolonging antidepressant trials for an additional one to two months is unlikely to be acceptable in most cases of TRD[92].

Switching antidepressants

Meta-analytic data are conflicting as to whether switching antidepressants increases the likelihood of response in TRD[179,180]. A related but separate concept that would justify switching class of antidepressants is that of "broadening the spectrum of efficacy". For example, a patient prescribed an SSRI who continues to manifest debilitating anhedonia, fatigue, and psychomotor retardation may exhibit significant improvement when switching to an antidepressant with a different mechanism of action[181,182].

Overall, switching antidepressants may be considered in some cases of TRD, and the new agent should be a "non-classmate" antidepressant.

Combining antidepressants

Persons with TRD are commonly treated with antidepressant polypharmacy, but few relevant studies have been conducted specifically in populations with TRD[183-187].

Results from a meta-analysis have supported the efficacy of adding mirtazapine or bupropion in persons with "early-stage" TRD (i.e., non-response to one adequate pharmacological or psychological therapy for depression)[188]. As mentioned earlier, level 2 treatment (i.e., TRD) from the STAR*D trial included seven possible switch/augmentation strategies in adults with non-psychotic depression not achieving remission with citalopram. The three augmentation approaches were bupropion, buspirone, and cognitive therapy. The proportion of patients achieving remission after receiving bupropion combined with citalopram was 39.0%, compared to 25.5% when switching to bupropion sustained release (SR) monotherapy[33].

A recent meta-analysis concluded that alpha-2 autoreceptor antagonists (i.e., mirtazapine, mianserin, trazodone) combined with SSRIs are superior to monotherapy in mixed populations including TRD, but the composition of the patient samples studied precludes any definite interpretation of the finding[189].

Overall, data supporting the combination of antidepressants as an efficacious treatment strategy is modest in TRD populations.

Ketamine/esketamine

Intravenous (IV) racemic ketamine has been found to rapidly improve depressive symptoms and suicidal ideation in adults with TRD, and its efficacy has been confirmed in real-world patient samples. Clinically meaningful benefit has been observed in both single and multiple infusion studies [190-193]. Intranasal esketamine spray co-initiated with an antidepressant has also demonstrated rapid clinically meaningful efficacy in patients with TRD. Unlike IV ketamine, there are also data demonstrating long-term (i.e., greater than 3-year) safety and tolerability for esketamine[194,195].

Item analysis indicates that ketamine and esketamine not only significantly improve overall symptoms of TRD, but also specific depressive symptoms that are over-represented in adults with TRD, such as anhedonia[196-199]. Meta-analytic data also indicate that glutamatergic treatment strategies may be superior to antipsychotic agents in adults with TRD[200,201].

In 2019, the FDA approved intranasal esketamine spray combined with antidepressants in adults with TRD, with subsequent approvals by other regulators globally (e.g., EMA). Less evidence is available for ketamine and/or its derivatives delivered through other routes of administration[191]. Moreover, the concomitant administration of ketamine and psychological interventions ("ketamine-assisted" therapy) is insufficiently characterized and as such cannot be recommended for TRD[202].

Results from the recent ESCAPE-TRD trial indicate that intranasal esketamine combined with an antidepressant is significantly more effective than quetiapine XR in TRD, with a remission rate at week 8 of 27.1% vs. 17.6% ($p=0.003$)[203]. Remission rates continued to increase in both arms after the primary endpoint, with a significantly greater proportion of patients in remission at week 32 in the intranasal esketamine than in the quetiapine XR arm (55% vs. 37%, $p< 0.001$)[203].

Preliminary evidence indicates that the effectiveness of IV ketamine in individuals with TRD and history of non-response to neurostimulation (i.e., ECT or rTMS) is not reduced as compared to individuals with TRD and no prior neurostimulation treatment[204]. Available evidence also indicates that the efficacy of ketamine/esketamine in the acute treatment of TRD is also apparent in individuals with greater degrees of antidepressant resistance[205].

