TREATMENT RESISTANT DEPRESSION:

DIAGNOSTIC PROFILE AND THERAPEUTIC ROLE OF ATYPICAL ANTIPSYCHOTICS AND MOOD STABILIZERS

MAYKEL GHABRASH

Degree of Master of Science

Neurobiological Psychiatry Unit

Department of Psychiatry

Faculty of Medicine

McGill University

Montreal, Quebec, Canada

December, 2015

McGill University, Montreal

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science in Psychiatry

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ACKNOWLEDGMENTS

This thesis represents a zealous effort that could not have been achieved without the guidance, encouragement, and continuous support of several individuals. First, I would like to thank my supervisors, Professor and Dr. Gabriella Gobbi and Professor, Dr. Linda Booij. Without their mentorship, I would not have even known where to begin my research.

Dr. Gobbi has always demonstrated her belief in my potential, and has constantly challenged me to achieve it. I have the highest respect and admiration for her as a clinician, researcher, and individual. She has provided me with continual support and guidance to help me excel as a researcher, pushing me to achieve greater productivity while helping me to overcome challenges during difficult times. Likewise, Dr. Booij extensive expertise in the area of biostatistics has been an invaluable source of guidance throughout the development of this project. Her suggestions have significantly enhanced both the design and quality of this study.

I would also like to thank my mentor and friend Dr. Stefano Comai who treated me like a younger brother. During the past two years Dr. Comai has shown me the qualities of an exceptional and absolute mentor, even though he was always busy with work, he still took much care in teaching me the essential skills of clinical research and was always available to advise me on research or life in general.

Finally I would like to thank my friends and family for their endless love and support throughout the past two years. I am grateful to my beloved parents, Farag Ghabrash and Mariam Zaki, as well as my beloved sister and brother, Dalia Ghabrash and Hany Ghabrash for their continued support of my personal decisions and academic pursuits. Even though I am physically separated from them by hundreds to thousands of miles, their advice and care have never left my side.

My graduate experience would have been rather dull and difficult if it were not for all the friends that stood by me, including Kathryn Geib, John Tabaka, Danilo De Gregorio, Luca Posa, Rafael Ochoa Sanchez, Kelly Smart, Daniel Vosberg, Ali Nasr, Tania Sasson and Nico Nunez. They celebrated with me in times of joy and stood by me in times of need. I apologize for not naming everyone here, but you know who you are and I can only pay my dues by holding you deeply within my heart.

Last but not least, I would like to praise the Lord, my God, for His grace in sustaining me during times of weakness and for giving me a comfortable home in Montreal at McGill University. *"To appreciate beauty, to find the best in others, to leave the world a bit better, whether by a healthy child, a garden patch, or a redeemed social condition. To know that one life has breathed easier because you have lived, this is to have succeeded" by Ralph Waldo.* Over ten years ago this statement inspired me to peruse medicine, and in doing so I found myself pursuing psychiatry. At the very depth of this academic pursuit is passion, love for scientific discovery, and a genuine desire to make a positive difference in the world and in people's lives. It is with this great love and passion that I will continue my career in clinical research and in medicine as always.

Preface & Contribution of Authors

My supervisor Dr. Gabriella Gobbi was involved in all aspects of the study and thesis composition, including study design, acquiring data, rating patients treatment outcome using behavioral scales, performing analyses, communicating with the Research and Ethics departments, interpreting results, and writing and editing this thesis. I was responsible for collecting sociodemographic, psychopathological data, and specific comorbidities. I was also responsible for rating patient's treatment outcome using behavioral scales, inputting data on the Excel/SPSS file, coordinating lab members who helped with data collection or input, analyzing data, performing statistical analyses, constructing figures and writing this thesis.

Dr. Stefano Comai and Dr. Linda Booij trained and assisted me in data analysis and interpretation. Dr. Stefano Comai also assisted me in designing the figures for the Valproic acid augmentation subgroup. Dr. Nicolas Nuñez and John Tabaka provided me with help collecting sociodemographic and psychopathological data. Dr. Nicolas Nuñez assisted with rating patient's treatment outcome using behavioral scales and performing the overall interrater reliability statistic. Megan Singh and Jessica Di Santé provided substantial help with inputting all data on the Excel and SPPS programs. Dr. Lucas Posa assisted in the French translation of the abstract of this thesis.

This study was supported by the Quebec Network on Suicide, Mood Disorders and Related Disorders (RQSHA) and the Practice Plan fund of the Dept. of Psychiatry, McGill University Health Center. Dr. Gobbi received a salary award from the Fonds de Recherché du Quebec en Santé (FRQS) and Dr. Booij from the Canadian Institutes of Health Research (CIHR). Authors wholeheartedly thank Dr. Lawrence Annable and Dr. Shedon Levy for their assistance in ethical issues.

LIST OF ABBREVIATIONS

TRD	Treatment Resistant Depression
MDD	Major Depressive Disorder
TCA	Tricyclic antidepressants
TeCA	Tetracyclic antidepressant
SSRI	Selective serotonin reuptake inhibitors
MAOI's	Monoamine oxidase inhibitors
SR	Sustained Release
XR	Extended Release
NDRI	Norepinephrine dopamine reuptake inhibitor
SNRI	Seritonin norepinephrine reuptake inhibitor
T3	Thyroxin
VPA	Valproic acid
HDAC	Histone deacetylases enzyme
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
ECT	Electroconvulsive therapy
rTMS	Repetitive Transcranial Magnetic Stimulation
TMS	Transcranial Magnetic Stimulation
DBS	Deep Brain Stimulation

VNS	Vagus Nerve Stimulation
MST	Magnetic Seizure Therapy
WHO	World Health Organization
MSM	Maudsley staging Method
MGH-S	Massachusetts General Hospital staging method
DLPFC	Dorsolateral Prefrontal Cortex
mPFC	Medial prefrontal cortex
MRI	Magnetic Resonance image
NMDA	N-methyl-D-aspartate receptor
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
GABA	γ-aminobutyric acid
CNS	Central Nervous System
EAS	Excitatory amino acids
acyH3K14	Acetylated histone H3 at the level of lysine 14
OR	Odds ratio
RCT	Randomized controlled trial
CBT	Cognitive Behavioral Therapy
OFC	Olanzapine plus Fluoxetine combination
FDA	Food and Drug administration
5-HT	Serotonin
5-HT_{2C}	Serotonin 2C receptor
5-HT_{2A}	Serotonin 2A receptor

