Comparative Study Examining Psychopathological Traits and Clinical Outcomes in Patients with Unipolar Treatment Resistant Depression and Bipolar Depression

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PREFACE & CONTRIBUTION OF AUTHORS

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This study was approved by the Institutional Review Board of McGill University (13 – 375- PSY) and was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice with a registration date of November 2013.

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LIST OF ABBREVIATIONS

TRD-UP	Unipolar-Treatment Resistant Depression
MDD	Major Depressive Disorder
BP	Bipolar disorder
BP-I	Bipolar disorder type I
BP-II	Bipolar disorder type II
GAD	General Anxiety disorder
SUD	Substance use disorder
MDE	Major depressive episode
TCA	Tricyclic antidepressants
MAIO	Monoamine oxidase inhibitors
MS	Mood stabilizers
SGA	Second generation antipsychotics
AD	Antidepressants
SSRI	Selective serotonin reuptake inhibitors
BDNF	Brain-derived neutrophic factor
GAF	Global assessment of functioning
MADRS	Montgomery-Asberg Depression Rating Scale
HAM-D17	Hamilton Rating Scale for Depression
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
CANMAT	Canadian Network for Mood and Anxiety Treatments
STEP-BD	Systematic Treatment Enhancement Program for Bipolar Disorder
MSM	Maudsley staging Method
OR	Odds ratio
RR	Relative risk
CI	Confidence interval
CGI-S	Clinical Global Impression-severity of illness
ADHD	Attention Deficit-Hyperactivity disorder
IRB	Institutional Review Board
SCID	Structured Clinical Interview for Diagnosis

QIDS-C16	Quick Inventory of Depressive Symptomatology Scale
YMRS	Young Mania Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
SPSS	Statistical Package for the Social Sciences
MUHC	McGill University Health Center
MDC	Mood disorders clinic
SD	Standard deviation
GWAS	Genome wide association
GRIK4	Glutamate inotropic receptor kainate type subunit 4
SLC6A4	Serotonin transporter gene- Solute carrier family 6 member 4
KCNK2	Potassium two pore domain channel subfamily K member 2

ABSTRACT

Background

Despite many advances in the mood disorders field, depressive episodes continue to be a significant public health burden with a high impact on global functioning and increased mortality. During major depressive episodes (MDE) difficulties to distinguish unipolar (UP) from bipolar disorder (BP) commonly arise leading to ineffective treatments. Some authors have hypothesized that Treatment-Resistant Unipolar Depression (TRD-UP) should be considered as a new subtype of depression within the bipolar spectrum disorders. Furthermore, others considered bipolar traits as a risk factor for TRD-UP. Until now, no studies have examined demographic data and clinical predictors associated with each disorder and their respective pharmacological outcomes. Therefore, our efforts should be targeted to better characterizing clinical phenotypes and effective treatment strategies for TRD-UP and BP depression.

Methods

We conducted two individual retrospective cross-sectional chart analyses of patients followed at the McGill University Health Center (MUHC). In the first study, we examined sociodemographic and clinical features from 194 adult patients (age 19- 80) meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV/DSM-V) criteria for TRD-UP (n = 100) and BP (n = 94). The patient's diagnoses were ascertained by the Structured Clinical Interview for Diagnosis (SCID) and patients had to fail 2 or more adequate antidepressants (AD) trials. The following behavior scales were used to assess depression: Montgomery–Asberg Depression rating scale (MADRS), Hamilton-Depression Rating Scale (HAM-D17), Clinical Global Impression-Severity of Illness (CGI-S) and the Quick Inventory of Depressive Symptomatology (QIDS-C16). Binary logistic regression analysis was conducted to examine clinical predictors independently associated with the two disorders.

In the second study, we analyzed 86 TRD-UP patients who received ADs (n=36) or second generation antipsychotics (SGA) +AD (n=50) treatment. Patients were assessed by the same behavioral scales mentioned previously before (T0) and after the latest 3-month stable trial (T3).

Inter-rater reliability for individual scales was calculated using Cohen's kappa. Socio-demographic and clinical characteristics were analyzed by independent t-tests for continuous variables and Pearson's chi-square (χ^2) for categorical variables. Comparisons for all clinical scales of depression and general functioning between ADs and augmentation groups were evaluated using two-way repeated-measures ANOVA. A Logistic regression analysis was employed to study factors independently associated with treatment with SGA+AD. The statistical significance threshold p was set at $p<0.05$.

Results

For the first study, TRD-UP patients exhibited greater severity of depression on all scales ($p < 0.001$) with higher prevalence of anxiety and panic disorders ($p < 0.001$ for both), cluster C personality disorders ($p < 0.001$), melancholic features ($p < 0.001$), autoimmune diseases ($p = 0.014$) with fewer hospitalizations and later onset of depression ($p < 0.001$) compared to BP patients. Logistic regression showed that higher depression scores, comorbidity with anxiety disorders, lower global assessment of functioning and lower number of hospitalization and psychotherapies distinguished TRD-UP from BP. BP-II patients were mostly associated with higher suicide attempts compared to BP-I while the rate of unemployment, number of hospitalizations were mostly associated with BP-I.

In the second study, compared to ADs, the SGA+AD group showed an increased percentage of depression with psychotic features, co-morbidity for personality disorders and substance use disorders a higher number of failed ADs pharmacotherapies and depressive symptoms at T0 on all evaluated scales ($p<0.001$). Compared to baseline, both treatment modalities significantly decreased depressive symptoms on MADRS and HAM-D17 at T3 ($p<0.001$); however, the SGA+AD group had a higher decline in mean score. Logistic regression analysis indicated that psychotic features, personality disorders, and substance use disorders were independently associated with SGA+AD treatment.

Conclusion

By examining clinical and pharmacological outcomes in these two studies, our results strengthen the concept of TRD-UP as a possible distinct phenotype compared to bipolar depression. TRD-UP patients exhibited a statistically significant decrease in depressive symptoms while receiving augmentation treatment with SGA+AD which aligns with the FDA recommendation of SGA as augmentation for TRD. More clinical and pharmacological studies are needed to better comprehend the nature of resistant depression and to propose effective interventions.

RÉSUMÉ

Contexte

Malgré de nombreuses avancées dans le domaine des troubles de l'humeur, les épisodes dépressifs continuent d'être un lourd fardeau pour la santé publique, avec un impact élevé sur le fonctionnement mondial et une mortalité accrue. Pendant les épisodes dépressifs majeurs (MDE), des difficultés pour distinguer unipolaire (UP) du trouble bipolaire (BP) surviennent fréquemment, ce qui conduit à des traitements inefficaces. Certains auteurs ont émis l'hypothèse que la dépression unipolaire résistante au traitement (TRD-UP) devrait être considérée comme un nouveau sous-type de dépression dans les troubles du spectre bipolaire. De plus, d'autres considéraient les traits bipolaires comme un facteur de risque de TRD-UP. Jusqu'à présent, aucune étude n'a examiné les données démographiques et les prédicteurs cliniques associés à chaque trouble, et leurs résultats pharmacologiques respectifs. Par conséquent, il est urgent de mieux caractériser les phénotypes cliniques et les stratégies de traitement efficaces pour la dépression TRD-UP et BP.

Methods

Nous avons effectué deux analyses rétrospectives individuelles de tableaux transversaux de patients suivis au Centre universitaire de santé McGill (CUSM). Dans la première étude, nous avons examiné les caractéristiques sociodémographiques et cliniques de 194 patients adultes (âgés de 19 à 80 ans) répondant aux critères du Manuel diagnostique et statistique des troubles mentaux (DSM-IV / DSM-V) pour TRD-UP (n = 100) et BP (n = 94). Les diagnostics du patient ont été vérifiés par l'interview clinique structurée pour le diagnostic (SCID) et les patients ont dû échouer à 2 essais antidépresseurs (AD) adéquats ou plus. Les échelles de comportement suivantes ont été utilisées pour évaluer la dépression: échelle de Montgomery – Asberg Depression Rating (MADRS), Hamilton-Depression Rating Scale (HAM-D17), Clinical Global Impression-Severity of Illness (CGI-S) et Quick Inventory of Depressive Symptomatology (QIDS-C16). Une analyse de régression logistique binaire a été menée pour examiner les prédicteurs cliniques associés indépendamment aux deux troubles.

Dans la deuxième étude, nous avons analysé 86 patients TRD-UP qui ont reçu un traitement AD (n = 36) ou antipsychotiques de deuxième génération (SGA) + AD (n = 50). Les patients ont été évalués par les mêmes échelles comportementales mentionnées précédemment avant (T0) et après

le dernier essai stable de 3 mois (T3). La fiabilité inter-évaluateurs pour les échelles individuelles a été calculée en utilisant le kappa de Cohen. Les caractéristiques sociodémographiques et cliniques ont été analysées par des tests indépendants pour les variables continues et par le chi carré de Pearson (χ^2) pour les variables catégorielles. Les comparaisons pour toutes les échelles cliniques de la dépression et du fonctionnement général entre les AD et les groupes d'augmentation ont été évaluées en utilisant des mesures répétées bidirectionnelles ANOVA. Une analyse de régression logistique a été utilisée pour étudier les facteurs associés indépendamment au traitement par SGA + AD. Le seuil de signification statistique p a été fixé à $p < 0.05$.

Résultats

Pour la première étude, les patients TRD-UP présentaient une plus grande gravité de la dépression à toutes les échelles (p <0,001) avec une prévalence plus élevée d'anxiété et de troubles paniques (p <0,001 pour les deux), des troubles de la personnalité du groupe C (p <0,001), des traits mélancoliques (p < 0,001), maladies auto-immunes (p = 0,014) avec moins d'hospitalisations et apparition ultérieure de dépression (p < 0,001) par rapport aux patients BP. La régression logistique a montré que des scores de dépression plus élevés, une comorbidité avec des troubles anxieux, une évaluation globale plus faible du fonctionnement et un nombre plus faible d'hospitalisations et de psychothérapies distinguaient TRD-UP de BP. Les patients BP-II étaient principalement associés à des tentatives de suicide plus élevées que BP-I tandis que le taux de chômage, le nombre d'hospitalisations étaient principalement associés à BP-I.

Dans la deuxième étude, par rapport aux AD, le groupe SGA + AD a montré un pourcentage accru de dépression avec des caractéristiques psychotiques, une comorbidité pour les troubles de la personnalité et les troubles liés à l'usage de substances (SUD), un nombre plus élevé d'échecs de pharmacothérapies AD et des symptômes dépressifs à T0 sur tous échelles évaluées (p < 0,001). Par rapport à la ligne de base, les deux modalités de traitement ont diminué de manière significative les symptômes dépressifs sur MADRS et HAM-D17 à T3 (p < 0,001) ; cependant, le groupe SGA + AD avait une baisse plus élevée du score moyen. L'analyse de régression logistique a indiqué

que les caractéristiques psychotiques, les troubles de la personnalité et le SUD étaient indépendamment associés au traitement SGA + AD.

Conclusion

En examinant les résultats cliniques et pharmacologiques dans ces deux études, nos résultats renforcent le concept de TRD-UP comme phénotype distinct possible par rapport à la dépression bipolaire. Les patients TRD-UP ont présenté une diminution statistiquement significative des symptômes dépressifs lors du traitement d'augmentation avec SGA + AD, ce qui correspond à la recommandation de la FDA de SGA comme augmentation pour TRD. Davantage d'études cliniques et pharmacologiques sont nécessaires pour mieux comprendre la nature de la dépression résistante et proposer des interventions efficaces.

CHAPTER 1 –INTRODUCTION

1.1 MAJOR DEPRESSION AND TREATMENT-RESISTANT DEPRESSION

Epidemiological data show that approximately 11% of the people in industrialized countries suffer from a major depressive disorder (MDD), with a yearly incidence of approximately 4% representing a significant burden on the society (Patten *et al.*, 2009). Moreover, in the USA, it has been associated as the second cause of disability (Murray CJ *et al.*, 2013).

A major depressive episode can occur in the context of unipolar depression (i.e., presence of only depressive episodes) or bipolar depression (i.e., presence of both mania/hypomania and depressive episodes). It is characterized by the presence of two weeks of both low mood and anhedonia (loss of pleasurable activities) and five of the following symptoms: low energy, apathy or agitation, guilt or worthlessness, suicide ideation, poor concentration, psychomotor agitation/inhibition, and change in appetitive or weight. Additionally, DSM-5 has different specifiers for the episode, such as atypical features, melancholic features, catatonia, mixed features, seasonal patterns, psychotic features, anxious distress, or peripartum onset (American Psychiatric Association, 2013).

Despite the increased development of antidepressants (ADs) in the last few decades with more than 25 FDA-approved medicines for depression, 15% of the patients treated for depression will have an inadequate antidepressant response (Berlim *et al.*, 2007). Thus, patients who do not achieve therapeutic responses are diagnosed with treatment-resistant depression (TRD) (Fagiolini & Kupfer, 2003; Fava M, 2003; Sackeim, 2001). Considering data from the most extensive depression study, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, one out of three patients can suffer from treatment-resistant unipolar depression (TRD-UP) not responding to the first trial of an AD (Trivedi *et*

al., 2006). Although many definitions for TRD-UP have been proposed, the current consensus defines it as the inadequate response to at least two ADs (Berlim *et al.*, 2007; Souery *et al.*, 1999); the failure to achieve remission with two consecutive treatments is also associated with meager remission rates in subsequent treatments.

Unfortunately, thus far, there has been no adequate operational definition applied in clinical practice, and the diagnosis of TRD-UP continues to be a challenge because of the condition's complex pathophysiology, heterogeneous clinical presentation, and multiple strategies for therapeutic management. Despite the mentioned difficulties, attaining remission should still be considered the outcome goal to accomplish for those suffering from resistant depression (Schlaepfer *et al.*, 2012).

Therefore, the wide variation in the definition of TRD-UP and the low remission rates achieved with subsequent treatments and augmentation strategies poses the following questions: How can we accurately define and classify TRD-UP to avoid misdiagnosis and ineffective treatments? .Consequently, how does its phenotypic presentation and variants compare with other entities in the group of depression disorders (i.e., bipolar depression), and which of the pharmacological augmentation strategies leads to better outcomes (i.e., response and remission rates) and which clinical features are associated?.

Some exciting efforts to improve the outcomes for TRD have been made by identifying the patients at risk for a poor outcome during AD treatment (Uher *et al.*, 2012) as well as the development of clinical prediction algorithms, which include sociodemographic and clinical features (Perlis *et al.*, 2013). One of the main developments is from the Canadian biomarker network for depression (CAN-BIND) and its collaborative team. Its primary outcome is to fulfill this clinical need by integrating neuroimaging, molecular, and clinical data of the

treatment response to AD and adjunctive treatments. Importantly, this may provide a comprehensive understanding of the pathophysiology of depression, leading to novel biological biomarkers to adequately identify treatment-resistant patients (Lam *et al.*, 2016).

1.2 STAGING METHODS FOR TREATMENT-RESISTANT DEPRESSION

During the last few decades, different clinical staging models have been developed to systematize methods to identify patients with TRD-UP. These models have aimed to improve treatment outcomes by establishing specific criteria for patients with TRD-UP to determine the stage of the illness better, as has been done in other areas of medicine (Berk *et al.*, 2007; McGorry *et al.*, 2006).

One of the first models proposed by Thase and Rush classified TRD patients into different levels according to the number of therapeutic failures, according to AD classes (Thase & Rush, 1997). This earlier and pioneering staging model assumed the superiority of different classes of ADs over others upon inadequate response. Therefore, the conclusion of switching to a different class of AD would constitute a more effective strategy than switching to the same class of AD. This was exemplified by the updated assumption of a higher efficacy of tricyclic antidepressants (TCAs) over other ADs (Thase & Rush *et al.*, 1997). Currently, a challenge to this assumption was demonstrated in an extensive network meta-analysis, which compared the efficacy and tolerability of 21 ADs and placebo. The authors provided evidence that all the ADs as a group are more effective than the placebo and underscoring that the most efficacious ADs were: agomelatine, vortioxetine, venlafaxine, paroxetine, mirtazapine, escitalopram, and amitriptyline; the most acceptable were agomelatine, SSRIs (fluoxetine, (es)-citalopram sertraline) and vortioxetine (Cipriani *et al.*, 2018).

Previously, other models considered the number of optimization/augmentation trials with other agents as well as the number of treatment failures, which included the dose and duration, concluding with the degree of intensity of each trial (Fava, 2003; Souery *et al.*, 1999). Therefore, higher scores accounted for a more severe and resistant TRD clinical presentation.

One of the latest staging models proposed in the literature is the multidimensional model Maudsley Staging Method (MSM), which further improves previous models by considering the following: duration and severity of depression, number of failed treatments, and the use of different augmentation treatments, including the use of electrical convulsive therapies (Fekadu *et al.*, 2009). Recently, Geugies *et al.* (2018) conducted a study examining a large naturalistic cohort of depressed patients (N = 643) and suggested that the MSM was a promising tool to predict outcomes in depressed patients (Geugies *et al.*, 2018). Furthermore, van Belkum and colleagues investigated and attempted to validate the MSM. In a cohort of 643 subjects, the authors showed that the MSM significantly predicted the percentage of time depressed and the time of persistent depression as compared to the baseline after a two-year follow-up (Van Belkum *et al.*, 2018).

Therefore, the clinical utility of staging models (i.e., MSM) should be further investigated as an applicable clinical tool to identify patients at risk to offer intensive treatment regimens in the earlier phases of the illness. Moreover, these staging models can be used to identify patients with lower levels of treatment resistance, who may respond to different treatments. Future clinical trials and pharmacogenetic studies should examine whether different levels of treatment resistance can be tailored for specific pharmacological treatments.

1.3 BIPOLAR DISORDER

Bipolar disorder (BP) is a heterogeneous and complex mood disorder that contributes to a significant worldwide burden with high rates of morbidity (Frye, 2011). Overall in the general

population, prevalence rates for both bipolar-type I (BP-I) and bipolar-type 2 (BP-II) has been estimated to range between 3.4% and 4% (Kessler & Merikangas, 2005).

