

## TRENDS AND PERSPECTIVES

# The Impact of (the Concept of) Treatment-Resistant Depression: An Opinion Review

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## ABSTRACT

Treatment-resistant depression refers to major depressive disorder, treatment of the disorder, and failure to obtain an “acceptable” outcome. Regarding the disorder, the heterogeneous concept of major depressive disorder and the multiple definitions of treatment-resistant depression, hesitating between a categorical and a more dimensional approach, as well as the divergence between diagnostic criteria and the items in the assessment scales are a source of confusion. Classifications do not take into account the dramatic influence of patient characteristics strongly impacting outcome, although these can be the cause of so-called pseudo-resistance. Outcome is the result of spontaneous evolution, nonspecific factors (including placebo), and active treatment factors. These should be differentiated to have a reliable estimation of the impact of different treatment modalities before we can assess treatment-resistant depression or before we can ascertain the (non)efficacy of treatments for treatment-resistant depression.

The impact and burden of major depressive disorder and treatment-resistant depression are immense and go far beyond their economic cost. It is often forgotten that both are not only associated with increased suicidality but also with nonsuicidal mortality and that both can even result in requests for assisted dying. The caregiver burden and associated stigma are also too often overlooked despite that it has been suggested that they do influence (treatment) outcome.

**Keywords:** burden, depression, difficult to treat depression, treatment-resistant depression

## Introduction

This paper aims to be an opinion piece putting the impact and burden of treatment-resistant depression (TRD) into a broader perspective. The impact of TRD literally refers to the burden and impact of (the concept of) depression and of resistance to treatment.

Regarding the concept of major depressive disorder (MDD) and TRD, it should first be remembered that both are somewhat confusing concepts: not considering the large heterogeneity of patient profiles in MDD can impair our knowledge of the neurobiology and of the (non)efficacy of different treatment modalities of MDD and hence of TRD. The various definitions of TRD

hesitate between a categorical approach and a more dimensional approach (staging), and they further complicate comparisons between treatments and their impact. Moreover, the discrepancy between the diagnostic criteria (of MDD or TRD) and the items included in the questionnaires used to assess changes are a further source of confusion regarding the (non)efficacy of treatment modalities.

Regarding the resistance to treatment and the efficacy of different treatment modalities, it should be remembered that the (non)efficacy of a treatment is the mixture of spontaneous evolution, nonspecific factors, and specific pharmacological/

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psychotherapeutic/neuromodulation effects. It is widely accepted but often forgotten that spontaneous evolution and the nonspecific effect (placebo effect) account for more than one-half of the global changes during treatment: the person behind the disorder (MDD/TRD) and his or her beliefs, representations, and attitudes should be better considered when discussing (non)efficacy of treatments.

Regarding the impact or burden of MDD or of TRD, the discussion is too often limited to the economic aspects but should go well beyond direct and indirect costs estimations: MDD and TRD reduce life expectancy mainly through nonsuicidal mortality. In some countries, requests for assisted dying can be the consequence of TRD. Moreover, the caregiver burden as well as the stigma for TRD patients and for caregivers cannot be overlooked.

## The Impact of the Heterogeneity in the Concepts MDD and TRD

### Diagnostic Heterogeneity in MDD

Defining TRD assumes that we first define depression. MDD is considered one of the biggest causes of disability worldwide (World Health Organization, 2017). However, MDD is not “one” disorder but an almost endless number of patient profiles and symptom combinations. The categorical system of the DSM-5 (American Psychiatric Association, 2013) hypothetically allows for the identification of 227 unique depression profiles. Each of these profiles meets the requirements of scoring positive on 5 of 9 symptoms, even though there can be a large symptom variation between them. In fact, many of these MDD criteria are compound criteria including different or even contrasting symptoms, such as interest (referring to the anticipatory hedonic function) or pleasure (referring to the consummatory hedonic function), increased or decreased appetite, increased or decreased sleep, psychomotor retardation or agitation, and so on. If the differences in sleep, appetite, and psychomotor activation are taken into account, one even finds 945 unique profiles. A large study by Fried and Nesse (2015) has shown that those numbers are not just theoretical speculation. In a population of 3707 depressed outpatients, they identified 1030 unique symptom profiles.

But in clinical reality, many MDD or TRD patients present with associated anxiety, (painful) somatic, or cognitive symptoms not included in the DSM criteria. It does seem, as Goldberg (2011) put it, that considering all these types of MDD as a single mental disorder is close to “magical thinking.”

Moreover, current neurobiological hypotheses additionally support the heterogeneity of the MDD concept in distinguishing subtypes of depression, based on associations between neurotransmitters or neural circuits and specific symptoms, including the anxious, cognitive, somatic-vegetative, or anhedonia symptoms (Nutt, 2008).