Safety concerns attributable to long-term ketamine/esketamine exposure include potential for abuse and misuse, tolerance and withdrawal, effects on liver function, and possibly kidney and/or urogenital toxicity[206]. The risks for the foregoing safety concerns would be expected to be mitigated when administering ketamine/esketamine under medical supervision in accordance with best practices[205].

Second-generation antipsychotics

The only SGA evaluated in patients failing two or more prior antidepressant treatments (i.e., TRD) is the fixed dose olanzapine-fluoxetine combination[207-209]. The other SGAs assessed in MDD (i.e., aripiprazole, brexpiprazole, cariprazine, risperidone and quetia-

pine XR) have been studied only in patients with a partial response to at least one antidepressant[187,201,210-224].

Head-to-head comparisons of SGAs as augmentation in TRD are not available, nor are long-term recurrence prevention data. The absence of long-term data with SGAs is a point of differentiation with esketamine, which has long-term multi-year establishment of efficacy and safety[195]. Limitations of longer-term use of SGAs in MDD relate to tolerability and safety concerns (e.g., metabolic dysregulation, weight gain, and extrapyramidal adverse effects)[225].

Relatively few studies have compared the antipsychotic augmentation of antidepressants versus the combination of antidepressants in patients presenting with suboptimal antidepressant response. The VA Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) trial was a multisite randomized, single-blind, parallel-assignment trial of depression unresponsive to at least one course of antidepressant treatment[226]. Eligible subjects were randomly assigned to one of three treatments: switch to bupropion SR, augmentation of current treatment with bupropion SR, or augmentation of current treatment with aripiprazole. The remission rate at week 12 was higher for the aripiprazole group (28.9%) compared with the switch to bupropion SR group (22.3%), but not with the bupropion SR add-on group (26.9%). Response rates were significantly higher for the aripiprazole group (74.3%) than for both bupropion SR monotherapy and bupropion SR augmentation groups (62.4% and 65.6%, respectively)[226].

The VAST-D trial results replicate and extend the efficacy and tolerability of SGAs in individuals with MDD partially responding to antidepressants. As mentioned earlier, there are insufficient data for SGAs in TRD. However, results of the ESCAPE-TRD trial suggest superiority of intranasal esketamine to quetiapine XR.

Neurostimulation

Neurostimulatory treatments evaluated in TRD include vagus nerve stimulation (VNS), ECT, rTMS, magnetic seizure therapy, deep brain stimulation, and transcranial direct current stimulation[227-233].

VNS has proven to be efficacious in patients with higher-order TRD (i.e., equal or greater than four prior antidepressants), and has also demonstrated durability of effect with maintenance treatment[234-236]. The FDA has approved VNS in TRD patients with a history of at least four prior failed antidepressants.

ECT is a well-established therapeutic intervention in the treatment of TRD, with an average open-label remission rate of 48% in non-psychotic depression[237]. Efficacy may be higher in individuals with psychotic depression. Many modifications to the implementation of ECT have retained efficacy in TRD with improved tolerability profile (e.g., bilateral brief pulse ECT vs. right unilateral ultra-brief pulse ECT)[238].

Results from systematic reviews and meta-analyses consistently support the efficacy of rTMS in TRD[233]. Results also indicate that greater severity at baseline and higher number of prior antidepressant failures are associated with attenuated rTMS efficacy[239-243]. The cost-effectiveness of rTMS in adults with TRD is well established, and possibly higher compared to ECT, but available evidence also shows that ECT may be more effective than conventional rTMS in the acute and recurrence prevention treatment of TRD[244-246].

Newer forms of rTMS are being validated, including conventional intermittent theta burst stimulation (iTBS), whose efficacy in adults with TRD when compared to sham treatment is well established[247,248]. An accelerated high-dose iTBS protocol with magnetic resonance imaging (MRI)-guided functional connectivity targeting (Stanford neuromodulation therapy, SNT) has been found, in a double-blind randomized controlled trial (RCT), to be significantly superior relative to sham treatment four weeks after the end of the five-day protocol. The significant benefit observed was evident despite an average of five prior antidepressant medication trials[249]. The SNT approach was recently cleared by the FDA for TRD.