BP is characterized by the presence of a past or current episode of hypomania/mania (i.e., pressured speech, flight of ideas, increased goal-directed activity, psychomotor agitation, and decreased need for sleep) of a duration of four days and one week, respectively, alternating with phases of depression (American Psychiatric Association, 2013).

The depressive phase of the illness has been linked to higher disability and is considered the most challenging phase of the disease (Bauer *et al.*, 2018), considering the high rate of completed suicidality early in the illness (Tondo *et al.*, 2003). In a study that investigated suicidal risk factors in adult patients with BP and MDD, the authors highlighted that suicidal behavior (ideation and attempts) were higher in BP patients (Baldessarini *et al.*, 2019). According to many authors, the depressive symptoms of BP tend to be the first clinical presentation of the illness with a significant amount of time spent in this phase (Judd *et al.*, 2003; Judd *et al.*, 2003; Angst & Sellaro, 2000) resulting in higher work dysfunctionality (Kessler *et al.*, 2006).

1.4 UNIPOLAR VS. BIPOLAR DEPRESSION: DIFFERENT DISORDERS

In general, most depressive episodes can be diagnosed as MDD; however, depressive symptoms tend to overlap with other psychiatric conditions, such as attention deficit hyperactivity disorder, personality disorders, schizophrenia, other BP, and medical conditions (i.e., Parkinson's and hypothyroidism), or be induced by substance use disorders (SUDs).

As mentioned previously, during depressive episodes, difficulties to effectively distinguish UP from BP frequently arise with misdiagnosis resulting in inadequate and unnecessary treatments and higher health costs, leading in many cases to patients' mood instability or adverse events. Moreover, 69% of the BP patients are diagnosed as UP with a delay in diagnosis of approximately

ten years and an average of consulting with four clinicians (Goodwin & Jamison, 2007; Hirschfeld *et al.*, 2003).

The differential diagnosis between the two subtypes of depression has gained complexity, and the boundaries between UP and BP remain controversial. One plausible explanation is the symptomatic overlap of hypomanic symptoms, which have also been described in MDD patients (Smith & Craddock, 2011; Smith & Griffiths 2011). Secondly, patients might be poor historians of prior mil/hypomanic episodes and usually do not seek treatment for these symptoms.

Therefore, accurately diagnosing between the two types of depressions is of critical clinical relevance, as patients with depression may have MDD or BP, and the treatment strategies and prognosis differ (Post, 2005). For example, the misdiagnosis of MDD in patients with BP could result in clinicians prescribing ADs, which might contribute to mood instability or treatment-emergent mania or mixed episodes in patients with BP (Frye *et al.*, 2009).

Adult studies have compared BP to MDD, providing clinical features that might distinguish between both depressions such as atypical symptoms (increased appetite/sleep and psychomotor retardation) and subsyndromal manic symptoms, which were mostly associated with BP depression (Perugi *et al.*, 2015; Bowden, 2005; Benazzi, 2000). In addition, Perlis and colleagues analyzed data from three multicenter clinical trials from the USA ($N = 1551$), highlighting symptoms such as sadness, insomnia, cognitive, muscular, respiratory, and genitourinary complaints, and depressed behavior were more prevalent in MDD patients (Perlis *et al.*, 2006). Another study highlighted some of the following features to be associated with a BP depression: brief and recurrent depressive episodes, early age of onset, a family history of BP, presence of atypical features, psychotic depressions, psychomotor agitation, postpartum depression and antidepressant activation (Yatham *et al.*, 2018; Mitchell *et al.*, 2008). Nevertheless, some debates

regarding these studies have been raised, mainly discussing the considerable heterogeneity of methodological limitations and study groups (Cuellar *et al.*, 2005), therefore supporting a more integrative approach to mood disorders, which we will cover in Section 1.6.

1.4.1 Neuroimaging evidence

Considering the clinical difficulties of distinguishing between UP and BP, neuroimaging studies have attempted to suggest evidence to further support functional and structural abnormalities for both mood disorders (Philips & Kupfer, 2013). BP is associated with decreased ventrolateral prefrontal cortex activity during emotional processing and increased orbitofrontal cortex, ventrolateral prefrontal cortex, and striatum activity during reward tasks (Han *et al*., 2019). Some authors have suggested that BP patients may have more significant white matter functional connectivity abnormalities compared with UP patients as well as morphological changes such as higher reductions in the habenula volume for BP (de Almeida *et al.*, 2013). In comparison, UP has been characterized by increased anterior cingulate cortex and amygdala activity during an emotional stimulus (Phillips *et al.*, 2015; Phillips & Swartz, 2014); and some studies using arterial spin labeling have underscored that TRD-UP patients had hyperactivity (i.e., greater perfusion) in the anterior cingulate cortex, subcortical areas (i.e., amygdala), and left dorsomedial prefrontal cortex (Duhameau *et al.*, 2010).

1.4.2 Neuromodulation techniques

Electroconvulsive therapy (ECT) has been a cornerstone treatment strategy showing efficacy for both for UP and BP depression with a suggested greater efficacy than ADs (UK ECT Review Group, 2003). Moreover, a meta-analysis which examined the efficacy of ECT in UP and BP, underscored that both affective disorders responded well to ECT with a marginal higher

remission rate for BP (53.2% vs. 50.9%) (Dierckx, B *et al*., 2012). Additionally, ECT has been suggested as second line treatments for rapid response in patients with resistant BP depression (Yatham *et al*., 2018). Despite the aforementioned evidence for the utility of ECT in affective disorders, in some psychiatric practices it remains underutilized due to the challenges in accessibility such as increased health costs and cognitive side effects as well as social stigma (Fink, M., 1997).

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive technique which acts at specific cortical sites (e.g., prefrontal cortex) showing a wider effect at different brain regions (Fitzgerald *et al*., 2007). Importantly, the electrical pulse can be modified accordingly to stimulation protocols which have been evolving during the years modifying different parameters such as high or low frequency, intensity, area of stimulation (right or left dorsolateral prefrontal cortex) unilateral or bilateral application as well as number of sessions (Downar *et al.,* 2016). Specifically, different systematic reviews and meta-analysis have summarized the evidence for a clinical efficacy and tolerability for rTMS in TRD-UP (Sehatzadeh *et al.,* 2019; Gaynes *et al.,* 2014) being considered a first line treatment recommendation by the CANMAT guidelines (Milev *et al.,* 2016).

For BP, the evidence for the applicability of rTMS either for the acute or maintenance phase is still inconclusive. As an example, an open label study ($N = 11$) examined low frequency rTMS on the right dorsolateral prefrontal cortex as augmentation to ADs during a three week period showing a significant effect (Dell'Osso *et al.,* 2009). On the other hand, a randomized sham controlled trial ($N = 23$) failed to show a significant difference with rTMS (Nahas *et al.,* 2003) although sample sizes were small. In addition, a 4-week randomized trial of 38 BP-II subjects receiving right or left rTMS with quetiapine or sham showed no significant difference between

groups (Hu *et al.,* 2016). Consequently a meta-analysis (*N* = 181, 19 studies) showed that patients who received rTMS have a higher clinical response at endpoint compared to sham (44.3% vs. 25.3%) with a number needed to treat of 6 (McGirr *et al.,* 2016); however 65% of the population were BP non specified. Nevertheless, the CANMAT guidelines indicate rTMS as a third line agent (Yatham *et al*., 2018) due to studies heterogeneity with high risk of bias and unclear response rates; and up to today showing less efficacy than ECT (Eranti *et al*., 2007). However, further investigations with larger samples comparing its efficacy as monotherapy or as augmentation strategies with different stimulation protocols are warranted.

1.5 TREATMENT-RESISTANT DEPRESSION AND BIPOLAR DEPRESSION

Current modifications in our modern diagnostic classification system (i.e., DSM-5) still inadequately capture many phenotypes, thus leading to poor initial diagnosis and treatment outcomes. This aspect may be attributed to the fact that our classification systems are not based on neurobiological mechanisms, which consequently make the differential diagnosis and development of biological biomarkers particularly difficult (Frey *et al.*, 2013). One interesting proposal that has aided in clinical research has been the development of the Research Domain Criteria (RDoC) by the National Institute of Mental Health from the US. The RDoC aims to define basic trans-diagnostic dimensions to be approached from genetic neurobiological/behavioral perspectives to improve psychopathology and targeted treatments (Insel *et al*., 2010).

An important differential diagnosis was given by previous studies showing that TRD-UP by itself may constitute a risk factor for a diagnostic conversion from MDD to BP. Different authors have suggested several environmental risk factors related to TRD-UP and poor outcomes such as a lower educational attainment and socioeconomic status, adverse social

environment (stressors and family dysfunction), missed bipolarity, inadequate dose and duration of pharmacological trials, presence of comorbidities as well as treatment non-adherence (Thase, 2011; Fagiolini & Kupfer, 2003; Fava, 2003). Moreover, TRD-UP has also been proposed theoretically as a specific subtype of depression in the group of UP depressions similar to the case of atypical depression and anxious depression subtypes (Fagiolini & Kupfer, 2003).

Some authors such as Souery and colleagues (2007) analyzed from a European database, a large sample of patients (N = 702), concluding with a total of eleven clinical and demographic variables strongly associated with TRD which were: anxiety and personality comorbidities, panic disorders and social phobias, risk of suicide, severity of depressive episodes, depression with melancholic features, number of hospitalizations, recurrent episodes, an early onset of illness, and inadequate response to first antidepressant treatment (Souery *et al.*, 2007).

Thus far, there is no clinical study which both integrated and compared sociodemographic and the psychopathological features and treatment outcomes for TRD-UP patients. Moreover, the clinical characteristics and factors independently associated with the response to augmentation strategies have been insufficiently described. Therefore, a reappraisal of psychopathology where clinical features are thoroughly examined with an emphasis on diagnostic assessments and treatment outcomes in a natural setting is needed.

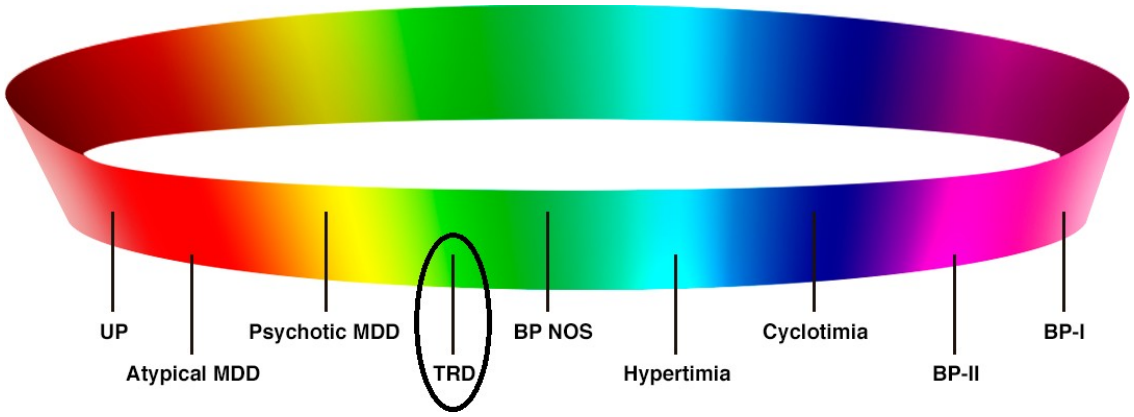
1.6 THEORIES ON A SPECTRUM APPROACH FOR MOOD DISORDERS

As seen in the previous section, intersections between mood disorders and particularly between UP and BP depression are quite common and raise continuous clinical challenges, which often obliges us to reconsider Kraepelin's original clinical descriptions and the broad, inclusive concept

of manic depression (Kraepelin, 1921).

A mood spectrum concept (similar to the color spectrum shown in Fig. 1.6.1 showing a gradual separation of its components according to the wavelength of the colors) can contribute to approach the symptomatic overlap in mood disorders conceptually. This concept was initially conceived by Akiskal as bipolar spectrum disorders (which also included temperaments) and was posteriorly expanded to unipolar disorders (Akiskal *et al.*, 1983).

At one end of the spectrum ring, we have the classic BP (fulfilling criteria for manic and depressive episodes) and, on the other extreme, the classic UP depression (no manic or hypomanic symptoms) with phenotypic variations (constituting distinct entities) fulfilling the gap.



1.6.1 Figure 1. Spectrum for mood disorders from bipolar depression to unipolar depression.

UP: Unipolar depression. MDD: Major depressive disorder; TRD: Treatment-resistant depression; BP NOS: Bipolar non-specified; BP-II: Bipolar disorder type II; BP-I: Bipolar disorder type I. Adapted from Ghaemi, 2008.

Some advantages of this concept are that both UP and BP lie in a continuum and that it considers intermediate phenotypes such as the case of BP-II, cyclothymic disorders, hyperthymia, and the

recurrent/resistant/atypical depressions between the extreme ends of the spectrum. Additionally, we can consider to what degree does a patient approaches one end of the spectrum more than the other posing the question as what is the percentage of bipolar components in this patient? (Phelps, 2016; Akiskal *et al.*, 1983).

Numerous clinicians and researchers have further supported these concepts. For example, Angst and colleagues have mentioned how the boundaries of the original bipolar spectrum (comprising BP-I and BP-II) developed by Akiskal have been expanded by demonstrating the occurrence of mild bipolar symptoms in the general population (Angst *et al.*, 2003).

1.6.2 Diagnostic conversion from unipolar to bipolar depression

More recently, predictive risk factors of a transition from MDD to BP have been described suggesting that patients with a family history of BP, earlier onset of episodes, and psychotic symptoms have a higher risk within the first five years of diagnosis (Ratheesh A *et al.*, 2017). In addition, a recent meta-analysis and systematic review found eight potential risk factors (gender, age at onset of depression, the prevalence of psychotic depression, number of depressive episodes, treatment resistance to ADs, family history of BP, the prevalence of chronic depression, and severity of depression) responsible for the diagnostic conversion. However, none of this was confirmed to predict the transition (Kessing *et al.*, 2017). Nevertheless, it is still uncertain whether the high rate of diagnostic conversions is mainly associated with a misdiagnosis or longitudinal effect product of mood instability or inadequate pharmacological treatments (Forty *et al.*, 2008; Sharma *et al.*, 2005).

1.7 PHARMACOLOGICAL APPROACHES FOR RESISTANT UNIPOLAR AND BIPOLAR DEPRESSION

Over the last decade, multiple treatment guidelines (for example, the American Psychiatrist Association practice guidelines or the Canadian Network for Mood and Anxiety Treatments) have been developed to provide guidance regarding the pharmacological management of depression and to address the cases of non-response.

It is essential to acknowledge concepts regarding antidepressant nonresponse, partial response, response, and remission. Often, a response is achieved when there has been an improvement from the baseline of greater than 50% assessed by the behavioral scales. A partial response occurs when there has been an improvement of between 25% and 49% and non-response when the improvement is less than 25%. Our primary efforts should be to achieve a remission-free state, which has been defined differently according to each behavioral scale measuring the severity of depression (i.e., a score less than 7 points in the HAMD-17) (Riedel M *et al.*, 2010).

1.7.1 Pharmacological strategies for treatment-resistant unipolar depression

The management of TRD constitutes a clinical challenge due to reasons such as dearth of direct clinical evidence comparing different augmentation strategies. Secondly, there are multiple definitions of TRD and different staging models for severity and disease progression which at the moment, lack a direct correlation with functional biomarkers. Overall, these limitations result in inaccurate diagnosis and treatment strategies for a complex heterogeneous illness such as TRD-UP.

An important consideration before any treatment modification is established should be to reassure the patients' diagnosis, as well as any comorbid medical or psychiatric conditions (i.e., substance use) and different psychosocial factors which might influence treatment adherence.

Additionally, before considering treatment resistance, we should consider whether the treatment was allowed an adequate duration (i.e., 4 to 8 weeks since initiation) and dose to observe a response (Gelenberg *et al.*, 2010).

Different treatment strategies such as dose increases, switching between ADs of similar or different class and different combination or augmenting pharmacological agents have been attempted to mitigate the low remission and response rates frequently encountered.

Dose increase

Although in many cases, the option of dose optimization is an initial strategy, we should consider the evidence and the likelihood of the occurrences of side effects. Overall, this strategy is not supported by several randomized controlled trials and systematic reviews (Cleare *et al.*, 2015; Adli *et al.*, 2005; Licht & Qvitzau, 2002; Schweizer *et al.*, 2001; Dornseif *et al.*, 1989).

Switching

There is inconclusive evidence to support switching within the AD class, such as from one SSRI to another (Rush *et al.*, 2009), and most of the evidence supports switching to a different AD class (i.e., from an SSRI to SNRI) (Cleare A *et al.*, 2015). According to the meta-analytical evidence (N = 1496) that examined switching within AD group or across classes, patients randomized to switch classes of ADs were most likely to achieve remission (Papakostas *et al.*, 2008). However, another study showed a significant effect of vortioxetine over agomelatine after failure to respond to an SSRI/SNRI (Montgomery *et al.*, 2014).

Combination

With the intention to expand the mechanism of action of the first AD drug, commonly, the term combination refers to the addition of the second AD. Interestingly, no antidepressant has been FDA approved as a combination treatment strategy (McIntyre *et al.*, 2014), and such a strategy

may lead to significant side effects or adverse pharmacodynamic interactions (i.e., as it has been the MAIO and TCA). Moreover, there is no conclusive evidence by adequate double-blind placebo-controlled trials to further support the different AD combinations, which are usually prescribed in the clinic. For example, insights from the STAR*D showed that the combination of citalopram with bupropion was better tolerated, although marginally effective as compared to buspirone. Importantly, mirtazapine and venlafaxine, when compared to tranylcypromine (a MAOI), had a significant decrease in depressive symptoms, although not statistically significant (Trivedi *et al.*, 2006; McGrath *et al.*, 2006). In contrast, small RCTs examining the combination of SSRI with mirtazapine or mirtazapine in addition to paroxetine were positive (Blier *et al.*, 2009; Carpenter *et al.*, 2002).

Augmentation

Augmentation refers to when, in non-responders, a drug is added to an antidepressant/mood stabilizer after several weeks of treatment because of a non-clinical effect or partial response (Altshuler *et al.*, 2003).