5-HT_6	Serotonin 6 receptor
5-HT_{1A}	Serotonin 1A receptor
DA	Dopamine
DA_2	Dopamine 2 receptor
DA_3	Dopamine 3 receptor
DA_4	Dopamine 4 receptor
NE	Norepinephrine
NERI	Noradrenalin reuptake inhibitor
PFX	Prefrontal cortex
AE	Adverse events
VTA	Ventral tegmental area
LC	Locus ceruleus
DRN	Dorsal raphe nucleus
CGI-S	Clinical Global Impression-severity of illness
EPS	Extrapyramidal Symptoms
ADHD	Attention Deficit-Hyperactivity disorder
MDC	Mood Disorder Clinic
MUHC	McGill University Health Center
IRB	Institutional Review Board
SCID	Structured Clinical Interview for Diagnosis
QIDS-C16	Quick Inventory of Depressive Symptomatology Scale
YMRS	Young Mania Rating Scale

TREATMENT RESISTANT DEPRESSION:

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Maykel Ghabrash, M.D, MSc

Department of Psychiatry-McGill University, 2015

Supervising Professor: Dr. Gabriella Gobbi, M.D, Ph.D.

ABSTRACT

Background: Major Depressive Disorder (MDD) is a highly prevalent and disabling or fatal disease. According to the STAR*D project, about 50% of patients with unipolar depression suffer from treatment-resistant depression (TRD). In addition, animal studies have suggested potential antidepressant properties of Valproate (VPA) possibly due to its implication in epigenetic programming.

Method: We evaluated socio-demographic, psychopathological profiles and treatment outcomes in 78 patients (46 females, 32 males) with TRD from the Register of the Mood Disorder Clinic at McGill University Health Center (MUHC) by chart reviewer analysis. Clinical response was investigated prior to treatment (T-0) and after 30-90 days (T-3) of stable therapy using Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAM-D17), Quick Inventory of Depressive Symptomatology (QIDS-C16) and Clinical Global

Impression-severity of illness (CGI-S). These patients underwent several antidepressant treatment strategies. Only the last trial, when the patient responded to treatment and remained stable for more than 6 weeks (mean 12.5±5.90 weeks, T-3), and the treating psychiatrist kept the treatment unchanged, was included in this study for statistical analysis.

Results: In the first research study, patients responded to three pharmacological interventions: A)antidepressants combination(21); B)mood stabilizers and antidepressants (16); C)atypical antipsychotics and antidepressant (41). Compared to T-0, patients in all treatment groups showed significant decrease in depressive symptoms on all scales at T-3 (P<0.001). Importantly, at T-0, Group-C showed higher depressive symptoms on all scales compared to Group-A (HAM-D17, 25.7±1 vs. 21.3±1.5, mean±S.E.M, P=0.02). In addition, Group-C, compared to Group-A showed increased previous suicide attempts (29.3% vs. 14.3%) and number of failed treatments (4.2±2.9 vs. 2.7±2, mean±SD). Finally, change from T-0 to T-3 (Δ) on HAM-D17 was significantly superior in Group-C (Δ=10.6) compared to Group-A (Δ=7, P=0.05).

In the second study, we were also able to identify 14 patients (7 males and 7 females; age 19-59) who received VPA (375-1000mg/d) in addition to their treatment and clinical response to VPA was investigated after 1 (T-1), 4 (T-4) and 7 (T-7) months of therapy using the MADRS and CGI-S. As for the VPA augmentation group, VPA significantly decreased MADRS score at T-1 (23.5±1.0, P<0.001), T-4 (18.6±1.3, P<0.001), and T-7 (13.6±1.6, P<0.001) (effect size: partial η^2=0.86). MADRS at T-4 was also lower than at T-1 (P<0.001) and at T-7 lower than at T-4 (P=0.008). Importantly, MADRS score at T-7 was closer to the reported value of remission (MADRS<10), and none of the patients relapsed during the observational period. Compared to T-

0 (5.1±0.3), VPA also decreased CGI-S at T-1 (4.0±0.1, P=0.03), T-4 (3.3±0.2, P<0.001), and T-7 (2.6±0.3, P<0.001) (partial η^2=0.74).

Conclusion: The results highlight the importance of antipsychotic and/or mood stabilizer augmentation as first-line treatment in patients with severe TRD. Moreover, in a subgroup of patients, VPA showed substantial clinical improvement and maintenance over a long period and thus deserves further exploration in large double-blinded trials. We have identified a sub-class of TRD patients presenting with specific psychopathological features (significantly higher HAMD-17 score at T-0, higher suicide attempts, higher number of failed treatments, and a significantly better response to atypical antipsychotics and/or mood stabilizers) that respond significantly better to atypical antipsychotics and/or mood stabilizers. Randomized-controlled trials evaluating the independent roles of augmentation with antipsychotics or mood stabilizers are warranted in order to assess the initial pharmacological options for patients with severe TRD and to better characterize this subgroup of patients from a psychopathological and therapeutic point of view.

Résumé

Contexte: Le trouble dépressif majeur (TDM) est une maladie fréquente et potentiellement invalidante ou fatale. Selon le projet de STAR*D, 50 % des patients souffrant de dépression unipolaire souffrent aussi de dépression résistante au traitement (TRD). En outre, des études précliniques *in vivo* ont suggéré des propriétés antidépressives du Valproate (AVP) en raison de son rôle dans la programmation épigénétique.

Méthode: Nous avons évalué avec TDM-TRD les résultats sociodémographiques, le profile psychopathologique et les traitements sur un échantillon de 78 patients (46 femmes, 32 hommes; 19-74 ans) tirés du registre du Centre de Santé McGill, en analysant les dossiers cliniques. La réponse a été étudiée avant (T-0) et après 30-90 jours du traitement stable (T-3), utilisant Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Rating Scale for Depression (HAM-D17), Quick Inventory of Depressive Symptomatology Scale (QIDS-C16) et la Clinical Global Impression (CGI-S) Scale. Ces patients ont été traités avec des antidépresseurs suivant différentes stratégies. L'analyse statistique a inclus seulement le dernier essai clinique, lors duquel le patient a répondu au traitement, en se stabilisant pour plus que 6 semaines, sans changement du traitement pharmacologique.