### Diagnostic Heterogeneity in TRD

Defining TRD also assumes that we define treatment resistance. Indeed, TRD refers to the failure in obtaining an acceptable outcome, yet what is considered an acceptable outcome is not a universally agreed upon definition. The standard definition of response and remission is 50% improvement from baseline and 3 weeks with virtual absence of depressive symptoms, respectively (Frank et al., 1991). But when treating TRD, we may have to lower this threshold, since even a smaller improvement could

be clinically meaningful. It was for example shown that in TRD patients treated with vagal nerve stimulation, responders had a 51% lower suicide risk than nonresponders, but it was also shown that even a 25% to 50% improvement resulted in a reduction in suicidality (Olin et al., 2012). Furthermore, it is important to consider that the duration of treatment as a factor determining treatment outcome can lead to flawed conclusions, in particular when treatment itself is inadequate despite its long duration: the PharMetrics Integrated Database indeed showed that the duration of each level of treatment was between 93 days and 183 days, which means staying on the same (non) efficacious treatment up to 6 months. That should be considered as bad practice (Kubitz et al., 2013). Most definitions of TRD do not take into account the difference between failure to have an “acceptable” outcome and failure to maintain an acceptable outcome: it was indeed shown that the latter loss of antidepressant efficacy (antidepressant tachyphylaxis or poop-out effect) gives worse next-step treatment effect (Targum, 2014).

The many attempts to define TRD further illustrate the diagnostic and classification hesitations. On the one hand, regulatory definitions are categorical but continue to hesitate whether the 2 failed treatments should be with antidepressants from different classes or whether they may be from a single class. On the other hand, most definitions move away from a categorical towards a more dimensional (staging) approach taking into account number of treatments (pharmacological or electroconvulsive treatment), duration of treatments, treatment modalities, and symptom severity (Petersen et al., 2005; Souery et al., 2006; Fekadu et al., 2009; Ruhé et al., 2012). The differential weight attributed to different treatment modalities (e.g., tricyclics vs SSRIs or antidepressants vs electroconvulsive treatment) are mostly arbitrary, and most classifications do not take psychotherapy into account (except Conway et al., 2017). Moreover, comorbidities, personality problems or disorders, and possible maintaining contextual factors are not addressed.

Apart from moving from TRD (categorical) to more or less resistant depression (staging) could more fundamentally even question the terminology itself: “treatment resistant” depression as well as “refractory depression” are at risk of being stigmatizing concepts as they blame the disorder (or the patient behind the disorder?). An example of this stigmatizing in the lay press is found in a recent issue of *Time Health* (July 21, 2017) where the term “stubborn” depression was used. That is why the more collaborative concept of “difficult to treat” depression may be a less stigmatizing end, hence a more appropriate term (Table 1).

It is therefore difficult to maintain that TRD is a homologous and unitary entity (Nemeroff, 2007), and any speculation on the prevalence and impact of TRD becomes questionable. It is understandable that prevalence estimates of TRD vary widely from 6.6% in the PharMetrics Integrated Database of 47,658 treated major depressive episodes to 44% in STAR\*D (Sinyor et al., 2010; Kubitz et al., 2013), while a Canadian study found a prevalence of TRD in primary care of 21.7% (12% to 28% depending on the geographical region) (Rizvi et al., 2014).

## Impact of Heterogeneity in Assessment Tools for MDD and TRD

When discussing an acceptable outcome (or treatment resistance) with antidepressant treatment in MDD or TRD, a closer look at the assessment tools is needed since they determine the outcome. These assessment tools further increase hesitations on the concepts of MDD and TRD. Some tools are mainly used

Table 1. Terminology: Treatment Resistant Depression, Refractory Depression, Difficult to Treat Depression

Term	Treatment-Resistant Depression (TRD)	Refractory Depression	Difficult to Treat Depression (DTD)
Etymology	• “re-sistere”: hold out againsts, oppose, make a stand against, stand firm blaming the disorder (or the patient?)	• “refractarius”: stubborn, obstinate blaming the disorder (or the patient?)	• “tractare”: manage, negotiate, deal with, handle collaborative concept (patient, family, physician)
Model	• Acute illness model	• Acute illness model	• Chronic illness model
Approach	• Mainly biological • Biomedical: cure	• Mainly biological • Biomedical: cure	• Biopsychosocial • Capability approach • Recovery movement • Optimizing symptom control • Minimizing impact of symptoms
Endpoint	• Categorical (remission or not)	• Categorical (remission or not)	• Dimensional (waxing and waning)

for confirming the diagnosis (of MDD and of TRD) while others are used mainly to assess change in symptom severity during treatment. Some are observer-rated while others are self-rated instruments. Many scales developed for one purpose (confirming diagnosis or assessing change in severity) are, however, often used for the other. Some of them reflect the DSM diagnostic criteria but others include additional symptoms: frequently used observer-rater scales assess between 6 (HAMD 6- item scale) and 30 (IDS) symptoms, and frequently used self-rating scales assess between 7 (HADs depression subscale) and 30 (IDS-SR) symptoms (Rush *et al.*, 1986). The different content and number of items assessed seem arbitrary, making the assumption that they are actually assessing the same disorder questionable.

Assessment of changes in symptom severity can be both observer-rated or self-rated, but these 2 “assessments” do not always result in a homogeneous picture. Despite the precautions in RCTs including double-blinding and use of a control group, there may be an essential problem of so-called objectivity and so-called subjectivity, when aiming to measure efficacy of treatment for (treatment-resistant) depression. Indeed, the “objective” observer-rated symptom decrease has been shown to be larger than the “subjective” self-rated symptom decrease (Demyttenaere *et al.*, 2015), making it difficult to reach consensus on an acceptable outcome. An illustration of this divergence in observer- and self-rating is found in the 3 pivotal trials of adjunctive treatment with aripiprazole in TRD. Indeed, the placebo-controlled RCTs published by Berman *et al.* (2007), Marcus *et al.* (2008), and Berman *et al.* (2009) all found that augmentation strategies with aripiprazole showed significant greater symptomatic improvements in observer-rated (MADRS) but not in self-rated assessment tools (IDS-S), and the self-rated functional outcome measure (SDS) gave a superiority of aripiprazole in only 1 of the 3 studies. Including both self-rating and observer-rating assessment tools is therefore advisable. According to clinical experience, family members and clinicians may be the first to spot some symptom improvement, even before the patient does so. Nevertheless, when dealing with depressive symptoms of a patient, we need to acknowledge that it is his or her experience of depression that determines whether a treatment is effective.