Augmentation with second-generation antipsychotics

There is robust evidence showing the efficacy of second-generation antipsychotics (SGA) for which at the moment, three have been FDA approved as augmenting agents: aripiprazole, quetiapine, or the combination olanzapine-fluoxetine (Cleare A *et al*., 2015; Spielmans *et al.*, 2013).

The use of augmentation with SGA has a clinical evidence based for the following agents: olanzapine/fluoxetine (Shelton *et al.*, 2010; Shelton *et al.*, 2008; Thase *et al.*, 2007; Corya *et al.*, 2006), quetiapine (Bauer *et al.*, 2010; El-Khalili *et al.*, 2010; McIntyre A *et al.*, 2007), aripiprazole (Marcus *et al.*, 2008; Berman *et al.*, 2007) and risperidone (Keitner *et al.*, 2009;

Mahmoud *et al.*, 2007). Furthermore, findings from two meta-analyses (Papakostas, 2009; Papakostas *et al.*, 2007) demonstrated that SGA augmentation in MDD is effective and well-tolerated. In addition, the two recent network meta-analysis reported aripiprazole and quetiapine as effective treatments such as augmentation strategies for patients with TRD-UP compared with placebo (Strawbridge *et al.*, 2018; Zhou X *et al.*, 2015). An important consideration is that effective doses are generally lower than for usual indications (El-Khalili *et al.*, 2010).

Augmentation with lithium and thyroid hormones

A modest body of clinical evidence supports the use of lithium as augmentation agent for different classes of antidepressants (for example SSRIs, TCA, or MAOIs). A meta-analysis of ten augmentation studies (N = 269) reported lithium's efficacy as augmenting ADs compared with the placebo (OR= 3.11, 95% CI=1.80-5.37) (Crossley & Bauer *et al.*, 2007). Nevertheless, we should consider some limitations such as most of the studies included a small sample size, and augmentation of TCAs which are generally less prescribed in our clinical practice compared to SSRIs. Additionally, Nierenberg *et al*., (2003), where lithium was used to augment an SSRIs had a negative outcome (OR=0.58, 95% CI = 0.08-4.01) which results are in agreement with the data from the STAR*D study. The STAR*D study documented low remission rates for lithium when compared with T3 (23% vs. 16%) (Nierenberg *et al.*, 2006), and in addition, another study reported no difference between lithium and thyroid hormone (T3) while augmenting SSRI (Joffe *et al.*, 2006).

Augmentation treatment with thyroid hormone, in particular liothyronine (i.e. synthetic tri-iodothyronine) has been used reported to enhance the effect of ADs but there is considerable variability in the efficacy of this intervention. Abulseoud and colleagues, demonstrated that higher free T4 levels at end of treatment in a cohort of depressed patients was associated with a

faster antidepressant response time and shorter hospital length (Abulseoud *et al*., 2007). However, a recent study examined the effect of adjunctive thyroid hormone for TRD in 10 studies (*N*=663) suggesting that there is not enough evidence to make a clinical recommendation (OR= 1.56, 95% CI= 0.50-4.84) (Lorentzen *et al*., 2020).

Augmentation with stimulants

Evidence supporting augmentation with stimulants or agents with stimulant-like properties for TRD is controversial. Thus far, there have been two negative studies for methylphenidate (Ravindran *et al.*, 2008; Patkar *et al.*, 2006). Recent meta-analyses showed evidence for the efficacy of modafinil/armodafinil compared with the placebo in both remission and response rates (Nunez *et al.*, 2019; McIntyre RS *et al.*, 2017; Goss AJ *et al.*, 2013), and two placebo randomized controlled trials have provided evidence for lisdexamfetamine (Madhoo *et al.*, 2014; Trivedi *et al.*, 2013).

Ketamine and S-ketamine

Several studies on ketamine, an antagonist of the N-methyl-D-aspartate (NMDA) receptor, have been conducted showing efficacy for TRD-UP (Zarate *et al.*, 2006; Murrough *et al.*, 2013). In addition, two meta-analyses have reported the efficacy of a single dose of intravenous ketamine (Coyle *et al.*, 2015; Wan LB *et al.*, 2015). Some concerns have been raised, such as the appropriate environment in which the medicine is administered (i.e., academic hospital settings compared to outpatient clinics).

Several short-term clinical trials have shown the efficacy of esketamine (ketamine S-enantiomer), which was recently approved for TRD (Kim *et al.*, 2019; Daly *et al.*, 2017; Singh, 2017).

1.7.2 Pharmacological strategies for bipolar depression

Several classes of medications, such as mood stabilizers, antipsychotics, and ADs, are generally used for both the acute and the maintenance or continuation phase of BP, which most commonly require polypharmacotherapy to achieve stabilization (Frye *et al.*, 2000). The treatment is mainly targeted at specific illness phases, either manic, hypomania, or depression, with the goal of obtaining mood stability.

Concerning treatment options for the acute phase of BP depression, there are currently four FDA-approved medications: quetiapine (Thase *et al.*, 2006; Calabrese *et al.*, 2005), olanzapine/fluoxetine (Tohen *et al.*, 2003), lurasidone (Loebel *et al.*, 2014), and the recently approved cariprazine (Durgam *et al.*, 2015).

The Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines suggest as the first-line options for acute BP-I depression the use of quetiapine, lithium, lamotrigine, and lurasidone as monotherapy (Yatham *et al.*, 2018). As the second-line treatment, monotherapy with divalproex can be considered as well as AD therapy (SSRIs/bupropion) with lithium/divalproex or SGA. For BP-II acute depression treatment, quetiapine is the only first-line option recommended. Lithium and AD, such as sertraline, venlafaxine, and lamotrigine, are considered second-line options (Yatham *et al.*, 2018).

In certain clinical presentations, inadequate response with monotherapy may require the addition of an SGA. Different randomized controlled trials have shown effective approaches of SGA (i.e., quetiapine, lurasidone, and olanzapine) for BP depression (Loebel *et al.*, 2014; Tohen *et al.*, 2003). Importantly, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) showed that there was no evidence to suggest that treatment with a mood stabilizers

and an AD conveyed a benefit over the use of a mood stabilizer alone (Sachs GS *et al.*, 2007; Belmaker, 2004).

For the maintenance phase of bipolar depression (i.e., prophylaxis), quetiapine, divalproex lithium, and lamotrigine have supporting evidence (Yatham *et al.*, 2018). Additionally, the CANMAT provides a recommendation for the second-line options of asenapine and aripiprazole.

Adjunctive treatments with thyroid hormones and stimulants

Adjunctive treatment with thyroid hormones, for example, with T3, has shown efficacy both as augmentation or accelerating response in rapid cycling BP. Supraphysiological doses of levothyroxine (T4) have been recommended in the recent treatment guidelines for bipolar disorders (Yatham *et al.*, 2018).

According to current evidence and consensus guidelines, stimulants are conceptualized as second to fourth line options for patients with resistant depression associated with BP (Goodwin *et al.*, 2016). However, there is controversy in the literature due to new evidence showing the efficacy of stimulants as augmenting agents for the acute depressive phase in BP as the case for modafinil/armodafinil and dopaminergic agents (Nunez *et al.*, 2019; Szmulewicz *et al.*, 2017).

Anti-inflammatory and alternative pharmacological agents (N-acetylcysteine and omega-3 fatty acids).

Depression has been widely associated with high levels of certain inflammatory markers such as cytokines (i.e. TNFα) affecting central and peripheral systems such hypothalamic-pituitary-adrenal axis and neurotransmitter pathways (Maes *et al*., 2011). Current evidence has shown that ADs have been associated with a decrease of TNFα achieving treatment response (Strawbridge *et al*., 2019) although data examining the role of TNF antagonists such as infliximab is controversial with a positive (Raison *et al*., 2013) and negative study (Bavaresco *et al.,* 2019).

Other agents such as N-acetyl cysteine (NAC), have been proposed as augmentation agents with a putative role to ameliorate depression. NAC is a precursor of glutathione which exerts antioxidants effects and has a role in modulating glutamatergic and inflammatory pathways (Dringen *et al.,* 2003) reducing different cytokines such as IL-6 which mechanistically may account for its role in depression. For example, for BP depression, a 24-week double blind randomized controlled study of 75 BP subjects examined the addition of NAC (2g/d) compared to placebo showing higher response rates at endpoint compared to placebo (51% vs.18%, respectively) (Berk *et al.,* 2008). Currently, CANMAT guidelines recommend it as a third line option (Yatham et al., 2018).

Supplements such as omega-3- polyunsaturated fatty acids have also been proposed as adjunctive treatments for UP and BP depression considering its anti-inflammatory effects and apparent lack of adverse effects although the data for its efficacy is still controversial. As an example, an 8 week randomized controlled trial ($N = 155$) examined the components of omega-3 fatty acids and underscored that those patients with high inflammation levels had a greater improvement with eicosapentaenoic acid (Rapaport M *et al.,* 2016). On the other hand a recent large meta-analysis examining 31 studies ($N = 41470$) over at least six months suggest no effect for omega-3 fatty acids (Deane K, *et al.,* 2019).

Ketamine

In the last few years, three randomized controlled trials (Grunemberg *et al.*, 2017; Zarate *et al.,* 2012; Diaz GN *et al.*, 2010) have been conducted to examine the use of intravenous racemic ketamine for BP ($N = 49$), showing a rapid and marked improvement in cases of suicidal ideations and anhedonia.

Antidepressants and risk to mood destabilization

A persistent debate continues in the mood disorder field regarding the use of ADs for BP depression, which may increase the likelihood of mania or mood instability; this is a switch from depression to mania, particularly in patients with BP-I (Undurraga *et al.*, 2012). Different studies have examined the use of AD as monotherapy or as combination therapies for patients with BP, highlighting its role in the management of depression phases, mostly for BP-II (Altshuler *et al.*, 2017; Amsterdam, 1998) although there is limited evidence supporting its use (Pacchiarotti *et al.*, 2013). Despite previous controversies, the consensus from experts is that if needed, ADs can be cautiously administered adjunctively with a mood stabilizer or SGA while monitoring for activation symptoms (i.e., hypomania) and avoided in patients with past or current risk factors for AD-induced mania (i.e., female gender, hyperthymic temperament, and comorbid anxiety) and the presence of mixed symptoms (Baldessarini *et al.*, 2020).

Importantly, a pharmacogenetic approach to identify the genetic risk factors for AD-induced mania may improve the treatment strategies for BP depression. For example, one of the most recent studies revealed that genetic associations with AD-induced mania involve the serotonin transporter gene (*SLC6A4*); this gene encodes the protein involved in the synaptic serotonin reuptake and the variants involved in its genetic expression. Notably, there is conflicting evidence towards the association of the two known polymorphisms of this gene *SLC6A4* with AD-induced mania with positive and negative findings (Biernacka *et al.*, 2011; Daray *et al.*, 2010).

1.7.3 Use of SGA as antidepressants (a focus on aripiprazole and quetiapine)

As discussed in the previous sections, the use of SGA has been supported by clinical data both for UP and BP and as monotherapy or adjunctive agents. In general, despite its well-known and

complicated metabolic side effects, SGA provides an essential strategy because of its anxiolytic or AD effects. SGA has a higher affinity for the serotonin 2A receptor (5-HT2A) than for the dopamine receptor (Meltzer *et al.*, 1989). Thus, the anxiolytic and antidepressant effects of SGA (quetiapine or aripiprazole) can be explained mechanistically because of the antagonism of the 5HT2A, 5HT7, 5HT2C, and histamine H1 receptors or the partial agonist actions at the 5-HT1A receptors (Harada *et al.*, 2006). Quetiapine, a pleomorphic molecule, has shown evidence for manic, depressive, and mixed state phases for patients with BP, as discussed in the previous section. Its antidepressant effect can be explained by mechanistically targeting the 5-HT1A receptor agonist and exerting a 5-HT2A and 5-HT7 antagonism (Jensen *et al.*, 2008). Two clinical trials support its use both as monotherapy and an augmentation treatment for MDD (El-Khalili *et al.*, 2010; Bauer *et al.*, 2009).

Aripiprazole mechanistically functions as a partial agonist of D2, D3, and 5-HT1A and 5-HT2A/5HT7A antagonist (De Bartolomeis *et al.*, 2015), which has received FDA approval for MDD (Nelson *et al.*, 2008); it also demonstrated evidence for augmentation strategies in MDD (Fava *et al.*, 2012; Berman *et al.*, 2009; Marcus *et al.*, 2008; Berman *et al.*, 2007) but not for BP (Yatham *et al.*, 2019). Mainly, its proposed antidepressant effect at low doses has been postulated by mechanistically acting at the presynaptic level and activating auto-receptors (D2), thus increasing the dopaminergic transmission (Praag, 1977).

CHAPTER 2 – PSYCHOPATHOLOGICAL AND SOCIODEMOGRAPHIC FEATURES IN TREATMENT-RESISTANT UNIPOLAR DEPRESSION VERSUS BIPOLAR DEPRESSION: A COMPARATIVE STUDY

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Abstract

Background: Some authors have hypothesized that Treatment-Resistant Unipolar Depression (TRD-UP) should be considered within the bipolar spectrum disorders and that hidden bipolarity may be a risk factor for TRD-UP. However, there are neither studies comparing clinical and sociodemographic data of patients with TRD-UP versus Bipolar (BP) disorders nor are there any examining differences versus Bipolar type I (BP-I) and Bipolar type II (BP-II).

Methods: Charts analysis was conducted on 194 patients followed at the Mood Disorders Clinic of the McGill University Health Center. Sociodemographic, clinical features and depression scales were collected from patients meeting DSM-IV criteria for TRD-UP (n=100) and BP (n=94). Binary logistic regression analysis was conducted to examine clinical predictors independently associated with the two disorders.

Results: Compared to BP, TRD-UP patients exhibited greater severity of depression, prevalence of anxiety and panic disorders, melancholic features, Cluster-C personality disorders, later onset of depression and fewer hospitalizations. Binary logistic regression indicated that higher comorbidity with anxiety disorders, higher depression scale scores and lower global assessment of functioning (GAF) scores, and lower number of hospitalizations and psychotherapies differentiated TRD-UP from BP patients. We also found that the rate of unemployment and the number of hospitalizations for depression was higher in BP-I than in BP-II, while the rate of suicide attempts was lower in BP-I than in BP-II depressed patients.

Conclusions: These results suggest that TRD-UP constitutes a distinct psychopathological condition and not necessarily a prodromal state of BP depression.

Keywords: Treatment-resistant depression, Bipolar depression, Psychopathology, Affective disorders, Bipolar spectrum.

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2.1 BACKGROUND

Depressive disorders are considered as one of the major worldwide public health burdens (Ferrari et al. 2013). Treatment-Resistant Unipolar Depression (TRD-UP) continues to be a clinical challenge due to its heterogeneous presentation with an impact on functional impairment, declined autonomy, and poor cognitive functioning (Greden 2001). Although advances have been made to improve our psychiatric diagnostic classification systems, many intermediate phenotypes have not been accurately diagnosed and proposed predictors of treatment outcomes in depression seem controversial with remission rates remaining unchanged (Kennedy, Abbott, and Paykel 2003).

Over the years there has been several definitions proposed as to adequately define TRD-UP (Souery, Papakostas, and Trivedi 2006; Fava 2003). TRD-UP can be defined either as the failure to respond to the first antidepressant (AD) trial (Trivedi, Fava, Wisniewski, Thase, et al. 2006) or two or more AD trials (Lam et al. 2009) of different classes of AD (Souery et al. 1999). It has been described that up to 15% of patients treated for depression will fall into this category (Berlim and Turecki 2007) and according to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study more than 50% of depressed patients do not respond to their first AD trial (Trivedi, Rush, et al. 2006). However, there is currently no universal definition of TRD-UP and controversies surrounding its prevalence rates, definitions and treatment outcomes remain ambiguous (Fornaro and Giosuè 2010a, 2010b).

A number of clinical and demographic characteristics have been found to be associated with TRD-UP. These include comorbidity with anxiety panic disorder, social phobia, personality disorder, suicidal risk, melancholia, number of hospitalizations, recurrent episodes, early age of onset, total number of unresponsive treatments to antidepressants received during a lifetime (Souery et al.

2007) as well as severity of depression and having a 1st relative with an affective disorder (Balestri et al. 2016).

It has been proposed that TRD-UP can be considered a "prodromal phase" of bipolar disorder (BP) included in the bipolar spectrum disorders and a sub-threshold bipolarity or hidden bipolarity as a risk factor for TRD-UP (Dudek et al. 2010). This hypothesis has been confirmed by a recent systematic review examining possible risk factors for treatment resistance in unipolar major depression, in which, among others, the presence of a non-diagnosed bipolarity was found to be an independent risk factor for treatment resistance (Bennabi et al. 2015).

The diagnostic distinction between TRD-UP and BP is of paramount importance for the treatment and prognosis of depression. While TRD-UP must be treated with a combination of different classes of antidepressants (AD) or with second-generation antipsychotic (SGA) augmentation strategies (Gobbi et al. 2018) in BP depression, AD must be carefully used and monitored considering that they may induce a switch in mania, hypomania or symptoms such as psychomotor activation, insomnia or irritability (Pacchiarotti et al. 2013; Ghaemi, Boiman, and Goodwin 2000). Unfortunately, it is still a challenge to accurately predict if a TRD-UP could be a masked form of BP depression.

Other studies examining the differences between unipolar (non-TRD) and BP depression revealed that the prevalence of characteristics such as age of onset was lower but that the total number of depressive episodes as well as the presence of a family history of depression was higher in bipolar than in unipolar depression (Marchand 2003; Geller and Luby 1997; Akiskal et al. 1983; Benazzi 2006). Therefore, while some different characteristics between unipolar and bipolar depression have been well characterized, the different demographic, social, and clinical characteristics associated with TRD-UP versus BP depression have not yet been studied, although this early

differential diagnosis is pivotal for improving diagnostic and therapeutic outcomes.