In addition, results from RCTs have supported the efficacy of magnetic seizure therapy, with additional evidence demonstrating continuation of effect[250,251]. A Cochrane review did not identify a significant difference between this therapy and ECT in adults with TRD[252].

Results of RCTs have not documented the efficacy of deep brain stimulation, when compared to sham treatment, in TRD[253-257]. Transcranial direct current stimulation is associated with variable outcomes across RCTs in the treatment of adults with TRD: the heterogeneity in response may be due to the broad range of treatment resistance included in the original trials, from treatment-naïve to ECT failing individuals[258].

In summary, of the foregoing neurostimulation modalities, ECT, rTMS, VNS and SNT are recommended in adults with TRD. Although there is a lack of head-to-head comparator data of proven treatments in TRD, preliminary evidence suggests that ECT may be non-inferior when compared to IV racemic ketamine in adults with TRD[259].

Psychotherapeutic interventions

There are multiple reasons for considering psychotherapeutic interventions in persons with TRD. For example, evidence indicates that these interventions are a preferred treatment option over pharmacotherapy amongst persons with lived depression experience[73,260,261]. Residual symptoms and comorbidities in persons with TRD are frequently amenable to psychological treatments. Psychotherapies, when combined with pharmacological treatments, are conceptually supported insofar as they facilitate learning, coping and resilience mechanisms that synergize with the hypothesized biological mechanisms of action of antidepressants[262]. Finally, individuals with persistent depression and history of trauma, both of which are more common in TRD populations, exhibit significant response rates with psychological interventions[263,264].

Notwithstanding the rationale for use of psychotherapies in TRD, data supporting them as standalone interventions in TRD are limited[265,266]. Available evidence does, however, support the efficacy of adjunctive psychological interventions in persons with TRD[267-271].

The psychotherapeutic modalities most frequently investigated include cognitive behavioral therapy (CBT), interpersonal psychotherapy, and mindfulness-based cognitive therapy[272]. Meta-analytic data have determined that psychotherapy added to on-

going treatment as usual (TAU) had a moderate and significant effect size (Hedges' g= 0.42) in comparison with TAU alone in TRD [272].

Overall, the available evidence indicates that manual-based psychotherapies are effective in persons with TRD when combined with antidepressants. There is insufficient evidence about combining these interventions in persons with a higher number of prior antidepressant failures and/or ECT non-response. Patient preference, potential for scalability with digital solutions, and efficacy in the treatment of comorbidities (e.g., anxiety disorders) are additional rationales for considering psychotherapies in patients with TRD. Preliminary evidence suggests that CBT may be capable of prolonging the effect observed in adults with TRD who acutely benefited from ketamine treatment[202].

However, a recent European study that rigorously defined TRD failed to demonstrate the efficacy of adjunctive psychological treatment[266]. It may be surmised that patient characteristics and the type of psychological intervention are critical moderators of efficacy in TRD populations.

INVESTIGATIONAL INTERVENTIONS IN TREATMENT-RESISTANT DEPRESSION

The public health implications of TRD provide the impetus for the development of new interventions specifically for this subpopulation. It is noteworthy that enrollment in most clinical trials of investigational agents in MDD exclude patients with TRD, especially those with a high number of failed prior antidepressant trials in the current episode, or those who have failed ECT or IV ketamine in this episode.

The class of agents imprecisely referred to as psychedelics has received the most attention as a potential investigational intervention in TRD[273]. Preliminary evidence suggests that psilocybin, combined with psychotherapy, may offer rapid and possibly sustained symptom relief in adults with TRD. For example, a phase 2 double-blind trial randomly assigned adults with TRD to receive a single dose of psilocybin 25 mg, 10 mg or 1 mg (control) along with psychological support[274]. All persons had failed at least two prior treatments before enrollment. Participants receiving the 25 mg dose, but not the 10 mg dose, exhibited a significantly greater least-squares mean change from baseline to week 3 compared with the 1 mg dose. The response and remission rates for the participants receiving the 25 mg dose were 37% and 29%, respectively[274].

