Current Nosology of Treatment Resistant Depression: A Controversy Resistant to Revision

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Abstract: Treatment-Resistant Depression (TRD) represents a source of ongoing clinical and nosological controversy and confusion. While no univocal consensus on its definition and specific correlation with major mood disorders has been reached to date, a progressively greater number of evidences tend to suggest a revision of current clinical nosology. Since a better assessment of TRD should be considered mandatory in order to achieve the most appropriate clinical management, this narrative review aims to briefly present current most accepted definitions of the phenomenon, speculating on its putative bipolar diathesis for some of the cases originally assessed as unipolar depression.

Keywords: Treatment Resistant Depression, Bipolar Disorder, Controversy.

EPIDEMIOLOGY OF TRD

Treatment-resistant depression (TRD) is a relatively common condition presenting with substantial challenges to both the clinician and researcher [1].

In fact, despite a progressively higher number of available antidepressant therapies, TRD occurs frequently in clinical practice, and is associated with profound psychosocial disability, personal suffering and economic cost burden. Between one and two thirds of Major Depressive Disorder (MDD) patients will not respond to the first antidepressant prescribed and 15 to 33 percent will "resist" to multiple interventions, including non-pharmacological therapies [2].

Increasing the burden associated with MDD, its high prevalence: World Health Organization (WHO) estimated that 5-10% of the population at any given time is suffering from identifiable depression needing psychiatric or psychosocial intervention, while the life-time risk of developing depression is 10-20% in females and slightly less in males [3].

Prevalence estimates for TRD are available from several sources, including large clinical trials [4], large meta-analyses [5], or naturalistic studies [6-8]. For example, in the first level of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, only about 30% of patients were in remission following up to 12 weeks of therapy with the Selective Serotonin Reuptake Inhibitor (SSRI) citalopram [9]. In addition, 15.8% of patients developed an intolerable adverse event, 38.6% moderate-to-severe impairment due to an adverse event, 8.6% discontinued treatment due to adverse events, and 4% developed a serious adverse event, findings that underscore efficacy and tolerability limitations of treatment with a typical first-line antidepressant agent.

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Papakostas and Fava [10] reviewed 163 randomized, double-blind, placebo-controlled trials involving the use of antidepressants for MDD. Approximately 53.4% of patients responded following treatment with an antidepressant, compared to 36.6% of patients who responded following the administration of a placebo pill. Corey-Lisle and colleagues [11] reported that approximately 22% of patients who received treatment for depression by their primary-care physicians remitted following 6 months of treatment, 32% were partial responders, while 45% were non-responders. Similarly, Rush and colleagues [8] reported an 11% remission rate and 26.3% response rate among depressed outpatients following 12 months of treatment of depression in one of several public-sector community clinics. Petersen and colleagues [6] report a 50.4% remission rate among outpatients with MDD enrolled in 1 of 2 hospital-based, academically affiliated depression specialty clinics (Massachusetts General Hospital, an affiliate of Harvard Medical School and Rhode Island Hospital, an affiliate of Brown University) following an average of 25.8 weeks of treatment. Finally, it is also worth noting that while partial or non-response are common, residual symptoms among remitters are also highly prevalent [12, 13], being usually associated with poorer psychosocial functioning [14] as well as an increased relapse rates [15], higher suicidal ideation and attempts, higher number of lifetime hospitalizations, more frequent healthcare resources utilization, general practitioner consultation, job loss and social retirement [16].

ISSUES IN DEFINING TRD: A CLINICAL CONTROVERSY "RESISTANT TO REVISION"

Attempts at overcoming treatment resistance in major depression begin with the clinical controversies in defining it.

Currently, there are no universally accepted operational definitions of TRD.

Since more effective treatment approaches are needed for treating TRD, regardless on how it is defined, the purpose of

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this narrative review is to assess current major definitions of TRD and to briefly discuss its putative bipolar diathesis for some of the affected patients.

Actual *definition* and clinical *classification* of TRD represent debated issues: while some literature evidences tend to progressively suggest to revise its current nosology, others tend to be more conservative, actually making TRD a "resistant clinical controversy".

According to research practice, a lack of response (not necessarily TRD per se) is usually defined by "failure to reduce of at least 50% in the Hamilton depression (HAM-D) [17] total score" or as "failure in reducing below a specific cut-off" while less objective TRD clinical definitions include "failure in symptoms resolution" or the more accepted "failure to respond to 2 or more *adequate* antidepressant trials" [18].