### Impact of the “Person” in Assessment of Outcome in MDD and TRD

When discussing an acceptable outcome (or treatment resistance) with antidepressant treatment in MDD or in TRD, it should be remembered that the overall effect is due to at least 3 factors: spontaneous evolution (and regression to the

mean), placebo effect (nonspecific effect), and specific pharmacological/psychotherapeutic/neuromodulation effect. An important issue in this regard is also whether treatments result in enhancing response rates or in increasing the speed of response: it was for example shown that lithium augmentation gives rapid effects in augmentation of tricyclics but not of SSRIs, or that augmentation with atypical antipsychotics result in a faster and increased response, but a more detailed discussion of this topic is beyond the scope of the present paper (Carvalho *et al.*, 2008). Not taking into account the importance of these 3 factors can lead to misinterpretation of treatment resistance, and it should indeed always be questioned whether the disorder or the person and his or her context is resistant (cfr *supra*). Although these components are worth distinguishing when investigating a therapeutic intervention, they could be partially related to the same neurobiological pathways (Mayberg, 2002; Benedetti *et al.*, 2005; Benedetti, 2008). Moreover, these 3 sources of change and hence of reaching an acceptable outcome or not should also take the person into account, since personal characteristics (sociodemographic variables, attitudes, and beliefs) already explain a significant part of the variance in the more or less successful outcome of a treatment modality. This has been largely documented in short- and long-term outcome of MDD and of TRD.

### Short-Term Treatment Outcome

The spontaneous evolution of depressive episodes (in MDD or even in TRD) should first be taken into account when discussing efficacy or inefficacy of antidepressant treatment. Spontaneous remission in untreated major depression was found to be 23%, 32%, and 53% after 3, 6, and 12 months, respectively, although lower figures were observed in more severely depressed patient (Whiteford *et al.*, 2013).

Being aware of spontaneous evolution is important to put the effect of treatment into perspective. Indeed, a meta-analysis of short-term, placebo-controlled, randomized trials showed response rates of 53.8% for antidepressants and 37.3% for placebo (Papakostas and Fava, 2009). Both figures (for placebo and active treatment) of course do comprise the well-known phenomena of spontaneous evolution and regression to the mean. These figures also suggest that 69% of the total effect is placebo effect and 31% is additional pharmacological effect. It is remarkable that the opposite ratio was found in a recent survey on physicians’ beliefs: placebo effect was believed to be 41% and additional pharmacological effect was believed to be 59% (Kampermann *et al.*, 2017).

The overall placebo and antidepressant effect is dramatically influenced by study design, by patients as well as physicians beliefs and expectations, and by psychosocial variables and all this could result in pseudo-resistance. A meta-analysis showed that response rates for antidepressants was 65.4% in head-to-head active treatment trials, 57.7% in 3-arm studies with 2 active treatment arms and 1 placebo arm, and 51.7% in 2-arm studies with 1 active treatment arm and 1 placebo arm (Sinyor et al., 2010). Response rates for placebo were 44.6% in 3-arm studies with 2 active treatment arms but only 34.3% in 2-arm studies with 1 active treatment arm. This effect was called the *lessebo* effect: a higher chance of being on placebo (in the mind of the patient and of the physician) lessened the effect of placebo and of active treatment. The influence of trial designs is further illustrated by response rates in TRD depending on how TRD was defined before inclusion in a RCT: overall response rates for augmentation with atypical antipsychotics was 44.2% (vs 29.9% for placebo), but in studies where the 2 failed trials (needed for the definition of TRD) were retrospective (historical) response rates were 55.2% vs 42.7%, respectively, while in studies where the 2 failed trials were 1 failed retrospective and 1 failed prospective trial response rates were as low as 38.6% vs 25.8% (Nelson and Papakostas, 2009). In both designs, atypical antipsychotics do better than placebo, but provocatively one could conclude that active medication in a trial where one of the failed trials was prospective performs worse than placebo in a trial where both failed trials were retrospective.

Another example of how expectation and persuasion influences outcome is illustrated with the re-analysis of the failed hypericum trial (where neither hypericum nor sertraline differentiated from placebo) (Hypericum Depression Trial Study Group, 2002). Indeed, considering physician or patient guess (on which treatment they guessed they were) gave highly significant differences between treatment arms: the highest remission rates (43% vs 6% for placebo) were found with sertraline when the physician guessed the patient was on sertraline and with hypericum (37% vs 22% for placebo) when the patient guessed he or she was on hypericum (Chen et al., 2011, 2015). Another example in MDD was an analysis showing the patient's baseline attitude towards taking antidepressant medication dramatically influenced placebo and antidepressant response: a rather negative attitude, a neutral attitude, and a rather positive attitude resulted in response rates of 34%, 36%, and 56% for placebo and in response rates of 51%, 56%, and 69% for active medication (Demyttenaere et al., 2011).