In this retrospective and observational cross-sectional chart-review study, we have examined clinical and demographic characteristics mostly associated with the diagnosis of TRD-UPI or BP that have been previously described in the literature as risk factors or predictors for these disorders (Bennabi et al. 2015; Balestri et al. 2016; Perlis 2013). The goal was to find clinical and socio-demographical characteristics to assist clinicians to better differentiate between TRD-UP from depression as part of the bipolar spectrum disorders. As a secondary goal, given the subtypes of the bipolar spectrum, we investigated whether there were clinical and socio-demographical characteristics that differed between Bipolar Type I (BP-I) and Type II (BP-II) disorders and between them and TRD-UP.

2.2 MATERIALS AND METHODS

The study was approved by the Institutional Review Board of McGill University (13-375-PSY) and was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice. Chart reviews were conducted by using the Patient Registry at the Mood Disorders Clinic (MDC) of the McGill University Health Center (MUHC). The Patient Registry at the MDC is a research database where uniform data is collected on all unipolar and bipolar disorder patients who are treated and followed at the clinic for more than 2 years (mean 7.5 years).

2.2.1 Patients

Patients meeting the DSM-IV criteria for a major depressive episode (MDE) within a unipolar or bipolar diagnosis were included in the study (American Psychiatric Association 2000). The medical charts of 194 outpatients between the ages of 19-75, with a MDE and meeting DSM-IV criteria for TRD-UP (n=100) and BP (n=94) were reviewed. Among the BP patients, 52 were

diagnosed with BP-I and 42 with BP-II. Patients with unipolar major depressive disorder met criteria for TRD-UP by failing at least two adequate trials with different AD in mono or combination therapy at the adequate dose and for at least three weeks (Lam et al. 2009).

The patient's diagnoses were ascertained by the Structured Clinical Interview for Diagnosis (SCID) (First et al. 2002) which was conducted by psychiatrists or professionals who received a training in SCID. The Maudsley Staging Method (MSM) was used to establish the severity of the TRD patients (Fekadu , Poon, and Cleare 2009). In addition, the Young Mania Rating Scale (YMRS) (Young et al. 1978) was used to evaluate whether patients currently displayed acute hypomanic or manic symptoms and if they did not meet the criteria for a mixed episode of depression at the time of the assessment.

The inclusion criteria included patients with a diagnosis of an MDE ranging from mild to severe intensity measured by a score greater than 20 on the Montgomery–Asberg Depression Rating Scale (MADRS) and a score greater than 13 on the Hamilton-Rating Scale for Depression (HAM-D17) (Zimmerman et al. 2013). The duration of the current episode had to be greater than two months. Patients with a mixed episode, currently in a manic episode or with the presence of a neurological/ developmental disorder and/or a mood disorder secondary to a medical condition were excluded. Patients were selected during the phase of depression, before the administration of a stable and effective psychopharmacological treatment (treatment not changed by the psychiatrist for at least three months).

Pharmacological treatment at time of evaluation was as follows: for the TRD-UP group, 38 patients were treated with AD mono/combination therapy and 62 patients were treated with an augmentation strategy that included AD in combination with SGA (n=49) or mood stabilizers (MS) (n=13). In the BP group, patients were treated with MS in combination with SGA (n=30), AD in

combination with SGA and MS (n=23), AD plus MS (n=21), AD plus SGA (n=10), MS monotherapy (n=5), and SGA monotherapy (n=5).

2.2.2 Clinical evaluation

A retrospective chart analysis was performed by two raters (two psychiatrists) and clinical features were evaluated in the two groups. The following scales were considered for depression severity: Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979); Clinical Global Impression-Severity of Illness (CGI-S) (Guy 1976a); Quick Inventory of Depressive Symptomatology (QIDS-C16) (Rush, Trivedi, Ibrahim, Carmody, Arnow, Klein, Markowitz, Ninan, Kornstein, and Manber 2003) and Hamilton-Rating Scale for Depression (HAMD-17) (Hamilton 1960b).

The following patient socio-demographic information was obtained from the MDC Patient Registry: age, ethnicity, gender, marital status, employment, level of education and living arrangement as well as previous psychiatric diagnosis including Attention Deficit-Hyperactivity disorder (ADHD), alcohol or substance abuse, anxiety disorders, sleep disorders and eating disorders. Information was also collected on family history of affective disorders, age of first psychiatric consultation, age of first depressive episode and the number of depressive episodes, age of first manic episode and number of manic episodes, age of first hypomanic episode and number of hypomanic episodes. Data was also collected on the history of psychotherapy, electrical or neurological therapy, use of psychiatric services, general medical history, and number of previous suicide attempts, major depression with psychotic features, axis II, III and IV DSM-IV-TR (American Psychiatric Association, 2000) pathology, previous and current pharmacotherapy. Patients were also assessed having depressive melancholic features and depressive atypical symptoms as defined by DSM-IV criteria (American Psychiatric Association 2000). Patients

within the TRD-UP group had a level of resistant depression of moderate intensity according to the MSM (Mean±SEM, 9.7±0.2) and patients with BP disorders did not display current manic episodes defined by the YMRS scale (Mean±SEM: 3.0±0.7).

2.2.3 Reliability and Inter-rater Agreement for Psychometric Scales

A reliability analysis was performed to determine the internal consistency by means of Cronbach's alpha. Overall, we reached an acceptable reliability for all the scales (MADRS: α=0.91; HAMD-17: α=0.82; QIDS-C16: α=0.77).

Inter-rater reliability was performed on a sample of 140 patients. Patients were assessed by three raters (two psychiatrists and a General Practitioner). We found moderate to good agreement (Cohen's kappa range: 0.58-0.85) (Viera and Garrett 2005)) (MADRS: 0.60; HAMD-17: 0.58; QIDS-C16: 0.61; CGI-S: 0.72; CGI-Global Improvement: 0.85) across all scales.

2.2.4 Statistical analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS-23; SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation (SD). Inter-rater reliability for individual scales was calculated using Cohen's kappa (Cohen 1968).

As an initial step, we considered 40 variables that were compared between TRD-UP and BP by Student's t test for continuous variables or by Pearson's chi-square (χ^2) test for categorical variables. Then, using a binary logistic regression analysis we examined which variables were specific predictors of the two affective disorders. Given the high number of variables under investigation, and to balance risk for type I and type II errors, we choose to include in the binary logistic model only those variables that in the initial step were significantly different between the two groups at an alpha level of 0.01. Moreover, we excluded from the model those variables for

which few individuals ($n \leq 5$) were affected by a specific disorder in at least one of the two groups. Predictors reaching $p<0.01$ were considered significant.

As final step, we investigated for possible differences in the clinical and demographic characteristics of TRD-UP, BP-I and BP-II patients. To examine possible differences for categorical variables, we first tested at an alpha level of 0.05 the overall 3x2 matrix containing all the three mood disorders. For statistically significant variables, we subsequently conducted multiple 2x2 cross tabulations using Pearson's chi-square (χ^2) test. For comparisons concerning continuous variables, we used the analysis of variance (ANOVA) followed by Bonferroni post-hoc test for multiple comparisons.

2.3 RESULTS

2.3.1 Table 1. Socio-demographic and clinical characteristics of patients with TRD-UP and BP disorder (N=194).

	TRD-UP (n=100)	BP (n=94)	Statistics
Age (Years) (Mean±SD)	46.5±13.3	40.6±14.3	t=2.97, ***p*=0.003**
Ratio of Males: Females	41:59	37:57	χ^2=0.05, p=0.816
Patients≤65 years of age	90 (90%)	91 (96%)	χ^2=3.59, p=0.058
Marital status	41 (41%)	15 (16%)	χ^2=14.79, ***p*<0.001**
Unemployed/Disability sick leave	74 (74%)	62 (66%)	χ^2=1.49, p=0.221
Age of first major depressive episode (Mean±SD)	37.7±15.3	26.4±9.8	t=6.14, ***p*<0.001**
Early onset of major depressive episodes(<25)	29 (29%)	52 (55%)	χ^2=13.80, ***p*<0.001**
Age of first psychiatric consultation (Mean±SD)	35.9±15.2	24.9±10.7	t=5.83, ***p*<0.001**
Age of first psychiatric hospitalization (Mean±SD)	40.1±15.0	29.4±11.7	t=4.15, ***p*<0.001**
Patients with recurrent depression (>3)	39 (39%)	47 (50%)	χ^2=2.37, p=0.123
Duration of illness-current episode (years) (Mean±SD)	11.9±11.5	15.4±12.1	t=-2.08, ***p*=0.039**
Patients with comorbid substance use	27 (27%)	32 (34%)	χ^2=1.14, p=0.287
History of Alcohol use	9 (9%)	16 (17%)	χ^2=2.77, p=0.096
History of Cannabis use	6 (6%)	19 (20%)	χ^2=8.71, ***p*=0.003**
History of Cocaine use	3 (3%)	3 (3%)	χ^2=0.006, p=0.939
Number of Failed pharmacotherapies (Mean±SD)	3.6±2.6	5.3±2.7	t=-4.31, ***p*<0.001**
Failed antidepressant trials (Mean±SD)	2.25± 1.8	1.63±1.4	t=2.63, ***p*=0.009**
Failed SGA (Mean±SD)	0.65±0.7	1.68±1.2	t=-7.17, ***p*<0.001**
Failed Mood stabilizers (Mean±SD)	0.3±0.6	1.3±0.9	t=-8.55, ***p*<0.001**
Patients currently having psychotherapy	41 (41%)	78 (83%)	χ^2=36.01, ***p*<0.001**

Number of hospitalizations for depression since 1st episode			
None	56 (56%)	15 (16%)	χ^2=33.48, ***p*<0.001**
>one	20 (20%)	60 (64%)	χ^2=38.41, ***p*<0.001**
Patients with 1st degree relative with affective illness	51 (51%)	63 (67%)	χ^2=5.13, ***p*=0.023**
Patients with Anxiety disorders	61 (61%)	22 (23%)	χ^2=27.97, ***p*<0.001**
Patients with Panic disorders	19 (19%)	3 (3%)	χ^2=12.04, ***p*<0.001**
Patients with Melancholic symptoms	74 (74%)	40 (42%)	χ^2=19.77, ***p*<0.001**
Patients with Atypical symptoms	14 (14%)	25 (26%)	χ^2=4.78, ***p*=0.029**
Patients with suicidal attempts	23 (23%)	42 (44%)	χ^2=10.22, ***p*=0.001**
History of MDE with psychotic symptoms	27 (24%)	59 (63%)	χ^2=25.11, ***p*<0.001**
Patients with Personality disorders (Axis II in DSM-IV)	44 (44%)	45 (48%)	χ^2=0.29, p=0.589
Cluster A	7 (7%)	1 (1%)	χ^2=4.31, ***p*=0.038**
Cluster B	19 (19%)	16(17%)	χ^2=0.128, p=0.720
Cluster C	25 (25%)	5 (5%)	χ^2=14.36, ***p*<0.001**
Patients with Medical condition potentially relevant to treatment (Axis III in DSM-IV)			
Autoimmune diseases	11 (11%)	2 (2%)	χ^2=6.101, ***p*=0.014**
Cardiovascular diseases	25 (25%)	18 (19%)	χ^2=0.962, p=0.327
Chronic pain disorders	25 (25%)	15(16%)	χ^2=2.421, p=0.120
Neurological conditions	13 (13%)	5 (5%)	χ^2=3.396, p=0.065
Metabolic disorder	10 (10%)	15 (16%)	χ^2=1.532, p=0.216

SD: Standard Deviation. TRD-UP: Treatment-Resistant Unipolar Depression. BP: Bipolar disorder type I and type II. MDE: Major depressive episode. SGA: Second Generation Antipsychotics. Boldface indicates significant difference at an alpha level = 0.05.

2.3.2 Table 2. Severity of depression and global functioning of patients with TRD-UP and BP. Data are reported as Mean±SD.

Depression severity	TRD-UP (n=100)	BP (n=94)	Statistics
MADRS	30.8±8.95	23.2±6.98	t=6.66, ***p*<0.001**
HAMD-17	23.2±6.24	17.0±4.61	t=7.92, ***p*<0.001**
QIDS	15.8±4.26	12.7±3.91	t=5.31, ***p*<0.001**
CGI-S	5.0±1.21	4.3±1.18	t=4.19, ***p*<0.001**
GAF	55.5±10.22	60.9±4.66	t=-4.93, ***p*<0.001**

TRD-UP: Treatment-Resistant Unipolar Depression. BP: Bipolar disorder type I and type II. MADRS: Montgomery–Asberg Depression Rating Scale. CGI-S: Clinical Global Impression-Severity of Illness. QIDS: Quick Inventory of Depressive Symptomatology; HAM-D17: Hamilton-Rating Scale for Depression. GAF: Global Assessment of functioning. SD: Standard Deviation.

2.3.3 Table 3. Logistic regression showing odd ratios associated with TRD-UP relative to BP disorder (N=194).

Variables	Coefficient B	SEM	Wald	P value	OR Exp(B)	OR 95% CI Lower	OR 95% CI Upper
Individual characteristics							
Age of 1st depression	-0.051	0.025	4.003	0.045	0.951	0.905	0.999
Marital status	1.583	0.701	5.108	0.024	4.872	1.234	19.235
1st relatives with affective disorders	0.262	0.593	0.195	0.659	1.299	0.406	4.157
More than one hospitalization for depression	-2.148	0.614	12.239	**0.001**	0.177	0.035	0.389
Psychotherapy treatment	-2.232	0.699	10.190	**0.001**	0.107	0.027	0.423
History of suicide attempt	-0.135	0.625	0.047	0.829	0.874	0.257	2.974
Comorbidities							
Current anxiety disorders	2.357	0.608	15.033	**0.001**	10.560	3.208	34.763
Severity of depression							
Melancholic depressive features	0.650	0.747	0.755	0.385	1.915	0.422	8.285
Failed pharmacotherapies	0.266	0.106	6.331	0.012	1.304	1.060	1.604
HAM-D17 score	-0.193	0.067	8.208	**0.004**	0.824	0.722	0.941
Level of functioning							
Global assessment of functioning score (GAF)	0.164	0.047	11.985	**0.001**	1.178	1.074	1.293

TRD-UP: Treatment-Resistant Unipolar Depression. BP: Bipolar disorder type I and type II. OR= Odds ratio. CI: Confidence interval. SEM: Standard Error of Mean. Boldface indicates significant association at an alpha level = 0.01.

2.3.4 Table 4. Socio-demographic and clinical characteristics of patients with TRD-UP, BP-I and BP-II (N=194).

	TRD-UP (n=100)	BP-I (n=52)	BP-II (n=42)	Statistics
Age (Years) (Mean±SD)	46.5±13.3	39.7±15.2$^{\$}$	41.7±13.2	$F_{2,191}$=4.6, ***p*=0.011**
Ratio of Males: Females	41:59	21:31	16:26	χ^2=0.11, p=0.949
Patients≤65 years of age	90 (90%)	49 (94%)	42 (100%)	χ^2=4.83, p=0.089
Marital status	41 (41%)	8 (15%) ***	7 (17%) ***	χ^2=14.81, ***p*=0.001**
Unemployed/Disability sick leave	74 (74%)	42 (80%)	20 (48%)***,$^{\#\#\#}$	χ^2=13.67, ***p*=0.001**
Age of first major depressive episode (Mean±SD)	37.7±15.3	28.9±10.1^{+++}	23.2± 8.6^{+++}	$F_{2,191}$=21.0, ***p*<0.001**
Early onset of major depressive episodes(<25)	29 (29%)	30 (58%) ***	22 (53%) ***	χ^2=14.07, ***p*=0.001**
Age of first psychiatric consultation (Mean±SD)	35.9±15.2	24.2±10.5^{+++}	25.9±11.2^{+++}	$F_{2,191}$=16.8, ***p*<0.001**
Age of first psychiatric hospitalization (Mean±SD)	40.1±15.0	28.1±11.7^{+++}	31.3±12.6^{+}	$F_{2,123}$=10.0, ***p*<0.001**
Patients with recurrent depression (>3)	39 (39%)	27 (52%)	20 (48%)	χ^2=2.55, p=0.279
Duration of illness-current episode (years) (Mean±SD)	11.2±10.4	12.2±11.6	16.7±12.2	$F_{2,191}$=2.6, p=0.075
Patients with comorbid substance use	27 (27%)	20 (39%)	12 (29%)	χ^2=2.21, p=0.331
History of Alcohol use	9 (9%)	6 (12%)	10 (24%)	χ^2=5.89, p=0.053
History of Cannabis use	6 (6%)	11 (21%)	8 (19%)	χ^2=8.81, ***p*=0.012**
History of Cocaine use	3 (3%)	1 (2%)	2 (5%)	χ^2=0.63, p=0.730
Number of Failed pharmacotherapies (Mean±SD)	3.6±2.6	5.0±2.5^{++}	5.6±2.8^{+++}	$F_{2,191}$=9.9, ***p*<0.001**
Failed antidepressant trials (Mean±SD)	2.5± 1.7	1.35±1.4^{++}	2.0±1.4	$F_{2,191}$=5.4, ***p*=0.005**
Failed SGA (Mean±SD)	0.65±0.7	1.9±1.1^{+++}	1.4±1.2^{+++}	$F_{2,191}$=30.2, ***p*<0.001**
Failed Mood stabilizers (Mean±SD)	0.3±0.6	1.3±0.8^{+++}	1.4±1.0^{+++}	$F_{2,191}$=37.5, ***p*<0.001**
Patients currently having psychotherapy	41 (41%)	43 (83%) ***	35 (83%) ***	χ^2=36.01, ***p*<0.001**
Number of hospitalizations for depression since 1st episode				