Résultats: Dans la première étude, les patients ont répondu à 3 traitements pharmacologiques différents: A) combinaisons d'antidépresseurs (21); B) combinaison de stabilisateurs de l'humeur et d'antidépresseurs (16); C) combinaison d'antipsychotiques atypiques et d'un antidépresseur (41). Par rapport à T-0, tous les groupes ont montré une diminution des symptômes dépressifs à toutes les échelles après 3 mois de traitement ($p<0,001$). Au départ, le groupe-C a démontré plus

de symptômes dépressifs par rapport au groupe-A (HAM-D17, 25,7±1 vs 21,3±1,5, *P*=0,02), une augmentation de précédentes tentatives de suicide (29,3% vs 14,3%) et des échecs thérapeutique (4,2±2,9 vs 2,7±2). Le changement entre T-0 et T-3 dans l'échelle HAM-D17 a été supérieur dans le group-C (Δ=10,6) comparé au group-A (Δ=7, p=0,05).

Dans la deuxième étude, nous avons identifié 14 patients (7 hommes et 7 femmes; 19-59 ans) qui ont reçu AVP (375-1000 mg/j) en plus de leur régime de traitement. La réponse clinique à AVP a été évaluée après 1,4,7 mois (T-1, T-4, T-7) de traitement en utilisant la MADRS et CGI-S. AVP a significativement diminué la valeur sur l'échelle MADRS au T-1 (23,5±1,0,*P*<0,001), T-4 (18,6±1,3, *P*<0,001), T-7 (13,6±1,6, *P*<0,001) (taille de l'effet: η2 partiel=0,86). MADRS au T-4 était inférieur à T-1 (*P*<0,001), T-7 était inférieur à T-4 (*P*=0,008). En particulier, MADRS au T-7 a été proche de la valeur déclarée de rémission (MADRS<10), et aucun patient n'a eu une rechute pendant l'observation. Par rapport à T-0, AVP a également diminué CGI-S à T-1 (5,1±0,3 vs 4,0±0,1,*P*=0,03), T-4 (3,3±0,2,*P*<0,001), T-7 (2,6±0,3,*P*<0,001) (η2 partiel=0,74).

Conclusion: Bien que la réponse clinique soit similaire dans tous les groupes, les résultats mettent en évidence que les patients avec dépression sévère montrent une amélioration suite au traitement avec antipsychotiques et stabilisateurs de l'humeur. En outre, dans un sous-groupe, le traitement avec AVP a fourni une amélioration clinique et une stabilisation sur une période assez longue. Cela nécessite, donc, un examen plus approfondi par de grands essais cliniques en double aveugle. Nous avons identifié une sous-classe de patients avec TRD qui montrent des caractéristiques psychopathologiques spécifiques (HAMD-17 à T-0 supérieur, augmentation des tentatives de suicide, numéro d'échecs thérapeutiques plus élevé, meilleure réponse aux antipsychotiques

atypiques et/ou aux stabilisateurs de l'humeur) qui peuvent être encadrés dans la bipolarité en référence à leur réponse aux traitements et leur histoire clinique. Un nombre majeur d'études est requis pour mieux caractériser ce sous-groupe d'un point de vue psychopathologique et thérapeutique.

CHAPTER 1: TREATMENT RESISTANT DEPRESSION (TRD)

1.1 Overview of Treatment Resistant Depression (TRD)

According to the World Health Organization (WHO) by the year 2020, unipolar major depressive disorder (MDD) will be the second greatest cause of disability in developed countries, led only by ischemic heart disease (Demyttenaere et al., 2004; Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). Every year in Canada, an estimated 8.2% of Canadians aged 18 or over are affected by major depressive disorder (MDD) while in the United States, up to 8.7% of adults are affected (R. C. Kessler et al., 2003; Sung et al., 2012; Vasiliadis, Lesage, Adair, Wang, & Kessler, 2007). Burdens associated with major depression include, but are not limited to, low levels of education, loss of productivity in the workplace, reduced quality of life for the individual and family, and in Canada, account for some of the highest expenses in medical care costs (Fleury, Grenier, Bamvita, & Caron, 2010; Merikangas & Low, 2004; Vasiliadis et al., 2007). Many MDD patients have a chronic or recurrent course, with symptoms lasting between episodes (Hagop S Akiskal & Akiskal, 1992; Schulberg, Katon, Simon, & Rush, 1998). It is estimated that up to 50% of patients diagnosed with MDD will not achieve an adequate response following an adequate trial and dose of antidepressant therapy, many of which are likely to suffer from unipolar treatment resistant depression (TRD) (M. Fava, 2003; Trivedi, Rush, et al., 2006; Wisniewski et al., 2007).

TRD may also be referred to as treatment-refractory depression (Souery et al., 1999). Although the term "refractory" implies higher resistance, both *resistance* and *refractory* represent equivalent significance and are used interchangeably within the literature (M. T. Berlim & G. Turecki, 2007a).

1.2-TRD-Challenges towards a universal definition

TRD by it broadest definition, typically refers to inadequate response to at least one antidepressant trial of adequate doses and duration (M. Fava, 2003; M. Fava & Davidson, 1996). An alternative and more conservative definition proposed by Australian, European and North American researchers defines TRD as a major depressive episode with poor/inadequate response to two adequate trials of different classes of antidepressants (Burrows, Norman, & Judd, 1994; Souery et al., 1999).

Indeed, despite the common prevalence and debilitating nature of TRD, there still remains no common consensus regarding a universally accepted definition or criteria delineating this morbid condition (M. T. Berlim & G. Turecki, 2007a; Lam et al., 2009) nor is there agreement regarding the type or number of antidepressant treatments that need to be failed for unipolar MDD to be labeled TRD (M. T. Berlim & G. Turecki, 2007a; M. Fava, 2003; Souery, Papakostas, & Trivedi, 2006). Furthermore, the interpretation of *inadequate response* has been an object of considerable debate. Although global scales including the Hamilton Rating Scale for Depression (HAM-D17) (Hamilton, 1960) and the Montgomery-Asberg Depression Rating Scale (MADRS) (S. A. Montgomery & Asberg, 1979) can detect changes in depressive symptomatology, the extent of change needed to determine if pharmacotherapy was successful or not, lacks formal guidelines. For example, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) project, the largest clinical study on the treatment outcome for depression performed on over 2800 patients considered adequate response to be improvement of over 50% on the HAM-D17 scale (Warden et al., 2007); on the other hand, according to the Canadian Network for Mood and Anxiety

Treatments (CANMAT) clinical guidelines for the management of MDD in adults, <20% reduction in depression scores was considered as failure or inadequate improvement (Lam et al., 2009).

Furthermore, there is a high level of discrepancy when it comes to what defines an adequate antidepressant trial in terms of dose and duration. For example, amongst two commonly used antidepressant prescription guidelines the minimum effective dose of the antidepressant paroxetine differed from 20mg (Stuart A Montgomery, 1995; Perroud et al., 2011) to 10mg (Deakin, 2001). Likewise, the minimum effective dose of the antidepressant sertraline differed from 50mg (Orenstein, 2010; Taylor, Paton, & Kapur, 2009) to 100mg (H. A. Sackeim, 2001).

