

**An Operational Definition of Treatment
Resistant Depression to be used in
Medicare Populations: a staged approach
and factors contributing to the definition**

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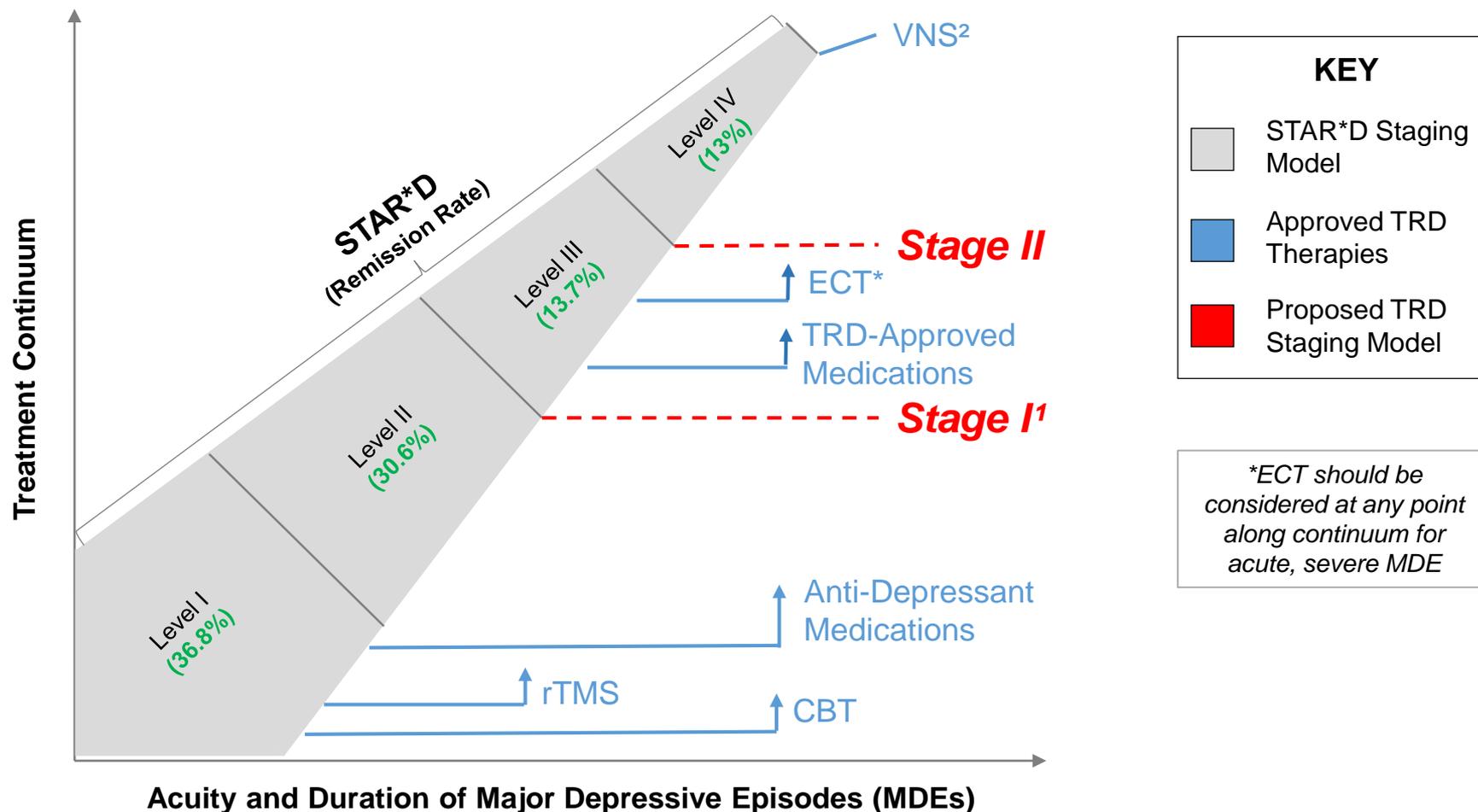
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Major Depressive Disorder (MDD): A Staged Approach to Determining Treatment Resistance



VNS: Vagus Nerve Stimulation
 ECT: Electroconvulsive Therapy
 rTMS: Repetitive Transcranial Magnetic Stimulation
 CBT: Cognitive Behavioral Therapy

¹Studies: Rizvi, 2014; Kubitz, 2013; Vieta & Colom, 2011; Albert, 2015

¹Guidelines: VA/DoD, 2009; NICE, 2009; AHRQ, 2011; APA, 2010

¹Health Tech Assessments: Oregon HERC, 2012; AHRQ, 2011; ICER-CEPAC, 2011

²AHRQ, 2011; APA, 2010

Critical Characteristics of a Research Operational Definition of TRD for Medicare Beneficiaries

In answer to CMS queries, what are the defining characteristics of TRD that are to be considered in clinical research:

- **The number, duration, dosage, and/or classes of antidepressants attempted**

Yes, as noted in previous slide, the STAR*D trial bases stages of resistance on the number of failed adequate dose-duration antidepressant trials¹. We believe two research quality trials of antidepressant treatment (pharmaco/psychotherapy need to be attempted.

