**Navigating challenges of defining geriatric Treatment Resistant Depression (TRD)**

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**Key Highlights**

1. There is no consensus on the definition of treatment resistant depression/TRD in the literature.
2. The most common definition used by regulatory agencies is “failure to respond to two antidepressants given at optimal dose and duration, with good adherence”.
3. More elaborate definitions have been developed incorporating distinct levels of resistance, characteristics of the depressive episode, and differentiation of remission from response; however, novel definitions have not been applied to older adults in clinical or research settings.
4. TRD is common in older adults and presents as early as the first antidepressant trial, often as a result of medical comorbidities, polypharmacy, and comorbid cognitive impairment.
5. Future clinical trials should recognize unique risk factors for geriatric TRD and utilize a more specific definition that could support the development of a solid algorithm for the management of this condition in older adults.

**Text**

**Introduction**

According to the World Health Organization (WHO) 2017 global health estimates, depressive disorders constitute the largest contributor to poor health and disability worldwide. Unfortunately, a great proportion of individuals do not respond to several antidepressant medication trials, leading to the emergence of the concept of treatment-resistant depression (TRD). TRD is associated with an increased burden of disease, greater healthcare utilization and associated costs, absenteeism, caregiver burden, and rates of completed suicides. Interestingly, there is no consensus on the definition of TRD across the literature, leading to variability in prevalence estimates. Global prevalence rates range between 30% and 55% in research and community populations. These numbers increase when subjects’ subjective reports for clinical improvement, quality of life and return to functionality are incorporated in the assessment of response or remission of depression (McIntyre, Alsuwaidan et al. 2023).

**Multiple Definitions of TRD**

The most used definition of TRD is the one adopted by regulatory agencies such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). It is “failure to respond to two or more trials of antidepressants of adequate dose, and duration”. Although the classes and doses of antidepressant medications are not specified in the definition, the duration of an appropriate trial ranges between 4 and 8 weeks per EMA and FDA, respectively. This definition is pragmatic and simple but clearly lacks precision. For instance, what does “failure to respond” really mean? Is it partial response or non-response? Other limitations of this definition include the lack of mention of augmentation strategies, psychotherapy, or adoption of neuromodulation techniques. Furthermore, this definition doesn’t consider the baseline severity or duration of the depressive episode, presence of comorbidities including personality disorders, or substance use disorders, nor any history of trauma and childhood adversities.

The Thase-Rush TRD staging model is a another well-known definition of TRD that implies a hierarchy in terms of efficacy among classes of antidepressants (Thase and Rush 1997). These authors view TRD as a continuum rather than a categorical measure, where the individual progresses into five stages as they develop resistance to different classes of antidepressants in a specific order, as shown in Figure 1. Although this definition is simple, pragmatic, and similar to day-to-day clinical practice, it is based on non-validated assumptions: for example, a monoamine oxidase inhibitor is deemed more potent than a tricyclic antidepressant reflected in stages 3 & 4. Another example is utilizing electroconvulsive therapy (ECT) as a last resort after the failure of 4 classes of antidepressants, despite being one of the most effective treatments for TRD. Similar to the FDA/EMA definition, there is no consideration of the severity or duration of the depressive episode, and there is no mention of the comorbidities or psychotherapy interventions.

Finally, a more recent model to define TRD is the Maudsley Staging Model (MSM), which includes three dimensions of resistance: treatment failure scored over 7 points (failure to antidepressants, augmentation strategies, and ECT), and duration and severity of the depressive episode scored over 3 and 5 points, respectively. TRD is identified early on, as soon as the first pharmacotherapy trial. Nonetheless, psychotherapy is not included in this definition (Fekadu, Donocik et al. 2018).

**What about TRD in the geriatric population?**

At least 30% of older adults live with TRD, and increased age itself is a risk factor for TRD. Older patients are subject to pharmacokinetic changes that affect plasma concentrations of antidepressant medications, and the amount of drug that arrives to the brain. In addition, older adults suffer from multiple comorbid medical illnesses, such as hypothyroidism and cancer, which are associated with atypical and complex presentations of depression. Older patients are often affected by polypharmacy (including chemotherapy, steroids, antihypertensives, and others), which can exacerbate depressive symptoms and increase the risk for drug-drug interactions. Clinicians should thus be cautious with prescriptions aiming to maximize the benefits of antidepressants while minimizing risks. Geriatric depression commonly presents with comorbid cognitive impairment, which can also increase the risk for treatment resistance and the likelihood of developing a major neurocognitive disorder (Subramanian, Oughli, et al.,. Moreover, comorbid cognitive impairment is associated with poor adherence to medications, leading to a situation of “pseudoresistance” to antidepressants. Hence, ensuring good adherence to medications is a must before evoking TRD in this population. Other overlooked risk factors for geriatric TRD include undiagnosed alcohol and substance use disorders, as well as psychosocial factors such as grief, retirement, and disability, all of which warrant specific psychotherapy interventions in this population (Bonner and Howard 1995).

Unfortunately, current clinical trials investigating treatments for geriatric TRD have been using the classical FDA/EMA definition, which doesn’t consider the unique risk factors for TRD in this population. In addition, the patients with the most severe symptoms and those with cognitive impairment are typically excluded from research trials; this limits the generalizability of the findings to the “true” geriatric population characterized by multiple medical comorbidities, polypharmacy and frailty. Augmentation strategies with some agents such as antipsychotics can be risky in older patients carrying a diagnosis of major neurocognitive disorder/dementia due to the box warning of increased risk of mortality and cerebrovascular events in this population. On the other hand, more conservative options such as psychotherapy are not always applicable due to comorbid cognitive impairment. Future research should focus on developing a more specific definition for geriatric TRD, which could lower the threshold for detection and incorporate important disease-modifying factors. Prompt and aggressive management of TRD will not only improve mood and quality of life, but will also affect the cognitive status of older patients by delaying onset or progression of cognitive impairment in this population.

**Figure 1. Thase and Rush Staging model for TRD.** Adapted from (Thase and Rush 1997)

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