Moreover, the goal of TRD management is to eventually achieve remission or return to premorbid level of functioning, since residual symptoms are associated with poorer outcome and increased relapse risk (Ballenger, 1998; Trivedi, DeBattista, Fawcett, & Nelson, 1998). For these reasons, it is mostly agreed upon that *inadequate response* is the failure to achieve a symptom free state or, in other words, achieve remission (Bakish, 2001). However, although some TRD patients may achieve an asymptomatic state at some point, they continue to fluctuate and experience depressive symptoms in the majority of months, mostly at mild severity or subclinical level (Vergunst et al., 2013). This means that although achieving a state of remission in TRD is possible, it is often short lived and difficult to interpret.

The wide variation in how TRD is defined or identified contributes to misclassification of patients as having TRD (H. A. Sackeim, 2001). Reducing variation, and establishing a formal definition will benefit clinical and research settings by allowing data from TRD patients to be compared across different mental health setting.

1.3-TRD Staging Models

The lack of an effective method for the identification and measurement of TRD also makes it difficult to develop effective antidepressant strategies for patients who do not benefit or achieve remission from conventional antidepressant therapy. Although specific guidelines do not exist, the number of previously failed antidepressants is commonly used to classify patients or establish models for TRD depending on outcome with regards to therapy (M. Fava, 2003; Souery et al., 1999). Staging models are systematic methods of defining, measuring and identifying TRD using specific guidelines. Amongst the earlier models is the Thase and Rush model of staging TRD (Thase & Rush, 1997) which classifies TRD into five different stages according to level of therapeutic resistance after an adequate trial of antidepressant monotherapy. However, there are several methodological weaknesses with respect to this model, such as assuming superiority of certain antidepressants over others; for example, the model assumes the superiority of Tricyclic antidepressants (TCA's) over Selective Serotonin Reuptake Inhibitors (SSRI's) and superiority of monoamine oxidase inhibitors (MAOI's) over TCA's and SSRI's which is neither supported by meta-analyses of clinical trials (Mace & Taylor, 2000) nor by crossover trials of imipramine and sertraline (Thase et al., 2002). In addition, this model assumes that cases with lack of response to two antidepressants of different classes are more difficult to treat than if lack of response was to two agents of the same class; implying that switching to an antidepressant of a different class should be more effective than switching to an antidepressant of the same class. Although this view may be supported by many authors (M. Fava et al., 2001; Poirier & Boyer, 1999), it is unwarranted by the STAR*D project. According to the STAR*D study, patients who did not initially tolerate

citalopram tolerated sertraline and bupropion-SR equally well, and a lack of citalopram efficacy did not signify a lack of efficacy with sertraline (Warden et al., 2007; Wisniewski et al., 2007). Furthermore, augmentation or combination strategies are not considered and there is lack of assertion in terms of dosing and/or duration in relation to the degree of intensity of each trial.

An alternative classification is the Massachusetts General Hospital staging method (MGH-S) which adopts points as continuous variables reflecting the degree of resistance, with higher scores implying a more severe form of TRD (M. Fava & Davidson, 1996). It also takes into consideration both the number of failed trials and the optimization of each trial without making any assumptions regarding a hierarchy of antidepressant classes thereby avoiding many of the pitfalls of the Thase and Rush model.

Another model is the Maudsley staging Method (MSM) which is a multidimensional staging method for TRD that incorporates clinical factors such as duration and symptom severity of depressive episodes as well as treatment factors such as number of treatment failures as well as use of augmentation treatment strategies (Fekadu et al., 2009).

Yet, despite the formulation of various staging models to better define or interpret TRD, it still continues to pose a challenge in terms of an appropriate or valid therapeutic approach mainly due to lack of a universal staging model or definition agreed upon by clinicians and researchers alike worldwide (M. T. Berlim & G. Turecki, 2007a; Lam et al., 2009).

1.4-TRD Clinical characteristics and current literature

The precise nature of clinical and sociodemographic characteristics defining a TRD model are difficult to establish and interpret. Many reasons contribute to this, including variability with

regards to how TRD is defined and study design/type of patients included in various studies e.g. variability between inpatient and outpatient populations, or studies only pertaining to a specific age group etc. In addition, an accurate label of TRD versus pseudo-resistance is crucial and requires taking several factors into account; such as duration and dose of pharmacotherapy or patient non-compliance due to poor understanding of illness or pre-existing axis I, II or III pathology (S. G. Kornstein & Schneider, 2001). This demands for careful evaluation of depression subtypes, atypical features or other specific comorbidities. For instance, depression with psychotic features is often unresponsive to antidepressant pharmacotherapy and will require the use of adjunctive antipsychotics or a course of ECT (Charney & Nelson, 1981); whereas atypical depression characterized by features of hypersomnia, hyperphagia, mood reactivity or leaden paralysis tend to have better response to MAOI over TCA therapy (Liebowitz et al., 1988). Specific comorbidities such as premenstrual dysphoric disorder which can be easily missed in women presenting with depression, tends to respond better to SSRI's (Freeman, Rickels, Sondheimer, & Polansky, 1999). Therefore, it is of utmost importance in TRD for patients to be carefully evaluated for all other conditions to confirm diagnosis.

Several factors have been discussed in the literature that may increase the likelihood of inadequate response to antidepressants and thus contribute to the overall paradigm of TRD. Indeed, the literature points towards an association between a comorbid psychiatric or medical illness in TRD, where coexisting conditions (comorbid axis I, II, or III as per DSM-IV) were found in over 53% of patients suffering from unipolar depression resulting in lower recovery rates and a more severe course of illness, termed "compound depression" as compared to patients with pure depression. (Keitner, Ryan, Miller, Kohn, & Epstein, 1991).