The definition of an adequate treatment trial of antidepressant medication varied widely over the years, as the corresponding definitions of treatment resistance did. In actuality, TRD patients present with histories of varying degrees of treatment adequacy. A high proportion of cases referred to university settings specifically for evaluation and treatment of "refractory" depressions have not received even a single adequate anti-depressant trial [19].

Clinical controversies related to TRD refer not only to its definition but also to the way this latter is conceived: the "adequacy" of a trial as well the definition of "non response" seem to be misleading concepts.

There are 3 major treatment-resistance classification systems: a 5-stages classification (stages get up depending on the number of previously failed adequate trials, with fifth one proposing bi-temporal Electroconvulsive Therapy - ECT), the National Institute for Clinical Excellence (NICE) guidelines (providing a short algorithm) and the multi-level structured Massachusetts General Hospital (MGH) criteria [20].

About the "adequacy" of a trial, there is no absolutely "correct" dosage for a specific antidepressant, since dosage requirements vary depending on factors such as age, weight, general health, concomitant medication usage, and tolerance of a particular medication. Confirmation of treatment adequacy by more objective means (e.g., serial plasma drug levels) is not the rule in clinical practice, and valid plasma level–response relationships are limited to only a subgroup of the Tricyclic Antidepressants (TCAs) and lithium salts. Conventionally, adequate trials should last at least for 8-weeks, considering full antidepressant doses (e.g. 20-60mg/day for the SSRI fluoxetine or 150-300mg/day for the TCA clomipramine) when needed. Yet, 8-weeks is just the average RCTs follow-up, with clinical practice often requiring more prolonged exposure time. Remission usually takes up to 6 months of MDD antidepressant therapy, while recovery – with substantial symptoms resolution – usually requires at least a 12 months follow-up. Remarkably, most of antidepressant medications have a lag-phase of at least 3-4 weeks prior exhibiting any substantial clinical response, thus making hyper-dosing a rational strategy if response observed by weeks 5 or 6 is insufficient, while a too praecox pharmacological switch should be avoided in all the cases [21].

With respect to psychotherapy, adequacy of treatment may depend on the number of sessions, the expertise of the practitioner, the therapist's adherence to a particular form of therapy, and/or the interaction of the patient–therapist dyad [22]. ECT may be gauged by the total number of treatments, the use of bilateral electrode placement, and the verification of seizure time by electroencephalographic monitoring. Therefore, the terms "relative" and "absolute" treatment resistance may best describe lesser and greater degrees of certainty about the adequacy of a specific treatment trial [19, 23].

Similarly substantial variability exists as to the definition of an acceptable treatment response.

The most common response criteria in clinical trials are a rating of at least "much improved" on the Clinical Global Impressions (CGI) scale, a pre-specified level of improvement on a depression symptom rating scale (e.g., >50% reduction in Hamilton Depression Rating Scale scores), a final absolute score on a symptom measure, or some combination of the above. Both the use of composite outcome criteria and documentation of persistent improvement (e.g., for 2 weeks or longer) may improve reliability and validity of classification [24].

At least a 50% reduction in depressive symptom severity generally corresponds to the clinician's global clinical impression of a moderate level of improvement [2]. However, some patients meeting this commonly used response definition continue to have considerable residual symptomatology. Residual symptoms convey a higher risk of relapse during continuation treatment and likely contribute to suboptimal restoration of vocational or interpersonal functioning. Therefore, complete symptom remission is the desired outcome of acute treatment. The term *remission* describes a response in which a formerly depressed person's level of residual symptomatology is essentially indistinguishable from someone who has never been depressed. With respect to standardized scales, a score of 6 or less on the 17-item Hamilton Rating Scale for Depression is often used to define a remission [17]. As for response, non-response quantification may vary ($HAM\text{-}D_{17} \geq 75\%$=remission; 50%-74%=response; 25%-49%=partial response; <25%=non-response), with "treatment-non-response" being also defined as poor response to a single adequate antidepressant trial and "treatment-resistant depression" and "chronic-resistant depression" if resistance lasts for at least 12 months despite 2 or more adequate antidepressant trials (including augmentation strategies).

As further confounding variable, the fact that TRD itself sometimes receives different appellations (e.g. "treatment-refractory" or "therapy-resistant" depression) as no univocal definition of the "adequacy" of an antidepressant trial does exist, making a desirable revision of current TRD nosology a difficult, "resistant", process.

CLINICAL MANAGEMENT

Overcoming TRD nosological boundaries require a careful evaluation of the associated clinical features.

First step should be an appropriate anamnesis, eventually integrating validated instruments as the Antidepressant Treatment History Questionnaire (ATRQ) [25, 26].