Several methodological problems affect available controlled trials with psilocybin in TRD. Aspects of unblinding as well as expectancy are undoubtedly contributing to the observed effects, as are the psychotherapeutic modalities that are considered integral to the process of taking psychedelics. Nevertheless, the results of available RCTs with psilocybin have provided the impetus for evaluating this drug in phase 3 pivotal trials for TRD[275]. Deconstructing the contribution of psychotherapy from the psychedelic intervention will be an inexact yet necessary endeavor in order to interpret study findings and provide appropriate treatment and implementation recommendations. Moreover, the psychotherapy that is currently combined with psychedelics does not have a standardized evidence-based protocol.

Additional investigational interventions in TRD include lithium, thyroid hormone, buspirone, L-methylfolate, S-adenosylmethionine, anti-inflammatory agents (e.g., COX-2 inhibitors, minocycline, statins, and tumor necrosis factor-alpha antagonists), zuranolone and dextromethorphan-bupropion combination[276-280]. The extant evidence supporting lithium and thyroid hormone largely refers to their combination with TCAs and MAOIs in patients with partial response to these agents. Medications that have been studied in TRD and demonstrated not to be efficacious are pindolol and buprenorphine[281,282].

Despite the widespread prescription of multiple psychotropic agents off-label in patients with TRD, there are no rigorous studies with large samples establishing the efficacy of any of the foregoing strategies.

CONCLUSIONS

Amongst individuals meeting criteria for MDD with access to high-quality measurement-based care, at least 30% will meet criteria for TRD. This estimate is derived from efficacy and/or effectiveness research findings. The prevalence of TRD in real world practice is not known, but would be expected to be higher, due to knowledge-implementation gaps, barriers to access, and illness presentation complexity[283].

With respect to illness presentation complexity, most individuals with TRD encountered in clinical practice would not be eligible for most clinical research studies, on the basis of illness characteristics (e.g., severity, number of prior episodes, suicidality), comorbidity and treatment history[13,284].

Multiple definitions of TRD have been proposed and are reviewed herein. The lack of a universal definition of TRD is a barrier to advancing mechanistic and translational research, as well as to identifying innovative and precision-based therapeutics. In addition, public policy decisions, as well as clinical decision-making, would be benefited by a more precise and valid definition of TRD. For example, considerations for reimbursement in TRD which are critical for access to treatment are limited by the fact that multiple definitions of this condition exist. Hence, decisions by policy makers on whether to include treatments for TRD as part of a reimbursement schedule are highly variable across jurisdictions. From a clinical perspective, the lack of a universal definition of TRD contributes to heterogeneity in treatment selection and sequencing. This heterogeneity is also reflected in clinical practice guidelines for MDD, that have different recommendations with respect to selection and sequencing of treatments for adults with TRD.

Consensus exists that the lack of a clinically meaningful improvement with a minimum of two antidepressants should be retained in any working definition of TRD. A quantifiable endpoint defining non-response should be provided. A comprehensive and conceptually valid definition of TRD with clinical utility should also include aspects of patient-reported outcomes, psychosocial function, as well as dimensional outcomes (e.g., anhedonia)[285].

The related, but separate, notion of DTD seems more aligned with the realities of the clinical ecosystem, and with patient experience of depression and sequential non-response to treatments[94,286]. A compelling case

is made that TRD is potentially judgmental insofar as it may be interpreted as blaming the patient. Instead, DTD is agnostic and represents a patient-centered and pragmatic approach to identifying therapeutic targets[84]. The construct of DTD could serve as a useful framework informing further characterization of TRD.

The variability in antidepressant response is widely recognized[287]. A confluence of sociodemographic and clinical characteristics is known to moderate this response. Clinicians are encouraged to identify modifiable factors that attenuate antidepressant outcomes and allocate resources to these factors in patients prescribed antidepressants. For example, non-adherence, illness and treatment illiteracy, stigma, and attitude towards treatment are modifiable with psychoeducation efforts and possibly peer-support[73].