1.4.1-Comorbid mental disorders

A study which screened 200 individuals with a diagnosis of MDD according to DSM-III found that 29% of patients had a history of panic attacks, 62% experienced psychic anxiety and 72% experienced moderate worry (Fawcett & Kravitz, 1983). In fact, the literature suggests that patients with unipolar MDD and severe comorbid anxiety disorder or panic attacks tend to not only be chronically depressed, but are also most likely to have the poorest outcome and may be liable to suicide attempts (Fawcett et al., 1990; VanValkenburg, Akiskal, Puzantian, & Rosenthal, 1984). This patient subpopulation are also more susceptible to AE; hence pharmacotherapy is often started at a lower doses consequently resulting in a slower course of recovery (McLeod, Kessler, & Landis, 1992). Patients with comorbid anxiety disorder in addition to MDD are also more likely to have a positive family history of unipolar depression (Clayton et al., 1991). Comorbid substance abuse is another condition which can worsen depression, affect compliance and directly result in treatment resistance. As much as moderate usage of alcohol has been shown to contribute to depression (McLeod et al., 1992). Other axis I disorders to be considered in TRD include obsessive compulsive disorder (OCD) and eating disorders which may be missed as patients may keep them silent often due to embarrassment or shame.

1.4.2-Comorbid personality disorder

Presence of a personality disorders is also common in chronic depression (Keller et al., 1998). However, given their current depressive state, it is almost impossible to elucidate the presence or absence of a personality disorder in MDD patients unless a diagnosis was established prior to the episode of depression (Thase, 1996). Personality disorders most frequently reported as comorbid

with depression are in the anxious-fearful cluster C, followed by the dramatic-unstable cluster B (Keller et al., 1998; S. G. Kornstein & Schneider, 2001). Finally, evidence suggests that patients with a comorbid personality disorder pathology are less responsive to pharmacotherapy than their patients without comorbid personality disorder and have a worse prognosis (Thase, 1996).

1.4.3 Medical comorbidities

Medical comorbidities can worsen or exacerbate depression. These findings were previously reported in a study examining an inpatient population where almost 50% of patients were found to have unrecognized medical illnesses (R. C. Hall, Gardner, Popkin, Lecann, & Stickney, 1981). Several medical illnesses have been documented to have a back and forth influence on depression. In diabetic patients for example, depression and poor glycemic control are interlinked by a direct neuroendocrine effect and since depressed patients are less compliant with a specific diet, medication or insulin (S. G. Kornstein, & Gardner, 2003). Other disorders such as hypothyroidism, Cushing's disease, Addison's disease, cancer, coronary artery disease, infections, Parkinsonism and pain disorders should all be considered in TRD (Franco-Bronson, 1996). Disorders such as fibromyalgia, chronic fatigue syndrome and irritable bowel syndrome which are intertwined between psychiatry and medicine can further complicate the management of TRD as they remain unrecognized and under treated. The use of glucocorticoids in treatment of autoimmune or inflammatory conditions has been found to be associated with depression, mania and delirium (Brown & Stoudemire, 1998). In general, patients suffering from a serious medical illness in association with depression are more likely to develop treatment resistance due to lower response rate to antidepressant pharmacotherapy (Popkin, Callies, & Mackenzie, 1985).

1.4.4 Other important comorbidities/factors

There are several other factors warranting consideration in TRD. Although there is lack of concrete evidence in support of the female gender being a risk factor for depression, it is a well-established fact that the prevalence of depression is higher in females as compared to males (R. C. Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993). Indeed, gender can be an important influential factor determining response to antidepressants. A published study in 2000 found that women respond significantly better to SSRIs than TCAs, while men respond significantly better to TCAs pharmacotherapy (S. G. Kornstein et al., 2000).

Another factor is family history of mental illness, specifically amongst 1st degree relatives who are significantly greater in TRD patients than non-chronic unipolar MDD patients (Scott, 1988). In addition, several studies point towards a common link between positive family history of depression and early onset/chronicity of depressive symptoms, which are both linked to TRD (Klein, Schatzberg, McCullough, Dowling, et al., 1999). Early onset is associated with higher rates of personality disorders, substance abuse and higher family history of mental illness (Klein, Schatzberg, McCullough, Keller, et al., 1999); indeed, a study found that early onset of MDD and positive family history of mood disorders are associated with a lower response rates, incomplete remission resulting in chronicity of depression (H. S. Akiskal, King, Rosenthal, Robinson, & Scott-Strauss, 1981). Late onset depression in patients' over 60 years of age is also associated with treatment resistance. This is due to higher prevalence co-occurring neurological disorders such as dementia; and a greater likelihood of psychotic depression which is unlikely to resolve with antidepressant mono therapy without the use of antipsychotics. In addition, geriatric patients may take longer to respond to antidepressant treatment (S. G. Kornstein & Schneider, 2001).

1.5-TRD-Current treatment options, a comprehensive literature review

A recent survey reported that only 10 % of Canadian clinicians opted for augmentation strategies, most commonly using bupropion and lithium in TRD (Mischoulon, Nierenberg, Kizilbash, Rosenbaum, & Fava, 2000). Studies such as the STAR*D project have tried to develop a set of guidelines on various approaches or methods to tackle unipolar depression with signs of treatment resistance by providing comparisons between various treatment options (Trivedi, Rush, et al., 2006; Wisniewski et al., 2007). Several strategies with antidepressant switches or combinations (Trivedi, Fava, et al., 2006) as well as with atypical antipsychotics (Nelson & Papakostas, 2009) have been suggested for patients with TRD. In addition, neuromodulation techniques such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), Vagus nerve stimulation (VNS) and deep brain stimulation (DBS) have also been proposed in patients suffering from TRD (R. Chen, 2000; Handforth et al., 1998; S. H. Kennedy et al., 2011; Payne & Prudic, 2009). Below is a comprehensive literature review of the various therapeutic modalities used in treatment and management of TRD.

*1.5.1 The STAR*D PROJECT- switch/augmentation strategies*

Multiple studies have investigated the best or ideal approach in TRD, but results are somewhat inconsistent. Perhaps the most noteworthy is the STAR*D project. This large (n=4,040), seminaturalistic clinical trial found that after up to four aggressive treatment strategies, about one-third of patients still had not achieved remission (Janicak & Dokucu, 2015; Warden et al., 2007). The study included only treatment seeking, non-psychotic MDD patients confirmed with a DSM-

IV checklist and a HAM-D17 score of greater than or equal to 14. Upon exclusion of non-eligible participants, 2876 patients were given an adequate dose of citalopram (mean dose=41.8mg/dl; mean time to remission = 6.7 weeks) and 47 % of patients remitted (HAM-D17 score of ≤ 7). Importantly, response and remission rates in the STAR*D sample resembled those seen in 8-week efficacy trials of citalopram in actual practice (Trivedi et al., 2014).