None	56 (56%)	1 (2%) ***	14 (33%) ***, ###	χ^2=43.36, ***p*<0.001**
>one	20 (20%)	39 (75%) ***	21 (50%) ***	χ^2=44.41, ***p*<0.001**
Patients with 1st degree relative with affective illness	51 (51%)	31 (60%)	32 (76%)*	χ^2=7.76, ***p*=0.021**
Patients with Anxiety disorders	61 (61%)	9 (17%) ***	13 (31%) ***	χ^2=29.74, ***p*<0.001**
Patients with Panic disorders	19 (19%)	2 (4%) **	1 (2%) **	χ^2=12.09, ***p*=0.002**
Patients with Melancholic symptoms	74 (74%)	22 (42%) ***	18 (42%) ***	χ^2=19.77, ***p*<0.001**
Patients with Atypical symptoms	14 (14%)	11 (21%)	14 (33%)*	χ^2=6.93, ***p*=0.031**
Patients with suicidal attempts	23 (23%)	17 (33%)	25 (60%) ***,##	χ^2=17.73, ***p*<0.001**
History of MDE with psychotic symptoms	24 (24%)	16 (31%)	4 (10%)	χ^2=6.18, ***p*=0.045**
Patients with Personality disorders (Axis II in DSM-IV)	44 (44%)	26 (50%)	19 (45%)	χ^2=0.50, p=0.777
Cluster A	7 (7%)	0 (0%)	1 (2%)	χ^2=4.65, p=0.098
Cluster B	19 (19%)	6 (12%)	10 (24%)	χ^2=2.49, p=0.287
Cluster C	25 (25%)	1 (2%) ***	4 (10%) ***	χ^2=15.38, ***p*<0.001**
Patients with Medical condition potentially relevant to treatment (Axis III in DSM-IV)				
Autoimmune diseases	11 (11%)	2 (4%)	0 (0%)	χ^2=6.65, ***p*=0.036**
Cardiovascular diseases	25 (25%)	10 (20%)	8 (19%)	χ^2=0.96, p=0.618
Chronic pain disorders	25 (25%)	8 (15%)	7 (17%)	χ^2=2.44, p=0.295
Neurological conditions	13 (13%)	3 (6%)	2 (5%)	χ^2=3.42, p=0.181
Metabolic disorder	19 (19%)	20 (38%)*	12 (29%)	χ^2=6.83, ***p*=0.033**
Depression severity (Mean±SD)				
MADRS	30.8±8.9	22.2±6.7^{+++}	24.3±7.2^{+++}	$F_{2,191}$=22.7, ***p*<0.001**
HAMD-17	23.2±6.2	16.7±4.7^{+++}	17.3±4.5^{+++}	$F_{2,191}$=30.8, ***p*<0.001**
QIDS	15.8±4.2	12.1±3.7^{+++}	13.4±4.0**	$F_{2,191}$=15.4, ***p*<0.001**
CGI-S	5.0±1.2	4.2±1.3^{++}	4.3±1.1^{++}	$F_{2,191}$=8.8, ***p*<0.001**
GAF	55.5±10.2	60.9±4.4^{+++}	60.3±4.9^{++}	$F_{2,191}$=11.7, ***p*<0.001**

SD: Standard Deviation. TRD-UP: Treatment-Resistant Unipolar Depression. BP-I: Bipolar disorder type I. BP-II: Bipolar Disorder type II. MDE: Major depressive episode. SGA: Second Generation Antipsychotics.

**p<0.01, ***p<0.001 versus UP-TRD; #p<0.05, ##p<0.01, ###p<0.001 BP-I versus BP-II by Pearson's chi-square test.
^{++}p<0.01, ^{+++}p<0.001 versus UP-TRD by One-way Anova plus Bonferroni post hoc analysis.

2.3.5 Sociodemographic characteristics

The mean age (± SD) of the total sample was 43.6 (±14.1) years with 58.3% of the participants consisting of females (n=116) and 39.2% (n=78) of males. At the time of evaluation, 68.3% of the patients were unemployed (n=136) and 40.1% had a single status (n=81). Table 1 summarizes and compares the sociodemographic and clinical features of TRD-UP and BP patients.

Patients with TRD-UP were significantly older than BP patients (46.5±13.3 vs. 40.6±14.3, p=0.003) whereas the two groups were equally distributed in terms of gender, with a female to male ratio close to 1.5.

The prevalence of patients who were married at the time of evaluation was significantly greater in the TRD-UP group compared to the BP patients (41% vs. 16%, respectively; p<0.001). Similar rates of unemployment or disability were noted in the two groups (74% TRD-UP vs. 66% BP, p=0.272).

2.3.6 Clinical features and comorbidities

BP patients had an early onset of MDE compared to TRD-UP patients (26.4±9.8 vs. 37.7±15.3; p<0.001). In line with this finding, BP patients had their first psychiatric consultation and their first psychiatric hospitalization at a younger age than TRD-UP patients (p<0.001).

No differences were found between TRD-UP and BP concerning the prevalence of patients having recurrent depression (> 3 episodes) as well as the presence of comorbid substance use. However, BP patients has a higher prevalence of a history of cannabis use than TRD-UP (20% vs. 6%, p=0.005). The duration of the current episode of major depression was longer in BP than in TRD-UP (15.4±12.1 vs. 11.9±11.5, p=0.039).

Patients with TRD-UP showed a lower failure to different pharmacotherapies than BP patients (p<0.001). Looking at the different pharmacological classes of psychotropic drugs, TRD-UP

patients failed a greater number of antidepressant trials (p=0.009) and a lower number of SGA (p<0.001) and MS (p<0.001) trials compared to BP patients.

Interestingly, the percentage of patients currently undergoing psychotherapy was significantly lower in TRD-UP than in BP patients (p<0.001).

The prevalence of patients who did not have any hospitalization for depression since the first episode was greater in the TRD-UP group than in the BP group (p<0.001). In contrast, BP patients showed greater prevalence of more than one hospitalization for depression since the first episode than TRD-UP (p<0.001). Family history was also another characteristic that differed among the two groups. BP patients showed a higher prevalence of having at least one first-degree relative with affective disorders than TRD-UP patients (p=0.029).

Of note, the prevalence of patients who had a history of suicidality was significantly higher in those affected by BP than those diagnosed with TRD-UP (p=0.002). TRD-UP patients displayed higher prevalence of anxiety (p<0.001) and panic (p<0.01) disorders as well as depression with melancholic features (p<0.001) than BP patients.

2.3.7. Personality disorders and medical conditions

Overall there was no difference in the prevalence of personality disorders (Axis II in DSM-IV-TR) and physical diseases (Axis III in DSM-IV-TR) between the TRD-UP and BP; however, when studying the individual clusters, TRD-UP patients had a significantly higher prevalence rate of Cluster C personality disorders (avoidant, dependent and obsessive compulsive personality) compared to BP patients (p<0.001). No differences were found for Clusters A and B personality disorders.

With the exception of autoimmune diseases that were more prevalent in TRD-UP than in BP patients, there were no differences on other Axis III co-morbidities.

2.3.8 Depression severity and functioning

Using different psychometric scales, we examined and compared the severity of depression (MADRS, HAMD-17, QIDS-C16 and CGI-S) and the global functioning (GAF score) among TRD-UP and BP disorders. As shown in Table 2, TRD-UP patients were move severely depressed than BP patients as indicated by higher scores on MADRS, HAMD-17, QIDS-C16 and CGI-S scales ($p<0.001$). In contrast, the global functioning of BP patients was higher than that of TRD-UP patients ($p<0.001$).

2.3.9 Predicting categorical diagnosis

We used binary logistic regression to evaluate which demographic and clinical characteristics were differently associated with TRD-UP or BP (Table 3). The binary logistic regression model consisted of 11 variables involving individual characteristics (i.e., age of first depression, marital status, psychotherapy, employment status, more than one hospitalizations, 1st relatives with affective disorders), presence of comorbidities (anxiety disorders), clinical features of depressive episode (i.e., HAMD-17 score, melancholic features, number of failed pharmacotherapies) and level of overall functioning (GAF score). We excluded from the model, panic and Cluster C personality disorders since very few individuals ($n \leq 5$) were affected by these disorders in at least one of the two groups.

Our classification analysis reflected an overall goodness of fit to the data ($\chi 2=168.8$ $p<0.001$ df =11). Nagelkerke's (0.775) indicated a moderately strong relationship between predictors and variable grouping. No multicollinearity between the variables was detected (VIF range: 1.137-1.725).

A combination of five variables (more than one hospitalization for depression, comorbidity with anxiety disorders, current psychotherapy, severity of depression (HAM-D17 score) and global

functioning (GAF score) was able to significantly differentiate patients with TRD-UP from those with BP (Table 3). Of note, patients who were in psychotherapy and who had more than one hospitalization for depression had respectively 82% and 89% increased likelihood to have BP instead of TRD-UP. In contrast, the presence of comorbidity with anxiety disorders increased by 10 times the likelihood of having a diagnosis of TRD-UP than of BP. Moreover, a lower depression severity as measured by the HAMD-17 score as well as a higher global functioning as measured by the GAF score increased the likelihood of having a diagnosis of BP instead of TRD-UP.

2.3.10 Sociodemographic and clinical characteristics in BP-I, BP-II and TRD-UP

As secondary aim of this study we examined the possible differences within the bipolar spectrum (BP-I vs. BP-II) and then towards TRD-UP. As reported in Table 4, we found that some sociodemographic and clinical characteristics differentiated BP-I from BP-II patients and either BP-I or BP-II from TRD-UP. BP-I but not BP-II patients were younger than TRD-UP patients (p=0.011). Patients with BP-II showed a lower rate of unemployment/sick leave than TRD-UP and BP-I patients (48% vs. 74% and 80%, respectively; p<0.001).

The prevalence of patients who did not have any hospitalization for depression since the first episode was greater in BP-II than in BP-I (p<0.001). Family history was also another characteristic that differed amongst groups. BP-II patients showed a higher prevalence of having at least one first-degree relative with affective disorders than TRD-UP patients (p=0.010).

Of note, the prevalence of patients who had a history of suicidality was significantly higher in those affected by BP-II than those diagnosed with TRD-UP (p<0.001) and BP-I (p <0.01). We did not observed difference between BP-I and BP-II patients concerning the prevalence of comorbid substance use, of anxiety disorders, of Axis II personality disorders, and Axis III physical diseases.

In addition, no difference was found between BP-I and BP-II for the levels of both depression severity and global functioning.

2.4. DISCUSSION

These results indicate that patients with TRD-UP exhibit different psychopathological features compared to depressive episodes in patients with BP, suggesting that TRD-UP is a distinct psychopathological condition and not a prodromal state of BP depression.

TRD-UP patients show higher depression severity, higher prevalence of anxiety and panic disorders and of Cluster C personality disorders, a later onset of depression and fewer hospitalizations than BP patients. Within the bipolar spectrum, BP-II patients show lower rate of unemployment and hospitalizations for depression and higher prevalence of history of suicide attempts than BP-I patients.

Using a binary logistic regression model, it was possible to distinguish TRD-UP from BP disorders. The following variables were mostly associated with TRD-UP than with BP: increased anxiety, lower score on the GAF scale, higher depression symptoms (HAMD-17 score), lower number of hospitalizations and psychotherapies.

Overall, these findings are in agreement with previous literature comparing major depressive disorder (MDD) (non-TRD) with BP (Mitchell et al. 2008; Dudek et al. 2010; Mitchell and Malhi 2004). Indeed, the higher depression severity in TRD-UP than in BP was also reported in previous studies differentiating BP from MDD (non-TRD) patients. Additionally, earlier onset of depression, a greater prevalence of family history of affective disorders and a higher rate of suicide attempts were found in BP compared with unipolar (non-TRD) depression (Mitchell et al. 2008; Dudek et al. 2010; Mitchell and Malhi 2004).

Mitchell and Malhi (Mitchell and Malhi 2004), in an extensive review, described a higher

prevalence of depressive episodes and lower functioning in BP compared with UP (non-TRD) depression. In our study, TRD-UP showed the same number of recurrent episodes but higher number of hospitalizations and a lower GAF score compared with BP, pointing out the severity of the TRD-UP condition in comparison with UP (non-TRD) and BP. The lower functioning in TRD-UP patients is in line with previous studies indicating that TRD-UP, unlike BP patients, tend to experience more unremitting depressive states and higher fluctuations with depressive symptoms despite receiving appropriate treatment (Vergunst et al. 2013). Patients with BP disorder showed a greater prevalence of atypical symptoms and lower prevalence of melancholic features than TRD-UP patients as previously indicated by Benazzi (Benazzi 2000). However, when accounting for possible confounding variables, in the binary logistic model, depression with atypical or melancholic features was not significantly associated with TRD-UP, as suggested in a previous study (Zaninotto et al. 2013).

In TRD-UP, we found a greater prevalence of Cluster C personality disorders in keeping with Kornstein and Schneider (Kornstein and Schneider 2001) and a meta-analysis reporting that patients with affective disorders had more than 50 % comorbidity with personality disorders (Friborg et al. 2014).

We have shown that BP patients had a greater prevalence of metabolic disorder comorbidity compared with the TRD-UP group. These findings are in line with some studies where lifetime comorbidity in BP-I patients were reported to be between 50% up to 70% (Vieta et al. 2001). However, it cannot be ruled out that the higher rate of metabolic disease observed in BP patients was caused by the higher use of SGA in BP than in TRD-UP patients (as described in the methodology section).

Finally, patients with TRD-UP have less number of failed pharmacological trials compared to BP,

especially for SGA and MS. This might be due to the polypharmacy required in BP versus TRD-UP, as previously mentioned in a youth population at risk for BP disorders (Strawn et al. 2014). Altogether, these findings suggest that TRD-UP may constitute a unique subtype of depression compared with other affective disorders, and thus depressive episodes in BP are different than those in TRD-UP. Moreover, they are in support of a bi-dimensional approach for TRD-UP and BP disorders, recognizing points of differentiation that might contribute to distinguish a diagnosis within the affective disorders. Of note, it seems that differences also exist between TRD-UP and the different sub-types of BP. Further studies with a larger sample size may allow to deeply examine the psychopathological features that may be specifically associated with either TRD-UP, BP-I or BP-II. These results could seem in apparent contrast with Angst et al. (Angst et al. 2005) arguing that a diagnostic change from depression to BP-I and BP II occurs in about 1% and 0.5% of patients per year, respectively, and supporting a bipolar spectrum theory, in which unipolar depression and bipolar depression are in a continuum spectrum (Angst 2007).

In our study, we have chosen a priori patients followed in the Mood Disorders clinic for at least 2 years (mean 7.5 years), in which the possible risk of novel manic/hypomanic episode and thus consequent change in diagnosis was minimized and ruled out. This is also in agreement with a recent systematic review and meta-analysis underscoring that the rate of conversion from UP to BP disorders decreases with time reaching 0.8% in 10 years of initial diagnosis (Kessing and Andersen 2017). For this reason, compared to the systematic review by Bennabi et al. (Bennabi et al. 2015) and Dudek et al. (Dudek et al. 2010), bipolarity was not a risk factor for TRD. However, in keeping with Bennabi et al. (Bennabi et al. 2015), comorbidity for anxiety disorders was a clear risk factors for TRD-UP.

In contrast with Cassano et al. [51] and Benazzi (Benazzi 2006), we have not used scales such as

the Structured Clinical Interview for the Mood Spectrum or the Hypomania interview guide that by characterizing threshold and subthreshold mood episodes, hypomanic or "temperamental" features related to mood dysregulation allow assessing hypomanic symptoms. This limitation has prevented us to detect if TRD-UP could also present sub-threshold hypomanic symptoms. Another limitation of our study is that this is a retrospective and observational cross-sectional chart-review analysis that consequently lacks randomization and a longitudinal follow up. Prospective longitudinal studies are warranted to demonstrate that TRD will not convert in BP depression, or at least in a non-significant extent.

Despite the above-mentioned limitations, this study has several strengths: this is the first comparison study examining different clinical and sociodemographic data from an outpatient tertiary clinic for affective disorders proposing different predictors to distinguish TRD-UP from BP depression. Moreover, it adds clinical evidence towards the differentiation of TRD-UP as a unique type of depression as previously hypothesized by Fagiolini and Kupfer (Fagiolini and Kupfer 2003b) suggesting that TRD-UP may have specific clinical characteristics, neurobiological profile, and environment in which TRD develops, requiring a combination of AD and SGA as a first-line treatment (Gobbi et al. 2018).

Therefore, our study supports the ancient hypothesis of K. Schneider differentiating endogenous periodic unipolar depression (a chronic condition with several episodes in lifespan, and resistant to treatment) from bipolar phasic depression (characterized by phases of mania and depression) and exogenous depression (caused by exterior factors, with less episodes during life) (Schneider 1920, 1959).

However, to fully validate Schneider's hypothesis, these results should be replicated with larger controlled studies and include a comparison group with unipolar depressive patients who are not treatment resistant.

Finally, further analysis of longitudinal studies addressing neurobiological markers, clinical features between the TRD-UP and BP disorders should provide insight concerning these particular questions and evaluate the implications on pharmacological outcomes. This integrated approach will aid clinicians and researchers to disentangle initial diagnostic controversies between unipolar and bipolar spectrum improving the differential management and therapeutics of patients suffering from depression.

2.5 CONCLUSION

This retrospective and observational cross-sectional study shows that patients with depressive episodes in TRD-UP have a different history and distinct psychopathological features compared with BP depressive patients, thus TRD-UP constitutes a distinct psychopathological condition and not necessarily a prodromal state of BP depression. Further studies are needed to differentiate the pharmacological responses and outcomes in these distinct groups.

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INTERIM DISCUSSION

In the previous chapter, we discussed the clinical features associated with TRD-UP when compared with BP. Importantly the identified clinical predictors associated with TRD-UP were: anxiety disorders, greater severity of depression, a lower number of hospitalizations, and a lower number of non-pharmacological treatments.

These findings underscore the following: a) the identification of several clinical variables can be easily performed during a clinical assessment interview. b) A high functional disability in TRD-UP is represented by its chronicity and non-remitting course because of the inadequate treatment strategies. c) The urgent need for the development of biological biomarkers for early diagnosis and prognosis.

The complexity that surrounds the depressive disorders and adequately defines a phenotype for TRD-UP from a clinical and biological standpoint requires an integrative approach including genetic biomarkers and clinical and neuroimaging data, to identify new biological targets and stratify patients accordingly to the risk and the severity of TRD-UP.