A last example of the influence of preference on outcome is the patient's attitude towards pharmacotherapy or psychotherapy. Indeed, Kwan et al. (2010) found that 48% of a depressed patient population preferred psychotherapy, 28% preferred antidepressants, and 34% had no preference. Patients were then randomized and those with a mismatch (they preferred psychotherapy but got antidepressants, or they preferred pharmacotherapy but got psychotherapy) had a significantly worse outcome than those with a match or those with no preference. Matching of type of treatment can indeed increase the commitment to and engagement in therapy, thereby inducing an (in) direct effect on the depressive symptoms. Resistance to treatment could therefore be partially due to resistance to treatment modality.

Before treatments for MDD or TRD can proceed towards (only biologically defined) personalized or precision medicine, more attention should indeed be paid to the global person suffering from depression. The STAR\*D study showed that at step 1 (12 weeks of treatment with citalopram) overall response rates were

rather disappointing (47%) (Warden et al., 2007), but taking into account some psychosocial variables (education, employment, gender) and some clinical characteristics (anxious depression or not, trauma distress, episode duration) response rates varied as much as between 31% and 63% (Sinyor et al., 2010). Other studies also showed that psychosocial characteristics (like [un]employment, age, living alone or together in MDD; and educational achievement or social support in TRD) are very significant predictors of outcome (Demyttenaere et al., 2009; Fekadu et al., 2012).

### Long-Term Treatment Outcome

For MDD, long-term outcome studies in treated in- and out-patients showed that 93% remitted within 10 years: 11.5% did not recover in 5 years and 7% did not recover in 10 years, suggesting that even after 5 years of chronic depression, one-third of patients will still recover in the following 5 years (Mueller et al., 1996).

For TRD, a 3-year follow-up study of treated patients showed that 60.2% showed full remission (including 48.3% sustained full recovery, i.e., full remission for at least 6 months), 19.5% showed persistent subsyndromal, and 20.3% persistent depression (Fekadu et al., 2012).

When investigating outcome, most studies unfortunately only report endpoints at the moment of treatment termination, without looking at differences in onset of global improvement or in onset of some aspects of improvement (e.g., more rapid improvement of suicidality or at persistence of improvement after termination of treatment) and this could hide significant differences between different treatment modalities. In MDD, it was shown that despair, mood, and interest improved more rapidly with escitalopram or duloxetine than with cognitive behavior therapy, but after 12 weeks there was similar improvement with antidepressants or with psychotherapy. One example of the effect of treatment on changes after treatment termination in TRD patients is the study published by Fonagy et al. (2015), where patients with TRD got either treatment-as-usual or adjunctive long-term psychodynamic psychotherapy. At the end of the 18-month treatment period, there were only slight differences between the treatment-as-usual group and the group with adjunctive psychotherapy group. But 2 years later, a significant delayed therapeutic benefit was observed in the adjunctive psychotherapy group, both observer-rated and self-rated and both for full remission as well as for partial remission. Full remission rates at 18 months were 9.4% vs 6.5%, respectively, and full remission rates at 2-year follow-up were 14.9% vs 4.4%. It is therefore remarkable that most definitions of TRD do not mention psychotherapy as a treatment modality.

### Impact and Burden of TRD

Despite our critique of the inconsistencies and problems concerning the concept of TRD, let alone its exact prevalence, the impact and burden of long-lasting depression are enormous.

### The Economic Burden of Mood Disorders

It was reported that mood disorders top the list of costs for neurological or psychiatric disorders in Europe and the cost estimation was 113.4 billion euro (Olesen et al., 2012): 37% of the cost was due to direct costs (treatment related) and 63% was due to indirect costs (absenteeism, presenteeism, cost of suicide). Data from the US moreover showed that the cost for mood disorders

increased by 21.5% between 2005 and 2010 (from 173 to 210 billion dollar); 45% of that cost was due to direct costs, 5% to suicide related costs and 55% to indirect costs (Greenberg and Birnbaum, 2005; Greenberg et al., 2015). In a recently published study based on UK data, mental disorders top the claims for disability benefits (46.5% of all claims) and among mental disorders, 44.4% were due to mood disorders (Viola and Moncrieff, 2016).

For TRD, the direct costs are even larger, resulting from higher chances of being hospitalized, more outpatient visits and more use of psychotropic medication (Crown et al., 2002). A US study showed that the annual direct cost of TRD was 40% higher than for non-TRD and was correlated with the severity of TRD: a 1-point increase in the Massachusetts General Hospital clinical staging score for TRD was associated with a 590 dollar increase in annual costs (Gibson et al., 2010).

### Impact of MDD and TRD on Nonsuicidal or Suicidal Mortality and on the Request for Assisted Dying

The burden goes well beyond economic impact, however. Mental disorders in general are associated with higher mortality and hence decreased life expectancy. Although suicide risk receives much attention, the largest part of excess mortality is due to physical illnesses, including cardiovascular disease, respiratory disease, and cancer (Lawrence et al., 2013). Even in a young population of 1.095.338 Swedish men (18 year old), the mortality hazard ratio was 1.51 for those with a diagnosis of MDD and was even 4.66 for those with a hospitalization for MDD: it is important to notice that these hazard ratios were corrected for age, socioeconomic status, BMI, blood pressure, IQ and that deaths from suicide were excluded (Gale et al., 2012).