Non-responders (n=1439) entered Level 2 which included augmentation (n=565) and switch (n=727) strategies of different class versus same class antidepressants as well as cognitive psychotherapy (n=147). Of non-responders, 50.5% received switch therapy with either bupropion-Sustained Release (SR), a norepinephrine dopamine reuptake inhibitor (NDRI); sertraline, another SSRI; or venlafaxine-Extended Release (XR), a Serotonin norepinephrine reuptake inhibitor (SNRI). 39.3% received augmentation strategies by adding either bupropion-SR or buspirone, an azapirone anxiolytic drug (Cowen, Anderson, & Grahame-Smith, 1990) to citalopram therapy. Finally, 10.2% opted for switch or augmentation strategies using cognitive psychotherapy. For those with inadequate benefit from cognitive therapy as switch or augment in Level 2, the next step (Level 2A) was a switch to a second medication (bupropion-SR or venlafaxine-XR) to ensure that all Level 3 enrollees had received and not obtained adequate benefit from at least two prior adequate trials of antidepressants. As previously mentioned, while there is no consensus definition for TRD, the one most commonly used is failure (i.e., Lack of improvement, or <20% reduction in depression scores) following adequate trials of two or more antidepressants (Lam et al., 2009). Therefore, level 3 and level 4 included patients with a formal diagnosis of TRD according to standard CANMAT clinical guidelines.

Of patients entering level 3 (n=377), 37.6% (n=142) were switched to mirtazapine, a Tetracyclic antidepressant (TeCA), or nortriptyline, a TCA and 62.4% (n=253) had their medication augmented using thyroid hormone (T-3) or lithium, a mood stabilizer. Level 4 (n=109) included switch to tranylcypromine, a MAOI (n=58) or to venlafaxine-XR plus mirtazapine (n=51).

*1.5.1.1 STAR*D- Results*

The STAR*D project highlights several important key aspects to be considered while implementing medication changes (switch/augmentation) in non-responders. First, as previously mentioned, the study found that patients intolerant to citalopram (Level 1), tolerated sertraline and bupropion-SR equally well after switch implementation (level 2), and the mean time to remission equally ranged from 5.4 to 6.2 weeks for both agents. In addition, the lack of response to citalopram did not signal a lack of response to sertraline suggesting that switch within or out of class is a reasonable second step in treatment. On the other hand, about one third of participants randomized to augmentation (level 2) remitted. There was no significant difference in outcomes between bupropion-SR or buspirone augmentation of citalopram; although bupropion-SR displayed greater baseline-to exit symptom improvement, lower exit symptom severity, and fewer dropouts due to intolerance (12.5% vs. 20.6%) upon delivery at adequate dose when compared to buspirone (Trivedi, Fava, et al., 2006). Interestingly, about one third of cognitive therapy augment and medication augment participants remitted, with no significant differences in remission rates; and a little more than one fourth of cognitive therapy switch and medication switch participants remitted, with no significant differences in remission rates (Thase et al., 2007). However it should be noted that mean remission time for cognitive therapy augments was 55 days versus 40 days for

medication augments suggesting that when speed of remission is important, medication augmentation has an advantage over psychotherapy.

In level 3, the mean HAM-D17 score of patients who opted for switch treatment versus patients who opted for augmentation treatment was 19.2 vs. 18.1 respectively; corresponding to moderate-severe depression on the HAM-D17 scale (Hamilton, 1960). Modest remission rates were achieved with switching to either mirtazapine or nortriptyline (12.3% and 19.8% respectively) and modest remission rates were also achieved for lithium or T-3 augments (15.9% and 24.7% respectively). However, patients taking lithium were more likely to leave the study due to adverse effects (AEs) despite the use of moderate dosage. The mean HAM-D17 score at level 4 entry was 19.6, and remission rates were remarkably low both in patients switched to tranylcypromine and those switched to venlafaxine-XR plus mirtazapine although the latter were twice as likely to experience remission (6.9% and 13.9% respectively) (Warden et al., 2007). Moreover, patients randomized to tranylcypromine were more likely to experience AEs and demonstrated less tolerability and acceptance than patients randomized to venlafaxine-XR plus mirtazapine.

*1.5.1.2 STAR*D- Limitations*

The STAR*D project was able to compare effect of switching within class (sertraline), out of class (bupropion-SR), or to a dual action agents (venlafaxine-XR) in level 2. Both sertraline and bupropion-SR were tolerated equally well, and venlafaxine-XR did not produce significantly higher remission rates; this data is consistent with results from meta-analyses indicating similar therapeutic efficacy of SSRI's vs. bupropion and also provides comparison with the dual action

agent venlafaxine-XR (Thase et al., 2005; Warden et al., 2007). Furthermore, level 4 included the use of mirtazapine as a form of adjunctive therapy (mirtazapine plus venlafaxine-XR) which is warranted by several studies on unipolar TRD (Pierre Blier et al., 2009; Wang & Ma, 2011).

However, there are several weaknesses and limitations with regards to the STAR*D study design that should be taken into consideration. First, it is unclear why the project design only incorporated cognitive therapy amongst other modalities of psychotherapy (e.g. psychodynamic psychotherapy) in level 2 which could potentially yield therapeutic value in MDD (Solbakken & Abbass, 2015). In addition, it is unclear why a level 3 switch included a TeCA and TCA and level 4 switch included a MAOI (tranylcypromine). As mentioned earlier, superiority of TCA's over SSRI's, and superiority of MAOI's over TCA's and SSRI's is neither supported by meta-analyses of clinical trials (Mace & Taylor, 2000) nor by crossover trials of imipramine and sertraline (Thase et al., 2002). Moreover, it is unclear why level 3 and level 4 did not include augmentation using atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole), which is warranted by both evidence based literature and systematic reviews (George I Papakostas, Shelton, Smith, & Fava, 2007; Wright, Eiland, & Lorenz, 2013). The project also failed to investigate the effectiveness of using mood stabilizers (lamotrigine, valproate) as add-on agents in TRD which is supported by multiple studies (Gutierrez, McKercher, Galea, & Jamison, 2005) and only choose lithium and T-3 for augmentation in level 3 without providing a reasonable rationale.

1.5.2-Therapeutic augmentation using Atypical Antipsychotics

Typical antipsychotics were effective in the treatment of MDD; however, interest in them declined due to high incidence of extrapyramidal side-effects (EPS) (Robertson & Trimble, 1982). Atypical

antipsychotics however, do not carry the same risk of EPS, hence their use for non-psychotic depressed adults has increased over the past decade from 4.6 % in 2000, to 12.5% in 2010 (Gerhard et al., 2014). An early meta-analysis including data from ten clinical trials and over 1500 patients suffering from TRD, found that remission and response rates were 47.4% and 57.2% amongst patients receiving augmentation with atypical antipsychotics, versus 22.3% and 35.4% amongst those not receiving augmentation therapy respectively (George I Papakostas et al., 2007). In addition, a systematic review including 16 placebo controlled clinical trials and over 3400 patients concluded that adjunctive treatment with atypical antipsychotics was more effective than placebo in achieving both response and remission (odds ratio; OR 1.69 and 2.00 respectively) and the OR did not differ among atypical agents nor was it affected by trial duration or method of treatment resistance (Nelson & Papakostas, 2009). However, it should be noted that the study also found a significantly high risk of discontinuation associated with the use of atypical agents due to related AEs (OR 3.91).