According to the literature, there is evidence for the augmentation of AD with SGA, which includes the following FDA-approved medicines for the acute treatment phase: aripiprazole, quetiapine, and olanzapine/fluoxetine. However, there is still a limited amount of direct evidence comparing the augmentation strategies (i.e., SGA *vs.* MS or MS + combination of ADs) in a clinical setting. Thus, in the next chapter, we will examine the clinical outcomes of patients with TRD-UP by comparing two augmentation strategies (AD or SGA + AD) and identifying the associated clinical features.

CHAPTER 3 – ANTIDEPRESSANT COMBINATION VS ANTIDEPRESSANTS PLUS SECOND GENERATION ANTIPSYCHOTIC AUGMENTATION IN TREATMENT-RESISTANT UNIPOLAR DEPRESSION

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Abstract

Patients with treatment-resistant unipolar depression (TRD) are treated with antidepressant combinations (ADs) or with second generation antipsychotics plus antidepressant (SGA+AD) augmentation; however, the clinical characteristics, the factors independently associated with response to SGA+AD and the outcome trajectories have not yet been characterized. We performed a naturalistic study on the latest stable trial (medication unchanged for about three months) in 86 TRD patients with resistance to ≥2 ADs trials, who received ADs (n=36) or SGA+AD (n=50) treatments. Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton-Depression Rating Scale (HAM-D17), and other scales were administered before (T0) and after the latest 3-month stable trial (T3). Compared to ADs, the SGA+AD group showed increased percentage of depression with psychotic features, co-morbidity for personality disorders and substance use disorders (SUD), higher number of failed ADs pharmacotherapies and depressive symptoms at T0 on all scales (p<0.001). Compared to T0, both treatments significantly decreased depressive symptoms on MADRS and HAM-D17 at T3 (p<0.001); however, the SGA+AD augmentation produced a greater decline in mean score. Logistic regression analysis indicated that psychotic features, personality disorders and SUD were independently associated with SGA+AD treatment. Given the greater improvement in depression following SGA+AD augmentation, SGA augmentation should be indicated as a first-line treatment in severe TRD with psychotic features, SUD, and personality disorders.

Keywords: treatment resistant depression, antidepressants, second generation antipsychotics, augmentation.

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3.1 INTRODUCTION

Treatment-resistant depression (TRD), defined as the failure to respond to the first antidepressant trial (Trivedi, Fava, Wisniewski, and al. 2006), or to two or more antidepressant trials (Lam et al. 2009) represents one of the most severe social, economic, and health burdens for industrialized societies (Kessler, Berglund, and Demler 2003). According to the STAR*D study, less than 50% of depressed patients remit with the first antidepressant trial; non-responders in the study were assigned to either augmentation of citalopram with cognitive therapy or medication, or a switch to either cognitive therapy or to another antidepressant (Thase, Friedman, et al. 2007).

Several strategies have been developed in the last 20 years to treat patients with TRD. While in the 1990s the most popular approach in dealing with TRD was the combination of antidepressants (AD) (Blier and de Montigny 1994), more recently, preclinical and clinical studies have provided an evidence base for the development of augmentation strategies that use a combination of an antidepressant and a second generation antipsychotic (SGA+AD) (Blier 2013; Dold and Kasper 2016). For a review, see the recent work by Dold and Kasper (2016).

The preclinical rationale for antidepressant combination is supported by one of the following three strategies: i) the activation of 5-HT through either selective serotonin reuptake inhibition (SSRI), ii) the noradrenergic system through selective noradrenergic reuptake inhibition (SNRI) or iii) alpha-2 antagonism with mirtazapine (Blier et al. 2009). The rationale for using AAP, on the other hand, is based on the blockage of specific receptors, such as the 5-HT(2A), 5-HT(1B) and 5-HT7 receptors, and the activation of 5-HT(1A) and dopamine 2 receptors, which ultimately enhance the monoaminergic systems through synaptic fine-tuning (Blier 2014).

The use of SGA as add-on to one single AD has been supported by several clinical studies, namely for aripripazole (Berman et al. 2007; Berman et al. 2009; Marcus et al. 2008),

olanzapine/fluoxetine (Corya et al. 2006; Shelton et al. 2005; Shelton and Papakostas 2008; Thase, Corya, et al. 2007), quetiapine (Bauer et al. 2010; El-Khalili et al. 2010; McIntyre, Gendron, and McIntyre 2007), risperidone (Keitner et al. 2009; Mahmoud et al. 2007). A recent meta-analysis, primarily using data from pharma-sponsored studies and examining augmentation therapy with SGAs in major depression, suggests that this therapeutic approach provides small-to-moderate benefits, with limited improvement in patients' quality of life or reduced functional impairment, paralleled by potential side effects (Spielmans et al. 2013). However, this meta-analysis pooled data from single drug clinical trials or Phase III studies, and may not be generalizable to real clinical situations.

Until now, no studies have examined how antidepressant combinations (ADs) and augmentation with SGAs are applied in naturalistic, clinical settings, and more importantly, the clinical trajectories and outcomes in TRD patients treated with ADs vs SGA+AD. Even though the STAR*D study analyzed the outcome of antidepressant combination or switches (or the addition of lithium, buspirone, or liothyronine), it did not analyze augmentation therapy using SGA (Rush et al. 2004). More recently, Dold et al. (Dold et al. 2016) in a naturalistic study, analyzed 1181 adult in- and outpatients with major depressive disorder (MDD) from 9 different European academic sites, and found no significant differences in terms of symptom severity and treatment response between different psychopharmacological classes, including SGA, used as augmentation strategies. However, this study collected patients with and without TRD from different countries, and thereby precluded targeting a specific subpopulation. Therefore, this is the first study evaluating SGA augmentation vs ADs combination in TRD patients. Here we report clinical characteristics, including socio-demographic, clinical features and comorbidities, as well as treatment outcomes in a population of severe unipolar TRD patients who have failed to respond to

two or more trials with an antidepressant and/or an augmentation strategy, treated with combinations of ADs or with SGA augmentation. Only the latest stable trial (medication unchanged for about 3 months) was included in order to ensure valid statistical analysis. Our goal was to determine the characteristics and trajectories of patients receiving the combination of ADs or SGA+AD, first, in an effort to better elucidate the outcomes of these two different pharmacological strategies, and secondly, to examine which factors were independently associated with SGA+AD, with the aim of trying to understand whether there are psychopathological traits associated with TRD that might suggest higher benefits if an augmentation strategy with SGA is undertaken.

3.2 MATERIALS AND METHODS

3.2.1 Patients

Data from 106 patients aged 19-80 years old was collected from the Mood disorders clinic (MDC) registry of McGill University Health Center (MUHC), a university tertiary clinic treating TRD and bipolar disorder patients. The study was approved by the Institutional Review Board (IRB) of McGill University (13-375-PSY). The Registry is an ongoing study at the MDC in which patients treated for TRD are systematically studied and followed-up for their treatment regimen and clinical evolution. Participants' diagnoses are ascertained by the Structured Clinical Interview for Diagnosis (SCID) (First et al. 2002) carried out by skilled professionals or by psychiatrists. All selected patients participants met DSM-V criteria for unipolar MDD and were currently in a unipolar major depressive episode without hypomanic or manic symptoms (American Psychiatric Association 2013). The study was conducted in accordance with the Declaration of Helsinki. From these 106 patients, 11 were excluded since treated with an antidepressant plus valproic acid and/or

lithium (Ghabrash et al. 2016), and 9 because received only one antidepressant. Only patients receiving ADs or SGA+AD were finally included (n=86).

3.2.2 Sampling procedures

All patients had a current unipolar major depressive episode with or without psychotic features lasting more than 6 months and a detailed past history of lack of response to at least two adequate AD mono or combination trials (at therapeutic dosage and for at least three weeks) operationally defined using the Antidepressant Treatment History Form (Sackeim 2001).

Patients were classified into two pharmacotherapy groups: (1) Group-ADs was composed of patients treated with antidepressant combination therapy (n=36), and (2) a Group-SGA+AD, consisting of patients treated with antidepressants in combination with second-generation antipsychotics (n=50; augmentation group).

3.2.3 Clinical measures

Chart reviewer analysis was performed by three raters (two psychiatrists and a General Practitioner) and evaluated before the beginning (T0) and after at least three months of unchanged treatment (T3), mean evaluation time occurring 13.6 ± 5.96 weeks after T0. At T0 and T3 patients were assessed on the following scales: Montgomery–Asberg Depression Rating Scale (Montgomery and Asberg 1979) (MADRS); Clinical Global Impression-Severity of Illness (Guy 1976b) (CGI-S); Quick Inventory of Depressive Symptomatology (Rush, Trivedi, Ibrahim, Carmody, Arnow, Klein, Markowitz, Ninan, Kornstein, Manber, et al. 2003) (QIDS-C16); and Hamilton-Rating Scale for Depression (Hamilton 1960a) (HAM-D17). Severity classification of depression as mild (<17), moderate (17-24) or severe (>24) was based on the HAM-D17 score and the cut-off values proposed by Zimmerman et al. (2013).

The following socio-demographic characteristics of patients are collected in the Registry: age, ethnic group, gender, marital status, employment, level of education and living status, previous psychiatric diagnosis, age of first psychiatric consultation, family history of mental illness, history of psychotherapy, electrical/neurological therapy, psychiatric programs and services, general medical history, number of previous suicide attempts, psychosis, DSM-IV axis II, III and IV pathology, previous and current pharmacotherapy as well as doses and psychopathology including behavioral problems, Attention Deficit-Hyperactivity disorder (ADHD), alcohol or substance abuse, anxiety disorders, sleep disorders and eating disorders.

The multidimensional Maudsley Staging Method (MSM) was used to estimate the severity of treatment resistance in both groups (Fekadu et al. 2009).

According to MSM, patients were classified to mild (3-6), moderate (7-10), and severe (11-15) levels of resistance.

The pharmacological treatments are reported in Table 2. Some patients in group AD (n=4) and group SGA+AD (n=7) also received low doses of lamotrigine (25-75 mg) and/or benzodiazepines. The use of Risperidone, Lurasidone, Haldol and Fluphenazine was considered off-label in Canada. Quetiapine XR is licensed in Canada (but not in USA) as monotherapy in MMD patients who failed treatments with currently available antidepressants.

3.2.4 Statistical analysis

Statistical analysis was conducted using SigmaPlot-13 and SPSS-23. Data are presented as mean ± standard error of the mean (SEM), mean ± standard deviation (SD). Inter-rater reliability for individual scales was calculated using Cohen's kappa (Cohen 1968). Group comparisons on socio-demographic and clinical characteristics of the participants were computed with independent t-tests for interval and continuous variables and Pearson's chi-square (χ^2) for categorical variables.

Comparisons for all clinical scales of depression and general functioning between antidepressants and augmentation groups were evaluated using two-way repeated measures (RM) ANOVA, with time (T0 vs. T3) as within-subject factor and treatment (ADs vs. SGA+AD) as between subject factor. These analyses were followed by Bonferroni post-hoc tests for multiple comparisons (total number of comparisons = 6). Logistic regression analysis (enter-method) with treatment group as dependent variable (ADs=0 and SGA+AD=1) was employed to study factors independently associated with treatment with SGA+AD. The Hosmer and Lemeshow test was used to assess the goodness of fit of the logistic regression model. Possible multicollinearity was examined using the variance inflation factor (VIF). The statistical significance threshold p was set at $p<0.05$. The sample size calculation was performed using the Power Analysis and Sample Size Software (PASS 11; NCSS, Kaysville, Utah). This study was designed to detect a difference between treatments of at least 5 points in the MADRS scale considering our previous report (Ghabrash et al. 2016) that produced an estimate for the SD of 8 points on the same scale, and given a power level of 0.8 and an alpha of 0.05. A sample size of 83 individuals was determined to be adequate (Group 1= 35 participants; Group 2= 48 participants).

3.3 RESULTS

3.3.1 Socio-demographic and clinical characteristics

The demographic and clinical characteristics of the study population are reported in Table 1. All patients received a diagnosis of Major Depressive Disorder and recurrent episodes of depression of moderate to severe intensity following the DSM-V criteria and the SCID interview. Among them, 78% were diagnosed with Unipolar-TRD without psychotic features and 65% were diagnosed with a comorbid anxiety disorder (PTSD, GAD, Agoraphobia, phobia, OCD, Panic disorder, Social Phobia, Anxiety Disorder Not Otherwise Specified), which has been observed in

other studies (Russell et al. 2001; Souery et al. 2011; Petersen et al. 2001). 75% of the patients had a comorbid Axis III medical condition potentially relevant to psychiatric illness and finally 94% reported a comorbid Axis IV psychosocial or environmental problem. Chronic physical diseases are very common in TRD patients (Hall et al. 1981; Popkin, Callies, and Mackenzie 1985).

3.3.2 Inter-rater agreement

Inter-rater reliability was tested on a sample of 74 patients. Patients were assessed by three raters (two psychiatrists and a General Practitioner). We found acceptable to good agreement (Cohen's kappa range: 0.54-0.88) (Viera and Garrett 2005) (MADRS: 0.60; HAM-D17: 0.54; QIDS-C16: 0.63; CGI-S: 0.75; CGI-Global Improvement: 0.88) across all scales.

3.3.3 Socio-demographic, pharmacological and clinical characteristics of the two treatment groups

Table 2 and Table 3 summarize the different psychopharmacological therapies of the two groups under examination and the most common side effects reported by the patients in the two groups during the T0-T3 treatment period, respectively. No overall difference in the percentage of patients displaying side effects between the two pharmacotherapies was seen ($\chi 2=13.515$, $p=0.141$). The overall low rate of complains for side effects was nevertheless biased by the fact that we selected only the latest stable trial (medication unchanged for about three months) when both patient and psychiatrist agreed in the treatment. However, as expected, metabolic side effects including weight gain, glucose intolerance and dyslipidemia were noted only in the group of patients undergoing SGA augmentation.

Concerning socio-demographic and clinical characteristics of the two groups, they did not differ in mean age of the participants, ratio of males to females, number of patients older than 65 years of age, number of suicide attempts, number of 1st degree family history of mental illness, presence

of comorbid anxiety disorders (Table 4), or Axis III and IV conditions. Interestingly, patients in the augmentation (SGA+AD) compared to ADs group had a greater number of previous failed ADs pharmacotherapies in mono/combination (t=-2.03, df = 84; p=0.046). Moreover, the proportion of patients with more than one hospitalization (30% vs. 2%; $\chi 2$=7.89, p=0.006) as well as of patients diagnosed with unipolar-TRD with psychotic features (36% vs. 3%; $\chi 2$=13.42, p<0.001),with Axis II personality disorders (60% vs. 28%; $\chi 2$=8.74, p=0.004) and/or history of substance of abuse (36% vs. 11%; $\chi 2$=6.81, p=0.012) was higher in the SGA+AD compared to the ADs group. Finally, patients undergoing augmentation therapy displayed at T0 a more severe treatment resistance measured with the MSM scale than patients on only ADs (Table 4; t=-4.18, df=84; p<0.001).

3.3.4 Pharmacological outcomes

At T0, the SGA+AD group had moderate to severe depression (MADRS score of 33.6 ± 1.2; HAM-D17 score of 25.6 ± 0.9; QIDS-C16 score of 17.2 ± 0.6 and CGI-S score of 5.4 ± 0.2) whereas the AD group had mild to moderate depression (MADRS score of 27.5 ± 1.4; HAM-D17 score of 20.4 ± 1.0; QIDS-C16 score of 14.2 ± 0.7 and CGI-S score of 4.5 ± 0.2) in spite of previous antidepressant trials (Table 4 and Figure 1). Two-way repeated measures ANOVA revealed a significant time x treatment interaction for both HAM-D17 (F 1,84=4.81, p=0.031) and MADRS (F 1, 84=3.95; p=0.050), main effects of both treatment and time for the MADRS (treatment: F1,84=7.54, p=0.007, partial $\eta 2$=0.038; time: F1,84=173.6, p<0.001), and HAM-D17 (treatment: F1,84=10.99, p=0.001, partial $\eta 2$=0.056; time: F1,84=179.0, p<0.001) scales. Two-way repeated measures ANOVA did not instead reveal a significant time x treatment interaction for QIDS-C16 (F 1,84=3.05, p=0.085), and CGI (F 1, 84=2.81, p=0.097) but significant effect for treatment in QIDS-C16 (F1,84=8.87, P=0.004, partial $\eta 2$=0.041) and in CGI (F1,84=9.41, P=0.003, partial

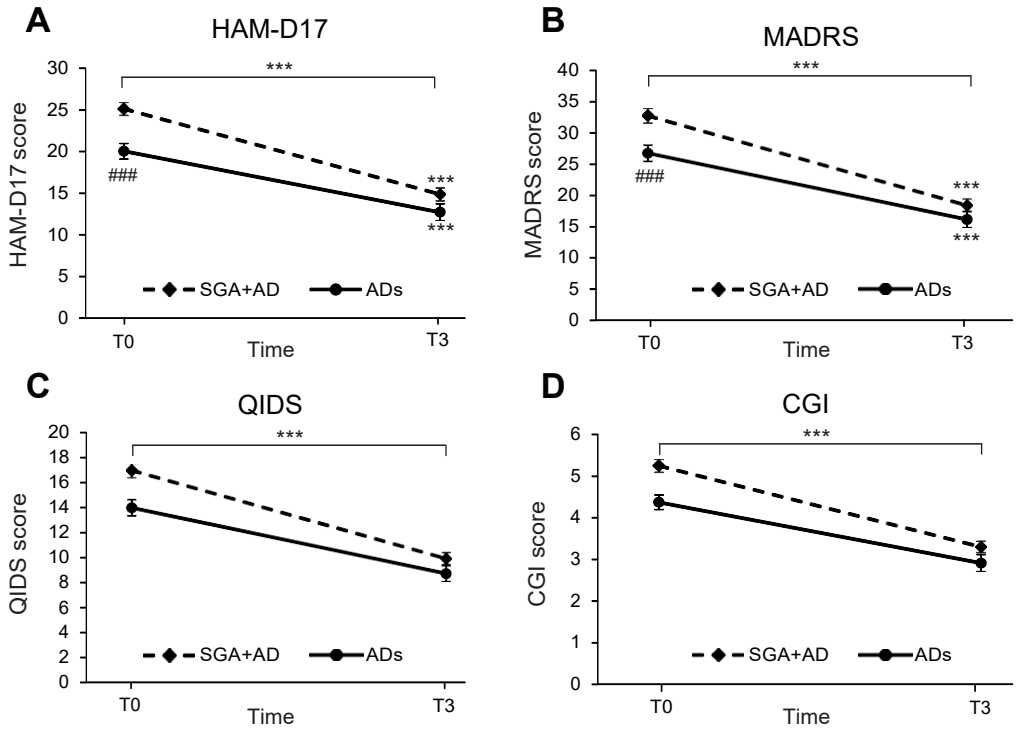
η2=0.044) and for time in QIDS-C16 (F1,84=153.8, *P*<0.001) and in CGI (F1,84=139.1, *p*<0.001). In both treatment groups, comparing T0 versus T3, a significant improvement of the disease status was observed (*p*<0.001 for all scales, Figure 1). Bonferroni's post-hoc test for multiple comparisons revealed that HAM-D17 and MADRS total scores were significantly higher (p≤0.001) at baseline (T0) in the SGA+AD group than in the ADs group. No significant difference between treatment groups at study endpoint (T3) was instead observed (Figure 1). We also quantified and compared the improvement in depressive symptoms due to the two treatments by analyzing the delta change (T0-T3) in HAM-D17, MADRS, QIDS and CGI scores. TRD patients in the SGA+AD group showed a significant higher reduction in depressive levels than TRD patients treated with ADs in MADRS and HAMD (see delta change in depression severity (T0-T3) in Table 4), but not in CGI and QIDS. Of note, a similar trend was found even when patients having SGA augmentation with more than one AD (n=18) were excluded from the SGA+AD group (data not reported).