The recognition of depression subtypes (particularly melancholic, psychotic, atypical, and seasonal) is an important element in the evaluation and management of TRD because individuals with different subtypes of depression may respond in somewhat different ways to the available therapies, or eventually predict a soft bipolar diathesis (e.g. in case of seasonal or atypical features). Additionally, resistance to treatment may also be related to *differential diagnosis* mistakes as misdiagnosis of a unipolar MDD in patients with declared (full-threshold) or undeclared (sub-threshold) BD.

Patients with BD present in the depressive phase 2 to 3 times more often than they do in the manic state and it is estimated that BD I is undetected in 35% to 45% of patients [27]. It is important to evaluate patients with TRD specifically for a history of manic or hypomanic episodes to rule out bipolar spectrum disorders since depressive episodes may be the (only) clinical presentation of Bipolar Disorders (BDs) for many years [28].

Compliance is also a sensitive issue, while a delayed "adequate" treatment should become ineffective if too much retarded: only 60% of persons with depression are treated for the disorder [2].

An *appropriate evaluation of psychiatric and medical comorbidities* as well a careful acknowledgement of current Major Depressive Episode (MDE) features is mandatory.

As mentioned, many of TRD cases show-up with psychotic or atypical features, often requiring more personalized therapies [29, 30]; for example, treating with SSRIs instead of Mono-Amino-Oxidase Inhibitors (MAO-I) or TCAs a MDE with atypical features may lead to "*pseudo-resistance*" instead of a true "resistance" phenomenon [31].

Concerning axis-I psychiatric co-morbidities, Souery et al. (1999) reported up to 3.2% ($p<0.001$) Panic Disorders, Social Phobia 2.1%; ($p<0.008$), other anxiety disorders 2.6% ($p<0.001$) and axis-II DSM-IV-defined Personality Disorders 1.7% ($p<0.049$). Remarkably, early age of onset (<18 years) 1.7% ($p<0.009$) and current DSM-IV-defined melancholic features 1.5% ($p<0.018$) were a frequent TRD association [20]. Also, most TRD cases have multiple co-morbidities and this further increases the burden load, reducing the chance of a substantial inter-episodic depressive symptoms resolution, therefore increasing the risk for relapse [15]. One of the most important set of comorbidities that contributes to inadequate treatment response in MDD and other disorders is substance (including alcohol) use disorders and it may be carefully considered too when treatment resistance arises in MDD patients since this may require specific treatment approaches [32] and eventually be in favor of a bipolar diathesis [33].

TRD comorbid psychiatric disorders are often missed or are sub-optimally treated, and they can confound both the evaluation and the management of depression.

TRD-associated biological factors include a reduction in frontal cortex and hippocampal volumes, increase in ventricular volume and amygdala hyperactivity with poor inhibition by prefrontal-cortex, contributing in making most TRD patients hypersensitive to environmental stressors [34]. Nonetheless, currently proposed biomarkers for TRD still require further evidences as false positives cases could occur [35].

Frequent TRD medical co-morbidities include infective diseases (e.g. HIV and *borna* virus) and endocrine disorders as hypothyroidism or HPA-axis imbalances (up to 50% of TRD cases present a non-suppression with the dexamethasone test due to HPA hyperactivity) [36]. Yet, a major medical comorbidities for most TRD cases is represented by cardiovascular disease and diabetes [37, 38].

The implication for treatment is to address these conditions simultaneously, if possible, to avoid consolidating treatment resistance [28].

THE NEED FOR THERAPEUTIC MANAGEMENT AND NOSOLOGICAL REVISIONS

What if TRD persists despite repetitive "adequate" trials and accurate considerations of the potential confounding or concomitant factors?

To date, the STAR*D study represents the broadest, multi-centric clinical trial ever conducted on MDD assessment [39]. STAR*D lasted for 7 years (Oct 1999-Sept 2006) involving both primary care and psychiatric facilities and adopting minimum exclusion criteria ("real world"), with "remission" as primary outcome instead of "response". Remarkably, 2876 patients (4041 enrolled) had at least one axis-I co-morbidity at baseline. Unfortunately, despite a multi-level algorithm including switches and augmentation strategies with different "antidepressant" classes, lithium, thyroid hormones and Cognitive Behavioral Therapy (CBT), remission rates were almost equivalent for stages I vs. II (32.9% vs. 30.6%) and stages III vs. IV (final), (13.6% vs. 14.7%); authors concluded that no specific antidepressant treatment was superior to any other one, with CBT role remaining a debated issue [40].