1.5.2.1-Aripiprazole

Aripiprazole is an atypical antipsychotic with a novel mechanism of action involving mixture of agonist, partial agonist and antagonist activity at dopamine (DA) and serotonin (5-hydroxytryptamine; 5-HT) receptors (D. A. Hall, Agarwal, Griffith, Segro, & Seeberger, 2009). Several studies have been published examining the use of aripiprazole as adjunct therapy in TRD. Three placebo controlled-randomized controlled trials (RCTs) (n=1092) using aripiprazole as adjunctive therapy at doses ranging from 2-20mg after failure of at least two adequate trails of standard antidepressants demonstrated a significant decrease in the mean MADRS score reduction

compared to placebo (n=362, mean dose=11.8mg, -8.8 vs. -5.8 respectively, $P<0.001$; n=381, mean dose=11mg, -8.5 vs. -5.7 respectively, $P=0.001$; n=349, mean dose=10.7mg, -10.1 vs. -6.4 respectively, $P<0.001$) (Berman et al., 2009; Berman et al., 2007; Marcus et al., 2008). Furthermore, a systematic review published in May 2015 reported that while all standard-dose atypical agents were significantly more efficacious than placebo, only aripiprazole and risperidone displayed statistically significant benefits in improving functioning and quality of life when compared to placebo as adjunctive treatments (Zhou et al., 2015). Based on results from these studies, the food and drug administration (FDA) approved the use of aripiprazole as adjunctive treatment for MDD patients in 2007 (Nelson, Pikalov, & Berman, 2008).

However, although efficacious, aripiprazole poses many serious AEs. All RCTs reported akathisia, restlessness and weight gain and two reported headaches and insomnia. Moreover, all RCTs reported an average weight gain of over 7% body weight compared to placebo; although the percentage of patients experiencing weight gain varied (3.4% to 7.1%). Other AEs included somnolence and fatigue. In addition, tardive dyskinesia and other movement disorders in neuroleptic-naïve patients have been previously documented with aripiprazole therapy (Goyal & Devi, 2014; D. A. Hall et al., 2009). No documented evidence was found in support of or against aripiprazole monotherapy in TRD or unipolar MDD.

1.5.2.2-Olanzapine

A recently published meta-analysis including pooled data from five outpatient studies (n=1446) comparing oral olanzapine plus fluoxetine combination (OFC) (n=462), fluoxetine (n=342) and

olanzapine monotherapy (n=342) upon failure of at least two antidepressants found that mean MADRS scores were significantly reduced in the OFC group within the first week of treatment and the 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).

Fluoxetine, like other SSRIs, binds to 5-HT reuptake proteins (the 5-HT transporter) with high affinity resulting in enhanced 5-HT neurotransmission. Considering that 5-HT pathways from the ventral tegmental area (VTA), locus ceruleus (LC) and dorsal raphe nucleus (DRN) are received by the frontal cortex (FCX); fluoxetine has been shown to reduce DA activity via 5-HT_{2C} -mediated suppression of VTA whereas the simultaneous antagonism of 5-HT_{2A}, 5-HT_{6}, 5-HT_{2C} and activation of 5-HT_{1A} mediated by olanzapine has been shown to increase DA release in the FCX (Bobo & Shelton, 2010). In addition, *chronic* but *not acute* increase in serotonergic activity at postsynaptic 5-HT_{2A} receptors by SSRI's results in suppression of LC firing and reduction in norepinephrine (NE) activity (Szabo, de Montigny, & Blier, 1999). On the other hand, olanzapine has been shown to bind to 5-$HT_{2A, 2C, 6}$, and DA_{2-4} receptors and results in increased LC firing with both *acute* and *chronic* administration in addition to increased release of NE in the FCX (Bobo & Shelton, 2010). Indeed, 5-HT_{2A} 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 (P. Blier & Szabo, 2005). Given this synergistic effect, and rapid reduction in depressive symptomatology observed clinically in multiple published RCTs using OFC in TRD, the FDA approved the use of Symbyax® (olanzapine and fluoxetine HCl capsules) for the treatment of bipolar disorder and TRD in 2009 (Bobo & Shelton, 2010).

However, an 8 week double-blinded-RCT including TRD patients (n=500) who were randomized to either OFC, olanzapine, fluoxetine or nortriptyline; concluded that no significant differences were found in mean MADRS score reduction for any of the four groups at the end-point vs. baseline (-8.7, -7.0, -8.5, -7.5 respectively) (R. C. Shelton et al., 2005) and the OFC arm demonstrated superiority only in terms of time to response providing a significantly greater reduction in MADRS scores than olanzapine at week 2, 4, 6 and 7 vs. fluoxetine at week 2 through 5 and vs. nortriptyline at week 1 through 4. Another 12 week double-blinded RCT including patients (n=483) receiving either venlafaxine, olanzapine, fluoxetine, or OFC also demonstrated similar results in terms of mean MADRS score reduction, with no significant difference in the OFC vs. fluoxetine or venlafaxine alone (Corya et al., 2006) and the OFC group showed a more rapid onset of effect yet did not yield superiority over fluoxetine or venlafaxine monotherapy at end-point.

In view of the similar outcomes of OFC and monotherapy groups at end-points in both RCTs, the superiority of olanzapine as adjunctive therapy is questionable in terms of its overall efficacy; although most studies concur on its dominance in terms of speed to recovery. Moreover, olanzapine has been well documented to cause significant changes in lipid and glucose profiles (Boku et al., 2011; Takahashi, Kamata, Yoshida, Higuchi, & Ishigooka, 2008) and both RCTs reported several side effects in the OFC group, mainly tremors, weight gain, increased cholesterol and prolonged QTc interval. Indeed, evidence suggests that increase in weight gain over the first 2 weeks of therapy using either mono or combination therapy with olanzapine is a strong predictor

of substantial weight gain for the patient if antipsychotic therapy were to continue (Degenhardt, Jamal, Tormey, & Case, 2011).

