Treatment-resistant depression: when should we consider bipolarity?

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Abstract

Despite effective pharmacotherapeutic and psychosocial strategies, approximately one third of adequately treated depressive patients do not reach remission and are considered "treatment resistant". There are several factors associated with treatment-resistant depression (TRD). Underlying bipolarity is one of the important causes of TRD as it leads to a delayed diagnosis of bipolar disorder and inappropriate treatment. Assessment of bipolar features in every patient diagnosed with major depressive disorder (MDD), specifically in patients with TRD, is crucial. In the presence of bipolar features, interventions for TRD should be carried out carefully.

Definition and clinical impact of treatment-resistant depression

Major depressive disorder (MDD) is one of the leading causes of disability and global burden of disease. MDD is associated with increased utilization of health care resources, diminished quality of life, and indirect personal and societal costs (1). The average lifetime and 12-month cross-national prevalence is 14.6% and 5.5% in high-income and 11.1% and 5.9% in low- to middle-income countries (2).

The primary aim of MDD treatment is the absence of depressive symptoms and complete recovery from impaired function (3). However, despite effective pharmacotherapeutic and psychosocial strategies, approximately one third of adequately treated depressed patients do not reach remission, and are considered "treatment resistant" (4). Sequenced Treatment Alternatives to Relieve Depression (STAR*D), the largest prospective study conducted on the treatment of depression, showed that only 37% of depressed patients remitted after an initial 12-week treatment trial, and overall only 67% reached remission after four treatment trials (5).

Definitions of TRD vary. It is most commonly defined as the failure to induce a clinically meaningful improvement with two or more different antidepressant compounds with different mechanism of action, used for a sufficient length of time at an adequate dose, with adequate affirmation of treatment adherence (6, 7). However, revision of this definition is necessary as the STAR*D results did not confirm the implied assumption that switching treatment within the same class is less effective than switching to a different class of antidepressant (6). The other definitions of TRD, which need further investigation of reliability and predictive utility, include single criteria, such as failure (defined as lack of response to antidepressants or need for electroconvulsive therapy (ECT)), and are based on staging models with multiple criteria such as number of treatment failures, symptom severity and use of ECT (8).

The clinical and economic burden seen in MDD is intensified in TRD. TRD patients are twice as likely to be hospitalized, have 12% more outpatient visits, use 1.4 to 3 times more psychotropic medications and experience more medical and psychiatric co-morbidities (9).These increased detrimental effects highlight the need for additional research regarding the definition, etiology, course, and treatment of TRD (9).

Causes of treatment-resistant depression: focus on bipolar diathesis

Attempts to identify potential predictors of TRD have included the evaluation of various clinical and sociodemographic variables. Several predictors of TRD have been consistently supported in the literature (9).

Studies show that older age, bipolarity, presence of atypical, melancholic or psychotic features, co-morbid anxiety, substance use and personality disorders, suicidal risk, co-morbid medical diseases, and higher

baseline severity and longer duration of depressive symptoms, were associated with increased rates of non-response/non-remission (4, 9, 10). In terms of psychiatric history, non-response to the first antidepressant treatment, early onset of first depressive episode, a high rate of depressive recurrences, lack of full remission after a previous episode, and higher number of previous hospitalizations were shown as predictive clinical factors for TDR (4, 9, 10).

Missed bipolarity is suggested as one of the important factors in TRD. This may lead to a delayed diagnosis of bipolar disorder (BD), with an average of 10 years between first symptoms and first treatment, potentially leading to favourable outcomes (11). Delayed diagnosis of BD is associated with decreased quality of life, more time spent in the depressive phase and increased severity of depressive episodes, greater number of episodes and higher health costs (11, 12). As most of the initial episodes in BD tend to be depressive in nature, and mania may simply not yet have occurred, unrecognised bipolarity could also give rise to inappropriate treatments which could precipitate mixed symptoms, result in suicide attempts, and increase the risk of manic switch and cycle acceleration (13).

A growing number of studies in the last decade have clearly shown the association of TRD with BD. In a retrospective cohort study with a mean follow-up of 18.5 ± 9.5 years, diagnostic conversion to BD in patients with a primary diagnosis of MDD was more prevalent in TRD compared to non-TRD with rates of 40% and 11% respectively (14). Another study showed that the number MDD patients who exhibited bipolar spectrum features was significantly higher in the TRD group, and increased diagnostic conversion rates to BD in TRD compared to non-TRD patients, even after a 6 month follow-up period (15). The largest study to date, with a sample of 2459 MDD patients and 8 year follow-up, also revealed that diagnostic change to BD was strongly associated with antidepressant resistance. Difficult to treat patients were five times more prone to diagnostic conversion (16).

Assessment of bipolar diathesis and related treatment recommendations in treatment-resistant depression

In every patient diagnosed with MDD, particularly in the subset of patients with TRD, previous and index depressive episodes should be routinely screened for manic and hypomanic symptoms (7). Clinical factors favouring bipolarity that are concomitant with treatment resistance in an index depressive episode should also be carefully examined. These factors could provide supportive information on probable BD diagnosis and include tension/fearfulness, psychomotor agitation, atypical and psychotic features, depressive mixed states, irritability, postpartum onset, early age at illness onset, late insomnia, mood lability within episode, and family history of BD (13, 17).

The Mood Disorder Questionnaire (MDQ) and Hypomania Check List (HCL-32) can be used for assessment of bipolar features. The MDQ is a self-report screening tool for a lifetime history of manic or hypomanic symptoms, and the cut-off point for bipolarity has been established as the presence of seven or more symptoms (18). The HCL-32 is also a self-report screening questionnaire to detect possible lifetime symptoms of hypomania with a cut-off point of 14 or more for bipolarity (19).

In the presence of bipolar features, interventions for TRD should be carried out carefully. Currently, there are no structured guidelines or standards which have been established. Prioritising treatment choices that are more effective in bipolar depression is highly recommended. Treatments that are suitable for unipolar depression but could cause undesirable outcomes in the presence of underlying bipolarity should be avoided and prioritising the treatment options that are shown to be effective in bipolar depression is highly recommended. Antidepressant monotherapy is not recommended because of the increased risk of manic switch, potential to destabilise mood, and modest efficacy in bipolar depression (20, 21). Tricyclic antidepressants, and probably other dual action drugs like venlafaxine (and possibly duloxetine), should not be used in treatment. Selective serotonin reuptake inhibitors (SSRIs) (other than paroxetine) or bupropion are the recommended antidepressants in bipolar depression and they should be given with an anti-manic agent (e.g. lithium, valproate or an atypical antipsychotic) (20, 21). Monotherapy with lithium, lamotrigine and quetiapine is also effective and a first line recommendation for the treatment of bipolar depression; these medications can be used safely in TRD with bipolar features (20, 21). Augmentation of cognitive behavioural therapy with pharmacotherapy may be an another option, as it has been shown to be effective in both bipolar depression and TRD (22, 23). As well as targeting depressive symptomatology, specific interventions for the prodromal period of BD should also be considered. Although there is little

evidence for any intervention for the early phase of BD, psychoeducational and psychotherapeutic interventions targeting prodromal BD symptoms are preferable in the first instance (24).

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