The association between depression and cardiovascular morbidity and mortality has been particularly studied and results indicate that depression increases cardiovascular morbidity and mortality. For example, a meta-analysis found that depression after myocardial infarction is associated with a 2- to 2.5-fold risk of impaired cardiovascular outcome. This included cardiac and general mortality after myocardial infarction, but equally showed an increased risk of new cardiac events (Van Melle et al., 2004). During a more recent follow-up of 4037 MDD patients after myocardial infarction, Scherrer et al. (2012) found that 6.9% of those with insufficiently treated depression, 2.4% of those with treated depression and 5.0% of those with treatment-resistant depression died. When corrected for sociodemographic characteristics, anxiety disorders, beta-blocker use, mortality risk factors and health service utilization, they found that patients with TRD were 1.71 times more likely to die in comparison to treated patients with MDD, while the risk was 3.04 times bigger for untreated patients with MDD.

To evaluate the effect of treatment interventions on cardiovascular morbidity and mortality, clinical trials like the ENRICHD study were designed. Results of this study support the idea that lack of response to treatment increases mortality (Carney et al., 2004). In addition, another study found that the 18-month incidence of cardiac events was 26% among depressive patients who were nonresponsive to the treatment intervention, compared to 11% in untreated control subjects, and 7% among intervention group patients who experienced response (de Jonge et al., 2007). In another clinical trial, evaluating the safety and efficacy of sertraline in patients with a recent acute coronary syndrome, results showed that patients with the most improvement on the Clinical Global Impression (CGI) scale after treatment with sertraline or placebo had the lowest rate of mortality

(11.5%), compared to those with moderate (22.5%) and minimal or no (28.4%) improvement (Glassman et al., 2009). Although current evidence does not seem univocally conclusive on the effect of treatment intervention on morbidity and mortality (Carney and Freedland, 2009), research does show that the risk of cardiovascular morbidity and mortality is higher in patients who are non-responsive to treatment.

It is therefore not surprising that TRD was found to be a significant independent predictor of mortality in a recent study focusing on depressive post-myocardial infarction patients, even when corrected for age, diabetes, heart failure or smoking (Banankhah et al., 2015). The same researchers argued that the lack of current evidence for the effect of treatment interventions for depression on cardiovascular morbidity and mortality may be caused by the impact of subgroups of TRD patients in those study populations. A subgroup of TRD with significantly worse survival would thus impede an overall improvement of the data. In fact, they concluded that when excluding TRD patients, treatment did decrease cardiovascular risks and suggested that a more effective treatment of TRD could equally improve survival after myocardial infarction for those patients. Overall, the impact of MDD and in particular TRD on cardiovascular health seems undeniable.

Mortality in depression is often associated with suicide. In general, patients suffering from affective disorders have a 2- to 4-fold risk of suicide in comparison to other patients. Although depression is a well-established risk factor for suicide, suicide among depression patients remains a rare event at less than 100 suicide deaths per 100 000 person years (Pfeiffer et al., 2013). Nevertheless, the identification of which patients may die by suicide remains important—albeit difficult (Bostwick and Pankratz, 2000). Souery et al. (2007) showed that TRD is associated with a bigger risk for suicide, even though it is not yet completely understood how suicide-related outcomes are related to the development of TRD (Pfeiffer et al., 2013). Olin et al. (2012) did find that even a partial response to treatment can already impact the suicide risk in TRD patients. Their data suggests that both response (as a reduction of more than 50% in MADRS score) and partial clinical benefit from treatment (25 to 49% reduction in MADRS score) reduces the risk of suicidal behavior. Thus, obtaining response or even a moderate reduction of symptoms (partial response) in TRD could effectively mitigate suicidal behavior.

Where legislation permits, patients can find TRD so burdening and disabling they consider assisted dying or euthanasia. In the United States assisted dying is permitted in four states, and it is restricted to terminal physical illness (Gostin and Roberts, 2016). In some European countries, particularly Belgium, The Netherlands, and Luxembourg, assisted dying (or euthanasia) is also allowed for non-terminal illness under strict conditions, and no difference is made between physical or mental disorders. In Belgium, the patient's request has to be deliberate, repetitive, persistent and written-down without external pressure. The criteria include persistent unbearable physical or psychological suffering, with no prospect of any improvement, being caused by a severe and incurable accidental or medical condition. TRD is often named as the ultimate example of psychiatric conditions possibly leading to a request for assisted dying. Numbers in Belgium and the Netherlands show that TRD accounts for around half of the requests due to psychiatric disorders, alongside personality disorders (Kim et al., 2016; Thienpont et al., 2015). Considering the predominance of TRD in psychiatric patients requesting life-ending measures, the possible gravity of TRD seems undeniable. With no intent to position this paper

into the debate, it is important to consider the case of TRD with regards to euthanasia and assisted dying: if the concept of TRD is indeed as questionable as we have argued, including estimation and evaluation of treatment effect (and of spontaneous evolution), this should have implications for the current practice of assisted dying. Moreover, it seems extremely difficult to evaluate “rational suicidality” or “a rational request for physician-assisted suicide in depression (Vandenberghe, 2018). Dutch data show that in a significant number of accepted requests for physician-assisted-suicide, the no-reasonable-alternative criterion was not met: e.g. in several patients with TRD, electroconvulsive treatment had not even been tried (Kim et al., 2016). Anyhow, it remains extremely delicate to judge whether such a request is competent, rational and authentic or not: to what degree does the TRD influence, cloud, or determine the individual’s view of reality including future prospects (or improvements) (Schuklenk et al., 2015).