While popular clinical augmentation or switch strategies for TRD include a broad number of compounds (e.g., thyroid hormones, estrogen, lithium, pindolol, atypical antipsychotics, stimulants, inositol, Omega-3 fatty acids, DA-agonists, herbal supplements, lamotrigine, etc…) most of them are not accounted in "official" TRD guidelines [41]. Also, meta-analyses data tend to suggest the switch strategy versus the augmentation one, with lithium and atypical antipsychotic medication as more favored choice [5, 42, 43].

Remarkably, lithium and atypical antipsychotics use is much more consolidated for bipolar disorders rather than unipolar depression. Should be this *an ex-adiuvantibus therapy*? Also, it is interesting to observe how a considerable number of TRD cases show-up with atypical-MDEs or have an earlier age of onset compared non-resistant MDDs?

Sharma *et al.* (2005) tried to answer at some of these questions investigating 69 patients diagnosed with treatment resistant-MDD ("failure to respond to 2 or more adequate clinical trials") at a local mood clinic; when patients were re-tested using the Structured Clinical Interview for Axis-I disorders (SCID-I) [44] 35% of them were diagnosed as bipolar. The whole sample, was re-tested 1 year later, showing 41% MDD, 3% BP-I, 43% BP-II, 13% bipolar-NOS. Interestingly, most of former-MDD-TRDs significantly improved

in Clinical Global Impression (CGI) [45] total score when switched from antidepressants to mood-stabilizers [46].

Indeed, most "false unipolar" [47] TRD cases presented a rapid pop-up on antidepressant, frequent motor agitation, somatic symptoms and fatigue and a history of polypharmacy, which may be accounted as a potential iatrogenic phenomenon for mixed states and cyclicity among those with a supposed bipolar diathesis [48].

Further evidences suggesting that some TRD-MDD patients may have (or acquire) a bipolar diathesis, have been also provided by the French national naturalistic "EPIDEP" study, which major outcomes included the evaluation of bipolar patients using also temperamental instruments (as the Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Auto-questionnaire – TEMPS-A) [49]. Cyclothymic-sensitive and Depressive temperaments, along with motor agitation, greater severity of current depressive episode, scored significantly higher among those with BP-TRD [50].

The adoption of less restrictive diagnostic criteria (e.g. 2 days of hypomania vs. the arbitrary DSM-IV 4 days duration one) and the use of sensitive (yet acceptable in sensitivity) instruments (e.g. Hypomania Check-List 32-items – HCL-32) [51] may lead to a prompter recognition of sub-threshold "resistance" clusters (e.g. "depressive mixed states" – MDE + 2 hypomanic features) [52] following a bipolar diathesis.

SHOULD SOME TRD CASES FOLLOW A BIPOLAR DIATHESIS OR SHOULD THE TRD NOSOLOGY BEEN REVISED?

While no data support the evidence that all TRD cases should follow a bipolar diathesis, neither they support the opposite.

It is interesting to observe how most recent evidences tend to suggest a bipolar diathesis in a subgroup of DSM-IV-defined unipolar depressed patients and how significantly should the clinical outcome be influenced by different therapeutic implications (as pointed out by preliminary Systematic Treatment Enhancement Program for Bipolar Disorder – STEP-BD evidences) [53].

Finally, when TRD lasts for a very long time (despite repetitive "adequate" trials), it should be prudent to promptly revise diagnosis and/or therapeutic choices.

In fact, prolonged antidepressant treatments may induce bipolar phenomena as rapid cyclicity and mixed states as well as antidepressant-resistance in some patients and their over-prescription should therefore be avoided [54], preferring lithium and atypical antipsychotics, as indicated by the BP-TRD algorhythm recently proposed by Pacchiarotti et al. [55].

Also, while a bipolar hypothesis for some TRD cases is definitely not a novel approach, it appears to become a gradually more popular remark, especially considering that further insights are progressively acquired about a potential bipolar diathesis for some of the features sometimes associated with TRD too: just to mention one, a history of substance abuse is today almost widely accepted as a strong bipolar feature.

In conclusion, directions for future research on TRD shouldn't apart from a substantial revision of the way TRD itself is defined. Adopting widely accepted criteria for the "adequacy" of a trial as well for the concept of "resistance" is mandatory in order to allow researchers to give rise to a hoped international collaborative group. Specifically, more attention should be placed on a plausible bipolar diathesis for some of the TRD cases as a progressively greater number of latest literature evidences tend to support this view.

Otherwise, till a consistent revision of current boundaries of TRD nosology will be performed, we'll have no opportunity to fully overcome the resistance phenomenon.

CORE ABBREVIATIONS

TRD: as Treatment Resistant Depression; MDD: as Major Depressive Disorder; BP: as Bipolar Disorder.

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