In addition, psychiatric and physical comorbidities not only attenuate antidepressant response but may also be a consequence of TRD. Targeting comorbidities at the same time as depressive symptoms would be predicted to improve treatment outcomes as well as reduce cost and health resource utilization in adults with MDD. In addition, closing the implementation-knowledge gap with fidelity to evidence-based treatments is a near-term cost-effective priority in the management of MDD today.

The evidence supports select SGAs, as well as rTMS and manual-based psychotherapies (in combination), as proven strategies in adults who have failed one prior antidepressant. For individuals with TRD (failing multiple antidepressants), evidence is best for ketamine, esketamine, adjunctive psychotherapy, ECT and rTMS. Psychotherapeutic interventions in combination with antidepressants may offer partial symptomatic relief in persons with TRD, but their efficacy as monotherapy is not established. Combination antidepressants, switching antidepressant treatment, dose optimization and the use of a host of augmentation strategies (e.g., lithium, thyroid hormone) have mixed data supporting their usefulness[288].

Intranasal esketamine combined with an antidepressant is the most rigorously evaluated pharmacologic strategy in the acute and maintenance treatment of adults with TRD. In addition to demonstrating acute efficacy, it has established relapse prevention, tolerability and safety in persons with TRD, with more than three years of maintenance data. IV racemic ketamine has also demonstrated robust rapid antidepressant efficacy in mostly acute studies. There are relatively few controlled studies, however, that have documented maintenance efficacy of repeat-dose IV ketamine in adults with TRD [289].

The relative efficacy of intranasal esketamine to ECT in TRD is unknown, but is currently being evaluated. Preliminary evidence suggests that ECT may be non-inferior to IV racemic ketamine in the acute treatment of TRD[259]. Results from large and rigorous controlled studies comparing IV ketamine to ECT are expected to provide further decision support and inform recommendations for treatment sequencing in TRD[259].

The investigational interventions in TRD that have received the most research, media and public attention have been psychedelics. Available evidence for psilocybin suggests acute efficacy that is rapid and sustained in well-characterized samples of persons with TRD. Unanswered questions as to the contribution of integrated psychotherapy in persons receiving psilocybin have not only conceptual and clinical relevance, but are also critical to address from an implementation perspective.

Future research vistas with respect to pharmacological treatment are testing whether ketamine derivatives or other glutamatergic agents may be useful in TRD. Additionally, GABAergic agents (e.g., zuranolone), opioid receptor modulators, orexin antagonists, voltage-gated ion channels modulators, anti-inflammatories, as well as agents targeting cellular metabolic processes are also under investigation in TRD[290].

It is recognized that TRD is an under-researched clinical population with disproportionate morbidity and mortality. Mechanistically novel interventions that offer meaningful benefit may be eligible for FDA "breakthrough status", incentivizing treatment discovery and development in this area.

Identifying biomarkers and biosignatures associated with TRD is an important future research vista. As reviewed herein, pharmacogenomic testing has preliminary support as a tactic in assessing TRD patients, especially in cases of medication poor tolerability. Notwithstanding, it cannot be recommended as a routine assessment in all persons presenting with TRD. It is anticipated that pharmacogenomics will advance, as will the ability to computationally interrogate multi-omic data, providing insights into the neurobiology of TRD and also potentially informing patient stratification and precision therapeutics with clinical ecosystem application potential.

Digital psychiatry encompasses aspects of health care delivery, illness surveillance, disease management and treatment[291-294]. Multiple proprietary and academically led product developments are underway to identify digital therapeutics that may have application in TRD populations.

The next decade can reasonably expect the regulatory approval of innovative pharmacological treatments targeting systems implicated in the pathophysiology of depression. The foregoing, along with advances in the digital delivery of psychological interventions and refinement of parameters of neurostimulation (notably rTMS with accelerated protocols), hold promise to improve general health outcomes and cost-effectiveness of care in TRD.

The extraordinary public health burden of TRD will unlikely be extinguished in the near future, but the proportion of individuals with debilitating symptoms of depression and dissatisfaction with treatment may be reasonably expected to be decreased with successful targeting of modifiable factors, reducing the knowledge-implementation gap, and rapid adoption of innovations across therapeutic modalities.

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