### Caregiver Burden and Stigma in TRD

Lastly, the caregiver burden of TRD is too often ignored. This burden encompasses physical, emotional, financial and social problems related to living with and caring for the depressed patient, including dealing with dependence and the fear of suicide (Tabeleão et al., 2017; van Wijngaarden et al., 2004). From an economic perspective, caring for a severely depressed person with little response to treatment often induces a loss of economic productivity for the caregiver as well (Gibson et al., 2010). Importantly, caregivers themselves are reported to have high psychiatric caseness (34% vs 4% in controls) (Rane et al., 2012). This could be partially attributed to or at the minimum aggravated by the phenomenon of stigma. Indeed, between 43 and 92% of caregivers of people suffering from mental illness indicate feeling stigmatized (Struening et al, 2001), while this perceived stigma is known to increase depressive symptoms of the caregivers themselves (Perlick et al., 2007; Phelan et al., 1998), complicating the situation for the person they are caring for.

### Conclusions

In conclusion, the somewhat confusing concepts of MDD and TRD and their assessment hamper our understanding of these disorders and of the effect of their treatment which are a combination of spontaneous evolution, non-specific and specific effects.

The impact and burden of MDD and of TRD are immense and go far beyond their economic cost. It is often forgotten that both are not only associated with increased suicidality but also with non-suicidal mortality and that both can even result in requests for assisted dying. The caregiver burden and associated stigma are also too often overlooked despite that it has been suggested that they do influence (treatment) outcome.

### Interest Statement

Koen Demyttenaere has received speaker’s fees and consultancy honoraria from Boehringer Ingelheim, Johnson&Johnson, Livanova, Lundbeck, Recordati, Servier, and Zeno Van Duppen.

### References

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association.

- Banankhah SK, Friedmann E, Thomas S (2015) Effective treatment of depression improves post-myocardial infarction survival. *World J Cardiol* 7:215–223.
- Benedetti F (2008) Mechanisms of placebo and placebo-related effects across diseases and treatments. *Annu Rev Pharmacol Toxicol* 48:33–60.
- Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta JK (2005) Neurobiological mechanisms of the placebo effect. *J Neurosci* 25:10390–10402.
- Berman RM, Fava M, Thase ME, Trivedi MH, Swanink R, McQuade RD, Carson WH, Adson D, Taylor L, Hazel J, Marcus RN (2009) Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. *CNS Spectr* 14:197–206.
- Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, Khan A (2007) The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 68:843–853.
- Bostwick JM, Pankratz VS (2000) Affective disorders and suicide risk: a reexamination. *Am J Psychiatry* 157:1925–1932.
- Carney RM, Blumenthal JA, Freedland KE, Youngblood M, Veith RC, Burg MM, Cornell C, Saab PG, Kaufmann PG, Czajkowski SM, Jaffe AS, ENRICHD Investigators (2004) Depression and late mortality after myocardial infarction in the enhancing recovery in coronary heart disease (ENRICH) study. *Psychosom Med* 66:466–474.
- Carney RM, Freedland KE (2009) Treatment-resistant depression and mortality after acute coronary syndrome. *Am J Psychiatry* 166:410–417.
- Carvalho AF, Machado JR, Cavalcante JL (2009) Augmentation strategies for treatment-resistant depression. *Curr Opin Psychiatry* 22:7–12.
- Chen JA, Papakostas GI, Youn SJ, Baer L, Clain AJ, Fava M, Mischoulon D (2011) Association between patient beliefs regarding assigned treatment and clinical response: reanalysis of data from the hypericum depression trial study group. *J Clin Psychiatry* 72:1669–1676.
- Chen JA, Vijapura S, Papakostas GI, Parkin SR, Kim DJ, Cusin C, Baer L, Clain AJ, Fava M, Mischoulon D (2015) Association between physician beliefs regarding assigned treatment and clinical response: re-analysis of data from the hypericum depression trial study group. *Asian J Psychiatr* 13:23–29.
- Conway CR, George MS, Sackeim HA (2017) Toward an evidence-based, operational definition of treatment-resistant depression: when enough is enough. *JAMA Psychiatry* 74:9–10.
- Crown WH, Finkelstein S, Berndt ER, Ling D, Poret AW, Rush AJ, Russell JM (2002) The impact of treatment-resistant depression on health care utilization and costs. *J Clin Psychiatry* 63:963–971.
- de Jonge P, Honig A, van Melle JP, Schene AH, Kuyper AM, Tulner D, Schins A, Ormel J, MIND-IT Investigators (2007) Non-response to treatment for depression following myocardial infarction: association with subsequent cardiac events. *Am J Psychiatry* 164:1371–1378.
- Demyttenaere K, Verhaeghen A, Dantchev N, Grassi L, Montejo AL, Perahia DG, Quail D, Reed C, Tylee A, Bauer M (2009) “Caseness” for depression and anxiety in a depressed outpatient population: symptomatic outcome as a function of baseline diagnostic categories. *Prim Care Companion J Clin Psychiatry* 11:307–315.
- Demyttenaere K, Reines EH, Lönn SL, Lader M (2011) Satisfaction with medication is correlated with outcome but not