- **The use of augmentation/combination pharmacological therapies**

Yes, the STAR*D trial did employ combination and augmentation trials as part of the sequential treatments. Empirically-based successful antidepressant combinations of adequate dose-duration should be considered an adequate trial¹.

1. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006; 163:1905-17.

Critical Characteristics of a Research Operational Definition of TRD for Medicare Beneficiaries (cont.)

In answer to CMS queries, what are the defining characteristics of TRD that are to be considered in clinical research:

- **Type of depressive episode (unipolar, bipolar, psychotic, atypical, other)**

Yes. Standard rating scales for TRD, such as the ATHF, rely on empirical evidence regarding the efficacy of particular interventions in depressive subtypes. In particular, distinctions are made between unipolar and bipolar depression, and between psychotic and nonpsychotic depression.

For psychotic depression, for a trial to be considered adequate an antidepressant must be combined with an antipsychotic medication, with both at adequate dose and duration. This is based on considerable evidence that effectiveness in psychotic depression is much greater for the combination than for monotherapy.

The treatment studies for bipolar depression appear to be different from unipolar illness; bipolar depression may respond better to mood stabilizing agents with/without antidepressants. Clinically distinguishing bipolar depression from unipolar is therefore likely to be critical.

The evidence for “pharmacological dissection” is weak or absent for other subtypes.

Critical Characteristics of a Research Operational Definition of TRD for Medicare Beneficiaries (cont.)

In answer to CMS queries, what are the defining characteristics of TRD that are to be considered in clinical research:

- **The use of nonpharmacological treatments such as electroconvulsive therapy**

We believe ECT has a distinct and critical place in the treatment of TRD; however, we do not believe it should be a mandatory therapy required for operational definition of TRD. This is based on the fact that some forms of ECT have risks of memory impairment, it requires repeated exposure to general anesthesia, patients may not work during a course or drive a car, and general patient preference.

- **The use of psychotherapy**

Yes, similar to the STAR*D trial, a trial of a proven psychotherapy (CBT, IPT) should be considered an adequate antidepressant trial.

Critical Characteristics of a Research Operational Definition of TRD for Medicare Beneficiaries (cont.)

In answer to CMS queries, what are the defining characteristics of TRD that are to be considered in clinical research:

- **Score changes on standardized and validated depression rating instruments (e.g. Hamilton Depression Rating Scale)**

Yes, we believe it would be reasonable to employ standardized measures of depression to assess for the presence of major depressive disorder.

We do not believe there should be a minimal score, as recent evidence suggests that there are many patients who experience TRD in mild, moderate, and severe range for years, even decades (i.e., it is not always present with severe symptomatology²).

- **Suicidal ideation and suicide attempts**

No, although suicidal ideation and attempts are more common in TRD^{2,3}, we do not believe suicidal ideation/attempts would be a good characteristic to include in an operational research definition of TRD.

2. Conway CR, Gebara MA, Walker MC, et al. Clinical characteristics and management of treatment-resistant depression. *J Clin Psychiatry*. 2015; 76:1569-70.

3. Amital D, Fostick L, Silberman A, et al. Serious life events among resistant and non-resistant MDD patients. *J Affect Disord*. 2008; 110:260-4.

How to apply a Research Operational Definition of TRD for Medicare Beneficiaries in Different Settings

In answer to CMS queries, how confident are you that this definition can be applied to Medicare beneficiaries:

a. In primary care settings

No, though it might be possible to apply an operational TRD definition of Stage II TRD (failure of two adequate dose-duration trials); however, most primary care settings have limited expertise in TRD management.

b. In general psychiatric settings

Yes, general psychiatric settings would be optimal for Stage I and II TRD studies.

c. In specialty psychiatric settings?

Yes, for collection of data determining the efficacy of a novel/invasive treatments, it would be critical to use centers with specific training and expertise in managing patients with TRD.

These centers would have previously been involved in studies of rTMS, VNS, DBS, ketamine, etc. and will have expertise in identification of TRD patients and management of these patients in clinical trial settings.

How to apply a Research Operational Definition of TRD for Medicare Beneficiaries in Different Settings

In answer to CMS queries, how confident are you that the strategies below, when applied to Medicare beneficiaries, represent meaningful and realistic study designs in research investigations performed to evaluate interventions for TRD?

a) randomized sham-controlled double blinded trial, b) randomized sham-controlled single blinded trial; c) randomized controlled unblinded trial; d) randomized crossover study; e) nonrandomized crossover study; f) Pre/Post study design; g) other.

We believe that the optimal study design for a given TRD treatment is determined by the nature of the treatment, e.g., pharmacotherapy/psychotherapy/neurostimulation therapy, etc., as well as the questions remaining regarding efficacy of the TRD treatment.

Each of the study designs listed above has some advantages. The most definitive of these designs is the randomized sham-controlled, double blinded trial, which would be most advantageous in making final determinations of TRD antidepressant efficacy.