Since augmentation with SGA was mostly reserved by the clinicians for the more resistant and more severe patients (HAM-D17>24; 22% in the ADs vs 58% in the SGA+AD group, χ2=9.51, *p*=0.002), we examined the efficacy of the two treatments in patients showing moderate depression (HAMD-D17 between 17 and 24; 63% in the ADs group and 38% in the SGA+AD group). As shown in Table 4, the delta change in depressive symptoms produced by the two treatments in moderate severe TRD patients was equal, confirming that SGA+AD was more effective in patients with severe depression.

No difference between the two treatment groups was found in the proportion of patients (33% in the ADs vs. 22% in the SGA+AD groups) who did not respond to antidepressant therapy (absence of response to psychopharmacotherapy was considered as delta HAMD-17 <25% (Bauer et al.

2013; Dold and Kasper 2016) (Table 4). Of note, only 25% of patients reached the remission (HAMD-17 score ≤7) at the end of the treatment in the ADs group, and 12% in the SGA+AD group (difference not statistically significant).

3.3.5 Fig. 1. Effects of antidepressant combination therapy (ADs) and second-generation antipsychotics plus antidepressants (SGA+AD) on depressive symptoms measured with (A) HAM-D17, (B) MADRS, (C) QIDS, and (D) CGI scales.



Values are reported as Mean±SEM. ***p<0.001, T3 versus T0; ###p<0.001 ADs versus SGA+AD group by two-way RM ANOVA followed by Bonferroni post-hoc test for multiple comparisons.

3.3.6 Characteristics associated with treatment with SGA+AD in TRD patients

Given the greater improvement on depressive levels with SGA+AD, we examined which factors at T0 were independently associated with their therapeutic efficacy. To this aim, we decided to include into the logistic regression model only those clinical characteristics that as shown in Table 5 were significantly different comparing AD vs. SGA+AD group (number of failed pharmacotherapies, presence of psychotic features, personality disorders, history of SUD, more than one hospitalization since the first depressive episode) and the depression levels at baseline measured with the MADRS, which is one of the most important factor modulating antidepressant

effect (Fournier et al. 2010). No multicollinearity between these six variables was detected (Table 5; Mean VIF=1.215. Logistic regression analysis indicated that SGA+AD treatment was significantly associated with the presence of psychotic features, personality disorders and history of SUD (Table 5). In particular, TRD patients with psychotic features were 26 times more likely to receive SGA augmentation, TRD patients with history of SUD 5 times more likely to receive SGA augmentation, and TRD patients with personality disorders 3 times more likely to receive SGA augmentation (Table 5). Moreover, we found a tendency (p=0.050) that for every failed ADs combination therapy the likelihood to receive SGA augmentation was increased of 34%. Classification analysis indicated that the model correctly classified 84.9% of the patients, and Hosmer & Lemeshow test of the goodness of fit suggested that the model was a good fit to the data ($\chi 2$=7.90, p=0.342).

3.3.7. Table 1. Clinical characteristics and demographics of participants.

Characteristics	**TRD population (N=86)**
Age (Years) (Mean±SD)	49.9±13.3
Ratio of Males: Females	36:50
Patients≤65 years of age	74 (86%)
Age of first psychiatric consultation (Years) (Mean±SD)	37.6±15.0
Ethnicity:	
Caucasian:	67 (78%)
Hispanic:	3 (3.5%)
Afro-American:	3 (3.5%)
Asian:	4 (5%)
Other:	9 (10%)
Education Level	
High School:	15 (17%)
College:	30 (35%)
Bachelor's:	21 (25%)
Master's:	8 (9%)
Doctorate:	9 (10%)
Vocational:	3 (4%)
Patients diagnosed with Unipolar-TRD without psychotic features	67 (78%)
Patients living alone at baseline	25 (29%)
Number of patients with 1st degree family history of mental illness	52 (60%)
Number of failed pharmacotherapies in mono or combination (Mean±SD)	3.5±2.4
Duration of illness-current episode (years) (Mean±SD)	11.9±10.7

Number of patients with comorbid anxiety disorder	56 (65%)
Patients with history of substance abuse	22 (26%)
Number of patients with other psychiatric illnesses (Anorexia Nervosa, Bulimia Nervosa, Eating disorder NOS, Circadian Rhythm Sleep Disorder, Trichotillomania, ADHD)	15 (17%)
Number of patients with suicide attempts	20 (23%)
Number of patients with a diagnosed personality disorder	40 (47%)
Number of patients with axis III (Medical condition potentially relevant to treatment):	
Chronic pain disorders	15 (17%)
Autoimmune diseases	8 (9%)
Neurological conditions	6 (7%)
Metabolic disease and endocrinopathies	13 (15%)
Cardiovascular diseases	23 (27%)
Number of patients with axis IV	81 (94%)

ADHD: Attention Deficit Hyperactivity Disorder. Anxiety Disorder NOS: Anxiety Disorder Non-otherwise specified. Eating Disorder NOS: Eating Disorder Non-otherwise specified. Unipolar-TRD: Unipolar-Treatment Resistant Depression. N/A: Not Available. SD: Standard Deviation.

3.3.8. Table 2. Pharmacotherapy of participants in each treatment group.

Antidepressant combinations (ADs) (n=36)	**Second generation antipsychotics plus Antidepressants (SGAs+ADs) (n=50)**	
SSRI/SNRI + Mirtazapine: 14 SNRI +SSRI: 2 SNRI +TCA: 1 SSRI+ SARI:4 SNRI/SNRI +TCA+Bupropion: 3 SNRI/SSRI/TCA + Bupropion: 12	**Quetiapine (total 26). Therapeutic Range 25-650 mg; Mean±SEM: 129±29mg**	
	SSRI/SNRI + Quetiapine:	10
	SSRI /SNRI+ Bupropion + Quetiapine	13
	BUPROPION + Quetiapine	2
	SSRI + Mirtazapine + Quetiapine:	1
	Risperidone (total 6). Therapeutic Range 0.25-2 mg; Mean±SEM: 1.88±0.51 mg	
	SSRI/Mirtazapine + Risperidone:	4
	Lurasidone + Risperidone + Aripiprazole	1
	SSRI + Bupropion + Risperidone:	1
	Olanzapine (total 6). Therapeutic Range 2.5-12.5 mg; Mean±SEM: 8.75 ±1.80 mg	
	SSRI/SNRI + Olanzapine:	4
	SSRI + Mirtazapine + Olanzapine:	1
	SNRI + Mirtazapine + Olanzapine	1
	Aripripazole (total 10). Therapeutic range 2-15 mg; Mean±SEM: 4.4±1.3 mg	
	SSRI/SNRI + Aripiprazole:	5
	Bupropion ± SSRI + Aripiprazole	3
	Mirtazapine + Aripiprazole + Quetiapine:	1
	TCA+ Lurasidone+ Aripiprazole	1
	Others (total 2). Therapeutic equivalent (1-5 mg)	
	TCA+ Typical agents (Haldol/ Fluphenazine)	2

SSRI: Selective Serotonin Reuptake Inhibitor. SNRI: Serotonin Norepinephrine Reuptake Inhibitor. TCA: Tricyclic antidepressant. SARI: Serotonin Antagonist and Reuptake Inhibitor.

Therapeutics (range, Mean±SEM) : SSRIs (Citalopram: 10-60 mg, 28.4±3.6 mg; Escitalopram: 10-50 mg, 13.1±1.6 mg; Fluoxetine: 20-60 mg, 42±9.1 mg; Paroxetine: 40 mg; Sertraline: 50-300 mg, 115.9±17.3 mg); SNRI (Duloxetine: 30-60 mg, 54±6 mg; Venlafaxine: 37.5-300 mg, 143.1±16.9 mg); TCA (Amitriptyline 10-125 mg, 17.6±7.5 mg; Clomipramine: 25 mg; Desipramine: 25-50 mg, 37.5±12.5 mg; Nortriptyline: 25 mg); Mirtazapine (7.5-45 mg, 24.3±4.1 mg); Bupropion (150-450 mg, 190.0±22.4 mg); Lurasidone (40 mg).

3.3.9 Table 3. Side effects reported by the patients in the ADs and SGA+AD groups during the T0-T3 treatment period.

Side effect	**ADs (n=36)**	**SGA+AD (n=50)**
None	19	21
Weight gain	0	6
Glucose intolerance	0	1
Dyslipidemia	0	1
Insomnia/Agitation/Irratibility	7	9
Somnolence	1	4
Anticholinergic symptoms	2	1
Sexual dsyfunction	2	5
Extrapyramidal symptoms	0	1
Gastrointestinal symptoms (diarrhea, constipation)	5	1

3.3.10 Table 4 Clinical characteristics and treatment outcomes of participants in antidepressant combination therapy (ADs) and participants using adjunctive second generation antipsychotics plus antidepressants (SGA+AD) for therapeutic augmentation.

	ADs (n=36)	**SGA+AD (n=50)**
Sociodemographic and clinical characteristic at T0		
Age (Years) (Mean±SD)	51.4±14.3	48.9±12.6
Ratio of Males: Females	13:23	23:27
Patients≤65 years of age	28 (78%)	46 (92%)
Age at first episode of MDD (Mean±SD)	40.1±16.0	35.7±14.1
Duration of illness-current episode (years) (Mean±SD)	10.9±9.5	12.5±11.6
Patients with Unipolar-TRD with psychotic features	1 (3%)	18 (36%)***
Patients with suicide attempts	6 (17%)	14 (28%)
Number of failed ADs pharmacotherapies in mono/combination (Mean±SD)	2.9±1.8	4.0±2.7[#]
Patients with 1st degree family history of mental illness	23 (64%)	31 (60%)
Unemployed/Disability sick leave before treatment	20 (56%)	34 (68%)
Patients with comorbid anxiety disorders	21 (58%)	35 (70%)
Patients living alone at baseline	13 (36%)	12 (24%)
Patients with Personality disorders	10 (28%)	30 (60%)**
Patients with history of substance abuse	4 (11%)	18 (36%)*
Patients with axis III:		
Neurological conditions	3 (8%)	3 (6%)
Metabolic disease and endocrinopathies	5 (14%)	9 (18%)
Cardiovascular diseases	11 (31%)	12 (24%)
Autoimmmune diseases	4 (11%)	4 (8%)
Chronic pain disorders	6 (17%)	9 (18%)
Number of hospitalizations for depression since 1st episode		
None	21 (58%)	27 (54%)
One	13 (36%)	9 (18%)
>one	2 (6%)	15 (30%)**
Patients with axis IV	33 (92%)	48 (98%)

Depression severity at T0 (Mean±SEM)		
MADRS	27.5±1.4	33.6±1.2$^{\#\#}$
HAM-D17	20.4±1.0	25.6±0.9$^{\#\#\#}$
QIDS	14.2±0.7	17.2±0.6$^{\#\#}$
CGI	4.5±0.2	5.4±0.2$^{\#\#}$
MSM (mild =3-6, moderate=7-10, severe=11-15)	8.8±0.3	10.4±0.3$^{\#\#\#}$
Depression severity at T3 (Mean±SEM)		
MADRS	16.7±1.4	19.0±1.0
HAM-D17	12.9±1.1	15.1±0.9
QIDS	8.9±0.7	10.1±0.6
CGI	3.0±0.2	3.4±0.1
Patients who did not respond to antidepressant therapy (delta HAMD-17<25%)	12 (33%)	11 (22%)
Patient in remission (HAM-D17≤7)	9 (25%)	6 (12%)
Delta change in depression severity (T0-T3) (Mean±SEM)		
MADRS	10.8±1.3	14.6±1.3$^{\#}$
HAM-D17	7.5±0.9	10.5±0.9$^{\#}$
QIDS	5.3±0.6	7.1±0.7
CGI	1.5±0.2	2.0±0.2
Delta change in depression severity (T0-T3) in TRD patients with moderate depression (total HAM-D17 between 17-24) (Mean±SEM)	**(n=23)**	**(n=19)**
MADRS	11.2±1.8	9.7±1.5
HAM-D17	7.5±1.1	7.2±0.9
QIDS	5.6±0.8	4.6±0.6
CGI	1.5±0.3	1.3±0.2

MDD: Major Depressive Disorder. MSM: Maudsley Staging Method for treatment-resistant depression. SEM: Standard Error of Mean. SD: Standard Deviation. Unipolar-TRD: Unipolar-Treatment Resistant Depression. *p <0.05; **p <0.01, ***p <0.001 ADs group versus SGA+AD group by Pearson's chi-square test; $^{\#\#}p$ <0.01; $^{\#\#\#}p$ <0.001 ADs group versus SGA+AD group by independent t-test.

3.3.11 Table 5. Clinical characteristics of TRD patients associated with augmentation treatment with second generation antipsychotics.

Clinical characteristics	Coefficient B	SEM	Wald	P value	OR Exp(B)	OR 95% CI		VIF
						Lower	Upper	
Failed ADs pharmacotherapies in mono/combination	0.290	0.148	3.829	0.050	1.337	1.000	1.788	1.085
Presence of psychotic features	3.250	1.165	7.785	0.005	25.791	2.630	252.897	1.397
History of substance abuse	1.615	0.721	5.020	0.025	5.027	1.224	20.642	1.095
Presence of personality disorders	1.182	0.599	3.898	0.048	3.262	1.009	10.551	1.169
More than one hospitalization for depression since first episode	1.447	0.958	2.281	0.131	4.250	0.650	27.798	1.227
MADRS score at T0	0.018	0.038	0.230	0.631	1.019	0.945	1.098	1.317

CI: confidence interval; OR: Odd ratio; SEM: Standard Error of Mean; VIF: variance inflation factor.

3.4 DISCUSSION

This is the first study examining the clinical characteristics and outcomes in TRD patients treated with ADs combinations and SGA+AD augmentation in a real clinical setting. The group receiving SGA augmentation had more severe symptoms, as reflected by higher scores on the MADRS, HAM-D, QIDS-C16, and CGI scores at baseline (Figure 1 and Table 4). Moreover, this group had a higher number of previous failed ADs mono/combination therapies, a greater prevalence of depression with psychotic features, a greater co-morbidity of personality disorders, and an increased likelihood of a history of SUD (Table 4). However, when treated with SGA+AD, their outcome was similar to the group treated with solely ADs combinations, in terms of both mean values on psychometric scales and remission rate. The medium effect size observed after SGA augmentation highlights the clinical relevance of considering this pharmacological strategy when a TRD patient presents either psychotic features, co-morbidity with personality disorders, or a history of SUD.

Generally, our study confirms previous literature reporting that the most difficult patients with severe TRD have comorbid personality disorders (Fagiolini and Kupfer 2003a; Grote and Frank 2003; De Carlo, Calati, and Serretti 2016). Personality disorders have been viewed as a predisposition or vulnerability that precede the affective disorder (Zanarini et al. 1998). Estimates of the prevalence of comorbid personality disorders in patients with major depressive disorder range from 14% to 85%, with a mean of about 50% (Thase 1996; Hirschfeld and Shea 1992). Depression is more common in Cluster C personality disorders (Points 2005), followed by the dramatic-unstable Cluster B (Kornstein and Schneider 2001; Keller et al. 1998). In keeping with these previous results, we found that 35% of patients were in Cluster C and 21% patients in cluster B. Our group had similar results in a forensic psychiatric setting, in which prisoners with

depression reported a high comorbidity of Cluster C (Comai et al. 2016). Two separate studies (Fava et al. 2002; Fava et al. 1994) have shown the high incidence of personality disorder traits in depressed patients that may change with adequate therapy. The fact that, at baseline, we observed a significant presence of personality disorder traits in the SGA+AD group further confirms the evidence that more severe patients had greater co-morbidity of Axes II.

Patients treated with SGA+AD had increased comorbidity of SUD, similar to Mrazek et al. (2014). In particular, alcohol and cannabis use disorders were the most reported. This association, in severe TRD patients, is most commonly explained by either a bidirectional relationship or a shared etiologic factor underlying both disorders (Swendsen and Merikangas 2000); recent studies have found that cannabis can be a precipitating factor of depression even in individuals without any familial risk of depression (Lev-Ran et al. 2014), demonstrating the possible role of drugs of abuse in the pathophysiology of some cases of depression.