- persistence in patients treated with placebo, escitalopram, or serotonin-norepinephrine reuptake inhibitors: a post hoc analysis. *Prim Care Companion CNS Disord* 13:PCC.10m01080.
- Demyttenaere K, Donneau AF, Albert A, Anseau M, Constant E, van Heeringen K (2015) What is important in being cured from: does discordance between physicians and patients matter? *J Affect Disord* 174:372–377.
- Fekadu A, Wooderson SC, Markopoulou K, Cleare AJ (2009) The maudslay staging method for treatment-resistant depression: prediction of longer-term outcome and persistence of symptoms. *J Clin Psychiatry* 70:952–957.
- Fekadu A, Rane LJ, Wooderson SC, Markopoulou K, Poon L, Cleare AJ (2012) Prediction of longer-term outcome of treatment-resistant depression in tertiary care. *Br J Psychiatry* 201:369–375.
- Fonagy P, Rost F, Carlyle JA, McPherson S, Thomas R, Pasco Fearon RM, Goldberg D, Taylor D (2015) Pragmatic randomized controlled trial of long-term psychoanalytic psychotherapy for treatment-resistant depression: the tavistock adult depression study (TADS). *World Psychiatry* 14:312–321.
- Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM (1991) Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry* 48:851–855.
- Fried EI, Nesse RM (2015) Depression is not a consistent syndrome: an investigation of unique symptom patterns in the STAR\*D study. *J Affect Disord* 172:96–102.
- Gale CR, Batty GD, Osborn DP, Tynelius P, Whitley E, Rasmussen F (2012) Association of mental disorders in early adulthood and later psychiatric hospital admissions and mortality in a cohort study of more than 1 million men. *Arch Gen Psychiatry* 69:823–831.
- Gibson TB, Jing Y, Smith Carls G, Kim E, Bagalman JE, Burton WN, Tran QV, Pikalov A, Goetzl RZ (2010) Cost burden of treatment resistance in patients with depression. *Am J Manag Care* 16:370–377.
- Glassman AH, Bigger JT Jr, Gaffney M (2009) Psychiatric characteristics associated with long-term mortality among 361 patients having an acute coronary syndrome and major depression: seven-year follow-up of SADHART participants. *Arch Gen Psychiatry* 66:1022–1029.
- Goldberg D (2011) The heterogeneity of “major depression”. *World Psychiatry* 10:226–228.
- Gostin LO, Roberts AE (2016) Physician-assisted dying: a turning point? *JAMA* 315:249–250.
- Greenberg PE, Birnbaum HG (2005) The economic burden of depression in the US: societal and patient perspectives. *Expert Opin Pharmacother* 6:369–376.
- Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC (2015) The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry* 76:155–162.
- Hypericum Depression Trial Study Group (2002) Effect of *Hypericum perforatum* (St John’s wort) in major depressive disorder: a randomized controlled trial. *JAMA* 287:1807–1814.
- Kampermann L, Nestoriuc Y, Shedden-Mora MC (2017) Physicians’ beliefs about placebo and nocebo effects in antidepressants—an online survey among German practitioners. *PLoS One* 12:e0178719.
- Kim SY, De Vries RG, Peteet JR (2016) Euthanasia and assisted suicide of patients with psychiatric disorders in the Netherlands 2011 to 2014. *JAMA Psychiatry* 73:362–368.
- Kubitz N, Mehra M, Potluri RC, Garg N, Cossrow N (2013) Characterization of treatment resistant depression episodes in a cohort of patients from a US commercial claims database. *PLoS One* 8:e76882.
- Kwan BM, Dimidjian S, Rizvi SL (2010) Treatment preference, engagement, and clinical improvement in pharmacotherapy versus psychotherapy for depression. *Behav Res Ther* 48:799–804.
- Lawrence D, Hancock KJ, Kisely S (2013) The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population based registers. *BMJ* 346:f2539.
- Marcus RN, McQuade RD, Carson WH, Hennicken D, Fava M, Simon JS, Trivedi MH, Thase ME, Berman RM (2008) The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 28:156–165.
- Mayberg HS, Silva JA, Brannan SK, Tekell JL, Mahurin RK, McGinnis S, Jerabek PA (2002) The functional neuroanatomy of the placebo effect. *Am J Psychiatry* 159:728–737.
- Mueller TI, Keller MB, Leon AC, Solomon DA, Shea MT, Coryell W, Endicott J (1996) Recovery after 5 years of unremitting major depressive disorder. *Arch Gen Psychiatry* 53:794–799.
- Nelson JC, Papakostas GI (2009) Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. *Am J Psychiatry* 166:980–991.
- Nemeroff CB (2007) Prevalence and management of treatment-resistant depression. *J Clin Psychiatry* 68:17–25.
- Nutt DJ (2008) Relationship of neurotransmitters to the symptoms of major depressive disorder. *J Clin Psychiatry* 69:4–7.
- Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jönsson B, CDBE2010 study group European Brain Council (2012) The economic cost of brain disorders in Europe. *Eur J Neurol* 19:155–162.
- Olin B, Jayewardene AK, Bunker M, Moreno F (2012) Mortality and suicide risk in treatment-resistant depression: an observational study of the long-term impact of intervention. *PLoS One* 7:e48002.
- Papakostas GI, Fava M (2009) Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. *Eur Neuropsychopharmacol* 19:34–40.
- Perlick DA, Miklowitz DJ, Link BG, Struening E, Kaczynski R, Gonzalez J, Manning LN, Wolff N, Rosenheck RA (2007) Perceived stigma and depression among caregivers of patients with bipolar disorder. *Br J Psychiatry* 190:535–536.
- Petersen T, Papakostas GI, Posternak MA, Kant A, Guyker WM, Iosifescu DV, Yeung AS, Nierenberg AA, Fava M (2005) Empirical testing of two models for staging antidepressant treatment resistance. *J Clin Psychopharmacol* 25:336–341.
- Pfeiffer PN, Kim HM, Ganoczy D, Zivin K, Valenstein M (2013) Treatment-resistant depression and risk of suicide. *Suicide Life Threat Behav* 43:356–365.
- Phelan JC, Bromet EJ, Link BG (1998) Psychiatric illness and family stigma. *Schizophr Bull* 24:115–126.
- Rane LJ, Fekadu A, Papadopoulos AS, Wooderson SC, Poon L, Markopoulou K, Cleare AJ (2012) Psychological and physiological effects of caring for patients with treatment-resistant depression. *Psychol Med* 42:1825–1833.
- Rizvi SJ, Grima E, Tan M, Rotzinger S, Lin P, McIntyre RS, Kennedy SH (2014) Treatment-resistant depression in primary care across Canada. *Can J Psychiatry* 59:349–357.

- Ruhé HG, van Rooijen G, Spijker J, Peeters FP, Schene AH (2012) Staging methods for treatment resistant depression. A systematic review. *J Affect Disord* 137:35–45.
- Rush AJ, Giles DE, Schlessler MA, Fulton CL, Weissenburger J, Burns C (1986) The inventory for depressive symptomatology (IDS): preliminary findings. *Psychiatry Res* 18:65–87.
- Scherrer JF, Chrusciel T, Garfield LD, Freedland KE, Carney RM, Hauptman PJ, Bucholz KK, Owen R, Lustman PJ (2012) Treatment-resistant and insufficiently treated depression and all-cause mortality following myocardial infarction. *Br J Psychiatry* 200:137–142.
- Sinyor M, Schaffer A, Levitt A (2010) The sequenced treatment alternatives to relieve depression (STAR\*D) trial: a review. *Can J Psychiatry* 55:126–135.
- Souery D, Papakostas GI, Trivedi MH (2006) Treatment-resistant depression. *J Clin Psychiatry* 67:16–22.
- Souery D, Oswald P, Massat I, Bailer U, Bollen J, Demyttenaere K, Kasper S, Lecrubier Y, Montgomery S, Serretti A, Zohar J, Mendlewicz J, Group for the Study of Resistant Depression (2007) Clinical factors associated with treatment resistance in major depressive disorder: results from a european multicenter study. *J Clin Psychiatry* 68:1062–1070.
- Struening EL, Perlick DA, Link BG, Hellman F, Herman D, Sirey JA (2001) Stigma as a barrier to recovery: the extent to which caregivers believe most people devalue consumers and their families. *Psychiatr Serv* 52:1633–1638.
- Tabeleão V, Tomasi E, de Avila Quevedo L (2018) A randomized, controlled trial of the effectiveness of a psychoeducational intervention on family caregivers of patients with mental disorders. *Community Ment Health J* 54:211–217.
- Targum SD (2014) Identification and treatment of antidepressant tachyphylaxis. *Innov Clin Neurosci* 11:24–28.
- Thienpont L, Verhofstadt M, Van Loon T, Distelmans W, Aude-naert K, De Deyn PP (2015) Euthanasia requests, procedures and outcomes for 100 belgian patients suffering from psychiatric disorders: a retrospective, descriptive study. *BMJ Open* 5:e007454.
- Vandenberghe J (2018) Physician-assisted suicide and psychiatric illness. *N Engl J Med* 378:885–887.
- van Melle JP, de Jonge P, Spijkerman TA, Tijssen JG, Ormel J, van Veldhuisen DJ, van den Brink RH, van den Berg MP (2004) Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med* 66:814–822.
- van Wijngaarden B, Schene AH, Koeter MW (2004) Family caregiving in depression: impact on caregivers' daily life, distress, and help seeking. *J Affect Disord* 81:211–222.
- Viola S, Moncrieff J (2016) Claims for sickness and disability benefits owing to mental disorders in the UK: trends from 1995 to 2014. *Br J Psych Open* 2:18–24.
- Warden D, Rush AJ, Trivedi MH, Fava M, Wisniewski SR (2007) The STAR\*D project results: a comprehensive review of findings. *Curr Psychiatry Rep* 9:449–459.
- Whiteford HA, Harris MG, McKeon G, Baxter A, Pennell C, Barendregt JJ, Wang J (2013) Estimating remission from untreated major depression: a systematic review and meta-analysis. *Psychol Med* 43:1569–1585.
- World Health Organization (2017) Depression and other common mental disorders: global health estimates.