50% of patients in the SGA+AD group were treated with quetiapine, with a range dose of 150-650 mg. This large use of quetiapine is likely due to its high tolerability and its minimal side effects, especially when used at relatively low doses, based on our clinical experience. Quetiapine is a 5HT1A receptor agonist and exerts 5HT2A and 5HT7 antagonism, which contributes to its overall antidepressant efficacy (Jensen et al. 2008). This drug has been approved by FDA as mono or adjunct treatment in MDD. In two large double-blinded RCTs, including over 850 MDD patients, quetiapine-XR 150-300mg augmentation significantly reduced mean MADRS scores (Bauer et al. 2009; El-Khalili et al. 2010). Not surprisingly, aripiprazole was the second most-used SGA. This drug also received FDA approval as adjunct treatment in unipolar MDD (Nelson, Pikalov, and Berman 2008). Its efficacy was demonstrated in four placebo controlled-RCTs in TRD patients using adjunctive aripiprazole at doses ranging from 2-20 mg/d after failure of at least two adequate

trials of standard antidepressants (Berman et al. 2007; Berman et al. 2009; Marcus et al. 2008; Fava et al. 2012). Only in one patient was aripripazole used at doses higher than 10 mg/d (12.5 mg/d), affirming the preclinical evidence that at low doses, aripripazole acts as a partial agonist, likely blocking the presynaptic D2 autoreceptor and thereby increasing dopaminergic neurotransmission (Blier 2014).

5-HT2A antagonism by olanzapine, in conjunction with ongoing 5-HT reuptake inhibition by SSRI's, has been shown to enhance release of both 5-HT and NE, and can reverse fluoxetine-induced suppression of NE activity (Blier and Szabo 2005). In a recently published meta-analysis, MADRS scores were significantly reduced in patients receiving olanzapine and fluoxetine (OFC; n=462) compared to fluoxetine (n=342) and olanzapine monotherapy (n=342), and overall response was significantly higher in OFC vs. olanzapine or fluoxetine monotherapy (38.1% vs. 26.9% and 22.2% respectively) (Tohen et al. 2010). In fact, olanzapine is the only FDA-approved atypical agent for TRD in combination with an SSRI (Symbyax®; OFC capsules) (Bobo and Shelton 2010). Finally, an open-label trial (n=386) examining the effect of risperidone adjunct vs. placebo in citalopram monotherapy found limited usefulness for risperidone in TRD (Rapaport et al. 2006), although a randomized trial found it efficacious in MDD (Mahmoud et al. 2007; Keitner et al. 2009).

Two patients in the SGA+AD group were treated with haloperidol and fluphenazine at very low doses (1 mg/d) in addition to atypical drugs. Both patients responded to this pharmacotherapeutic combination, confirming previous observations suggesting that low doses of first generation antipsychotic drugs may be efficacious in depression (Robertson and Trimble 1982). Their efficacy can be explained by their presynaptic D2 autoreceptor activation, as hypothesized by Van Praag in 1977 (Praag 1977). SGAs are often claimed to have antidepressant-like effects because they

improve sleep and anxiety items in MADRS and HAMD scales; even if they undoubtedly contribute to the improvement of these symptoms, it has been demonstrated that compared to placebo, quetiapine monotherapy, for example, not only improves sleep items, but also has incisive effects on depressive mood, sociality and work and activity items, confirming its distinct antidepressant effects (Weisler et al. 2012). In agreement, we found that SGA augmentation produced a significant improvement (delta change T0-T3) in MADRS and HAM-D17 items related not only with sleep, but also with depressive mood (data not shown).

The second aim of our study was to examine if there are some clinical factors that may suggest a better response to SGA+AD than AD combination therapy in TRD. We found that psychotic features, personality disorders and SUD were independently associated with SGA+AD therapy. In particular, in the presence of psychotic features, the likelihood of having a significant improvement in depressive symptomatology increased by 26 times if treated with SGA augmentation rather than solely with AD combinations. Consequently, these data offer a guide for clinicians in the choice of the best treatment option for patients with TRD.

The main limitations of this study are: 1) the relatively small sample size, which precluded the analysis of factors more strictly associated with response in the two groups, i.e., whether the response to the two treatments might vary according to the presence of psychotic features, SUD or personality disorders; 2) the heterogeneity in terms of medications prescribed; 3) the retrospective and observational chart-review analysis that consequently lacks patient randomization. It is, therefore, very likely that only the most severe patients were treated with SGA+AD by the psychiatrist. Indeed, patients treated in this naturalistic setting with AD+SGA were more severe, and even if they showed greater improvement, there was an initial bias in the treatment choice by the psychiatrist. Nonetheless, our goal was primarily to describe how TRD patients are treated in

a real clinical setting and what their final outcome is. This study suggests that clinicians prescribe SGA+AD in patients presenting severe symptomatology, co-morbidity for drug use disorders and Axis II, as well as psychotic features. Importantly, our study showed that severe TRD patients show a greater improvement after SGA augmentation than after solely AD combinations, suggesting that in the most severe cases, SGAs should be added as a first therapeutic strategy in order to avoid further, and likely unsuccessful, trials with AD combinations. Indeed, the number of failed pharmacotherapies in the SGA+AD group was significantly higher than in the ADs group, even if at the end, a greater improvement in depressive symptomatology was obtained with the SGA augmentation. Future randomized, double-blind trials will, however, be necessary to validate this hypothesis and to examine if there is a combination of ADs and SGA that might provide greater therapeutic efficacy in severe TRD patients.

3.5 CONCLUSION

The results of this study indicate the importance of considering SGA augmentation as a first-line treatment in severe TRD patients, especially in those presenting psychotic features, SUD, and personality disorders.

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CHAPTER 4 – GENERAL DISCUSSION

In this thesis, we further characterized demographic and clinical features that might aid in disentangling diagnostic difficulties during depressive episodes between TRD-UP and BP. Next, we provided new evidence to support the efficacy of SGAs + ADs as an augmentation strategy over the combination of ADs for patients with TRD-UP. Moreover, this augmentation strategy seemed to be associated with a better response for patients with severe TRD-UP, psychotic features, SUD, and personality disorders.

In the first section, our results provide further evidence suggesting the hypothesis of TRD-UP as a separate phenotype within the depressive disorders as it has been suggested by Fagiolini and Kupfer (2003). Moreover, our findings follow the aforementioned German psychiatric classification, which emphasizes on differentiating endogenous periodic unipolar depression from bipolar phase depression and exogenous depression (Schneider, 1959).

In our study, patients with TRD-UP had a significantly higher age at the time of assessment and a later age of onset of the first depressive episode (37.7 years), later age of the first psychiatric consultation (35.9 years), and a later age of psychiatric hospitalization (40.1 years) than patients with BP did. In contrast, BP patients had a longer duration of depressive episodes (15.4 years) and a higher number of failed pharmacotherapies, which might represent the high recurrences and inadequate treatment response, which ultimately leads to poly-pharmacotherapy (Gitlin *et al.*, 2006).

Overlapping comorbid features and clinical differences between BP and UP depression were previously reported in different studies (Kaustky *et al.*, 2017; Dudek *et al.*, 2010; Mitchell *et al.*, 2008; Perlis *et al.*, 2006). Our findings were consistent, showing differences in the age of onset (<25 years old) and clinical presentation, a greater number of first-degree relatives with mood

disorders, a greater length of the duration of episodes, an increased number of hospitalizations, and differences in the age of clinical presentation between the two entities. Additionally, our results showed that the association of comorbid anxiety disorders with TRD-UP might constitute a significant risk factor. Unfortunately, a small sample size precluded us from further analyzing panic disorders and generalized anxiety disorders, which have been described as risk factors for TRD (Souery *et al.*, 2007; Simon *et al.*, 2003).

Our findings showing an association between higher depression severity and lower GAF score with TRD-UP might result from the pervasive and chronic unremitting course of depressive symptoms. Consequently, these factors contribute to the high presence of residual symptoms and lower functionality reported in the TRD-UP population despite receiving pharmacological treatment (Vergunst *et al.*, 2013; Dunner *et al.*, 2006).

Personality disorders are highly prevalent in mood disorders associated with a greater illness severity (De Carlo *et al.*, 2016; Fagiolini & Kupfer, 2003) and an increased risk of suicide attempts (Jylha *et al.*, 2016). Our data showed also showed a high prevalence of cluster C personality disorders within the TRD-UP population.

Previous studies have suggested an increased risk of depression in patients with autoimmune diseases and cardiovascular diseases, which have implicated the activation of inflammatory pathways (interleukins, C-reactive protein, and cytokine among others) (Bai M *et al.*, 2020; Amare *et al.*, 2017; Maj *et al.*, 2017; Dudek *et al.*, 2010). In keeping, our results showed a higher prevalence of autoimmune diseases for TRD-UP patients. However, there was no significant association for cardiovascular diseases (Table 1, Section 2.3.1). One possible explanation would be to further explore the variability of how depression is diagnosed in primary care settings (such as in the study by Maj *et al.,* 2017) compared with the assessments in mood disorders clinics. In

the second section of this thesis, we investigated and compared the clinical characteristics and outcomes of 86 TRD-UP patients treated with two augmentation strategies (combination of ADs or SGA + AD). Patients receiving SGA + AD augmentation in comparison to AD augmentation had an overall greater severity of depression and higher prevalence of psychotic features, personality disorders, and SUD.

A complex shared etiology between SUD, personality disorders, and TRD has been suggested (Swendsen & Merikangas, 2000). A longitudinal study from a Swedish national register (N = 15631) reported that patients with TRD had an overall prevalence of SUD of 13%, thus a higher risk for SUD (hazard ratio = 1.4) consequently leading to low remission rates (Brenner *et al.*, 2019). Interestingly, in our sample, patients treated with SGA + AD had a higher prevalence of substance use than the AD group (36% vs. 11%), which also corresponded to a higher severity and complicated prognosis.

Our findings provide evidence for a higher efficacy of the use of SGA + ADs in patients with TRD-UP (a change from the baseline of 10.5 points on the HAMD-17). In particular, the presence of psychotic features increased the likelihood of having a significant response (26 times) if treated with SGA augmentation.

Interestingly, preclinical and clinical studies demonstrated an evidence-based approach using a combination of an AD and a second-generation antipsychotic (AD + SGA) (Dold *et al.*, 2017). We reported than more than half of the patients in the SGA + AD group were treated with either of the FDA-approved agents: quetiapine (mean dose: 129 ± 29 mg) and aripiprazole (mean dose: 4.4 ±1.3 mg) with good tolerability. However, we should bear in mind that one of the main limitations of this strategy is the significant side effects such as metabolic abnormalities and sedations of many SGAs (McIntyre *et al.*, 2007).

Importantly, our sample showed lower dosages for quetiapine (mean dose: 129 ± 29 mg) and aripiprazole (mean dose: 4.4 ± 1.3 mg). Interestingly, low dosages of aripiprazole have been reported to be more efficacious for BP-II (Yatham *et al.*, 2011). One possible explanation from pre-clinical studies is that at low dosages, the activation of dopamine D2 auto--receptors targets the trace-amine associated receptor1 (TAAR) pathways, resulting in the inhibition of the dopamine transporters, thus contributing to an antidepressant effect (Xie *et al.*, 2008).

Because of the nature of our primary outcome, we did not compare other augmentation strategies, which included mood stabilizers or other augmenting agents (i.e., liothyronine, lithium, and stimulants). However, in a previous pilot study by our group, the use of valproate in patients with TRD was shown to be effective (Ghabrash *et al.*, 2016).

Furthermore, the last two network meta-analyses that examined augmentation strategies for adults with TRD (Strawbridge *et al.*, 2018; Zhou *et al.*, 2015) (23 agents, $N = 2965$; 11 agents, $N = 6654$; respectively) demonstrated evidence for the use of SGAs as augmentation agents for TRD-UP. Strawbridge and colleagues reported a higher effect size for SGA for aripiprazole (1.33) than for quetiapine (1.05). Remarkably, the meta-analysis of Strawbridge *et al.,* (2018) reported a higher effect size (1.47) for the N-methyl D-aspartate (NMDA) antagonist (ketamine) compared to other augmentation strategies.

Interestingly, a genetic variant (rs1805502) in the *GRIN2B* gene, which codes for the NMDA receptors, and the *GRIK4* gene coding for the kainate receptor (r11218030 and rs194787) are also associated with TRD (Zhang *et al.*, 2014; Milanesi *et al.*, 2016).

An extensive body of research focused on glutamate modulating agents such as ketamine demonstrated the efficacy of subanesthetic doses of the drug for resistant MDD (Murrough *et al.*, 2013; Singh *et al.*, 2006); however, concerns regarding the tolerability, route of administration,

and the efficacy of these agents warrant further investigation.

In the past few years, pharmacogenetic studies have attempted to provide guidance and to identify genetic variants associated with treatment resistance or response. Upon the application of different techniques, such as analysis of candidate genes or genome-wide association (GWAS) studies of the genome, genetic polymorphisms for metabolizing enzymes, dopaminergic or serotoninergic genes, and neuronal pathways were found. Currently, up to 21 candidate genes were identified and three GWASs were associated with TRD, suggesting an association with the following genes—*GRIK4, BDNF, SLC6A4, and KCNK2*—although further replications are needed (Fabbri *et al.*, 2019).

These genetic variations could constitute potential biomarkers for disease and response (Fabbri & Serretti, 2018). One of the best studied genetic polymorphisms for treatment response has been the serotonin transporter gene promoter polymorphism (*5-HTTLPR*). For example, in a meta- analysis (*N*=1435, 15 studies) which examined the *5-HTTLPR*, a significant association was found for the long variant of the *5-HTTLPR* and treatment response (Serretti *et al.,* 2007) Moreover, a reduced risk for SSRI's-induced side effects was reported for the L allele (Kato & Serretti, 2008). However, other studies have reported negative findings have also been reported (Taylor *et al.,* 2010; Maron *et al.,* 2009). Maron and colleagues in a sample of depressed outpatients treated with escitalopram (*N*=135) did not find an association of the *5-HTTLPR* and a functional rs25531 for treatment response. Some discrepancies between studies may account due to variability in the pharmacological mechanisms between different SSRIs (Maron *et al.,* 2009) as well as not considering differences factors such as ethnicity or other clinical variables.

Examining the s allele (short variant) a randomized trial of 155 depressed patients treated with fluvoxamine during 6 weeks showed that the *5-HTTLPR* short variant was associated with an

inadequate response and augmentation with pindolol and lithium reduced the response rate difference between genotypes (Stamm *et al.,* 2008; Zanardi *et al*., 2001) which highlights the importance of augmentation strategies aimed to individualize treatment according patient's genotype (i.e., *5-HTTLPR*).

Regarding adjunctive strategies, an effect of liothyronine on accelerating the response to sertraline was reported in MDD patients who had a genetic polymorphism in thyroid deiodinase type I (*DI01-785*T-rs11206244 allele) (Cooper-Kazaz *et al.*, 2009). In addition, a pilot study showed that T3 supplementation in depressed patients with the *DI01-785T*-rs11206244 allele had an accelerating effect on decreasing the number of right unilateral ECT treatments (Nunez *et al.*, under review).

A different antidepressant efficacy was shown in the largest GWAS, which compared the responders and the non-responders to bupropion, SSRIs, and TRD, showing a significant association for the rs1908557 variant (*GPRIN3* and *SNCA* genes) in bupropion's response (Li *et al.*, 2016).

Nevertheless, recurrent limitations are frequently encountered in pharmacogenetic studies, such as a low statistical power for the detection of individual variants and the replication of findings in many studies, which on the whole impedes at present its broad clinical applicability (McCarthy S *et al.*, 2016).

We should acknowledge the results from this thesis considering several limitations. First, as we performed a retrospective cross-sectional chart-review analysis, most of the clinical data and behavioral scales were assessed retrospectively on the basis of the reviewer judgment based on physician assessments or notes in the health records. One common problem encountered with chart reviews is missing data, which may be responsible for a non-response bias. Secondly, the limited sample size in many cases did not allow for a further analysis of the variables of interest

(i.e., panic disorders/neurological conditions). More importantly, considering the study design, we did not examine other behavioral scales, such as self-reporting questionnaires (Beck Depression Inventory, the Personal Health Questionnaire, or the Mood Disorder Questionnaire). Another limitation relates to the generalizability of these results to other populations such as non-treatment-resistant depression, inpatient units, elderly, and adolescents, which should be confirmed.

Notwithstanding, our study contributes to the existing evidence on refining the clinical variables associated with a TRD-UP phenotype. Four clinical predictors were presented (comorbid anxiety disorders, higher illness severity, lower number of hospitalizations, and non-pharmacological treatments) for distinguishing unipolar depressive episodes from BP depression. Moreover, we identified a narrower subtype of patients with TRD-UP who responded successfully to augmentation with SGA as compared to ADs.

Importantly, by integrating the previously mentioned clinical predictors associated with TRD-UP and their treatment outcomes, this information can contribute to the development of new risk prediction models that can be explored for common genetic variations responsible for the treatment resistance/treatment response to individualized treatment selection.

CHAPTER 5 CONCLUSION

Our findings highlight that TRD-UP patients exhibit distinct clinical and sociodemographic features as compared to BP patients during depressive episodes. However, in order to validate these results, they should be replicated with larger controlled studies including other populations such as patients without treatment resistant depression. Furthermore, our findings underscore that compared to BP patients, TRD-UP patients showed a greater severity of depression. The described predictive variables suggested that TRD-UP has distinct psychopathological features during depressive episodes underscoring its separation from BP-I and BP-II, which may represent different neurobiological mechanisms important for treatment management.

In our second study examining treatment outcomes, we demonstrated that TRD-UP patients exhibited a significant decrease in depressive symptoms when treated with an SGA + AD augmentation strategy. This finding, although in a small sample size, needs to be replicated, as it provides the potential clinical evidence of a mechanistic advantage of SGA over augmentation with ADs. If proven, this augmentation strategy may avoid further unnecessary treatments, thereby increasing adherence rates, as well as the occurrence of side effects. New investigations should examine whether a specific augmentation treatment (i.e., combination of ADs and SGA) provides a greater therapeutic efficacy for severe TRD patients.

Future longitudinal studies and randomized controlled trials addressing neurobiological and genetic biomarkers with clinical features are needed. An integrated approach, including the genetic risk factors of disease onset and the association of predictors of treatment response, could provide greater selectivity for treatment recommendations thus leading to personalized medicine approaches in psychiatry, in particular for the treatment of mood disorders.

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