1.5.2.3-Quetiapine

Although quetiapine has trivial affinity for the noradrenergic transporter, its metabolite, N-desalkylquetiapine, is a potent noradrenalin reuptake inhibitor (NERI). In addition, it is a much more potent $5HT_{1A}$ receptor agonist than its parent drug (quetiapine) and exerts $5\text{-}HT_{2A}$ and $5\text{-}HT_{7}$ antagonism which contributes to its overall antidepressant efficacy (Jensen et al., 2008).

Indeed, the FDA approved the use of quetiapine-XR as adjunct treatment to antidepressants in MDD at a dose of 150-300mg (Šagud et al., 2011).

An open label comparative study, including TRD patients (n=20) who were randomized to either lithium (600mg starting dose followed by clinical adjustment) or quetiapine 300-700mg (mean dose=430mg) augmentation found a significant improvement on the HAM-D17 scale in both quetiapine ($P<0.0001$) and lithium ($P<0.0001$) comparing baseline to end-point (Doree et al., 2007) and difference in improvement between the two groups began at day 14 with quetiapine demonstrating superiority over lithium. Response rates on the HAM-D17 scale for quetiapine and lithium were 80% and 50% and remission rates were 80% and 40 % respectively. Importantly, quetiapine was well tolerated and the most common AE was somnolence (5 events).

A large 6 week, double-blinded RCT including MDD patients (n=493) who had their current antidepressants (dose and type) maintained and were randomized (n=424) to either adjunct quetiapine-XR 150mg, quetiapine-XR 300mg or placebo found that mean MADRS scores from randomization to week 6 was significantly reduced in both treatment groups (-15.26, -14.94 and -

12.21 in quetiapine-XR 150mg, 300mg and placebo respectively) and the proportion of patients who experienced a MADRS response (defined as >50% reduction in MADRS scores) at week 6 was 55.4%, 57.8% and 46.3% in quetiapine-XR 150mg, 300mg and placebo respectively (Michael Bauer et al., 2009). Only quetiapine-XR 300mg vs. placebo demonstrated statistical significance ($P<0.05$) at week 6 and quetiapine-XR 150mg vs. placebo did not produce statistical significance at study end-point. Similar to the only AE reported in the open label study, 16.8% of patients taking quetiapine-XR 150mg and 23.3% of patients taking quetiapine 300mg reported somnolence and 7 patients in each groups experienced an increase of body weight greater than 7%. Given the large sample included in this study, the main limitation was the short follow-up period of 6 weeks.

Another large (n=446), 8 week double-blinded RCT of similar design evaluated MDD patients (n=432) and produced similar results, where MADRS scores significantly improved with quetiapine-XR 300mg vs. placebo (−14.7 vs. −11.7, $P<0.01$) and quetiapine-XR 150mg improvement was only limited to the first two weeks after which there was no statistical significance (El-Khalili et al., 2010). Withdrawal due to AEs was highest in quetiapine-XR 300mg at 19.5%, followed by quetiapine-XR 150mg at 11.5%, and placebo at 0.7%. The most common AE leading to discontinuation was somnolence (50.3%, 46.6%, 8.8% in quetiapine-XR 300mg, 150mg and placebo respectively). Three patients withdrew from quetiapine-XR 300mg due to akathisia. In addition, more than 7% weight gain and EPS were more common in the quetiapine-XR 300mg group than 150mg or placebo groups (7.6%, 1.4% and 2.1% for weight gain respectively and 8.1%, 3.4% and 3.4% for EPS respectively). Other side effects included dry mouth, dizziness, constipation, nausea, insomnia, headache, and fatigue.

Considering that all previously mentioned studies (both RCTs and the open label study) demonstrated that only patients receiving add-on quetiapine-XR 300mg displayed significant improvement in depressive symptomatology comparing baseline to end-point among all other treatment groups (add-on quetiapine-XR 150mg, lithium or placebo), it is reasonable to conclude that 300mg is the optimum dose to provide quetiapine with an acceptable therapeutic advantage. However, all RCTs also suggest that AEs are more common with higher doses of quetiapine, more inclusively, somnolence at a dose of 300mg. Although this AE is of benign nature, other possible AEs including EPS and weight gain are also dose related and can result in serious morbidity.

1.5.2.4-Risperidone

Derived from the typical antipsychotic haloperidol, risperidone is able to bind with high affinity to both 5-HT and DA, resulting in potent antagonism of both 5-HT_2 and DA_2 receptors in the brain (Frankenburg, 1999). In Canada, risperidone is approved for treatment of schizophrenia, for acute treatment of bipolar mania, but not for maintenance therapy, and in severe dementia (Ravindran, Bradbury, McKay, & da Silva, 2007).

A large open label study (n=386) examining the effect of risperidone (mean dose=1.1mg) vs. placebo augmentation in citalopram monotherapy (mean dose=52.6mg) non-responders (< 50% reduction on HAM-D17 after 6 weeks of treatment) found that mean MADRS scores were significantly reduced from baseline in the augmentation group vs. placebo (27.7–13.2, $P<0.001$) (Rapaport et al., 2006). However, considering that the study included patients with a HAM-D17 score ≤ 7 which corresponds to mild depression (Hamilton, 1960); the overall rate of relapse was 53.3% in the risperidone augmentation vs. 54.6% in the placebo augmentation group where relapse

was defined as the presence of one or more of the following four criteria: (1) Clinical Global impression-severity of illness (CGI-S) score 6 or higher corresponding to severely ill, (2) HAM-D17 score ≥16 corresponding to moderate to severe depression, (3) discontinuation due to lack of effect, or (4) deliberate self-injury/suicidal intent. What this means is that relapse was much more likely to happen in patients with more severe TRD profile, with or without risperidone augmentation, rendering its usefulness to "limited" in such cases. Moreover, continuation of risperidone did not significantly increase time to relapse compared to placebo (102 days vs. 85 days for risperidone vs. placebo augmentation respectively; P=0.52). In addition, the study reported a significant increase in prolactin serum concentration at end-point vs. baseline (P<0.001), as well as 8.3% of patients gaining ≥ 7% of their body weight with risperidone augmentation therapy.

A 6 weeks double-blinded, placebo-controlled RCT evaluating risperidone augmentation (dose=1-2mg) vs. placebo in patients (n=274) after failing to respond to a 4-week trial of antidepressant monotherapy (SSRIs, SNRIs, trazodone, and bupropion) where SSRIs accounted for 60% of agents used; noted significant improvement in the HAM-D17 scores in the risperidone group compared to placebo at both week 4 (15.4 vs. 17.3, P=0.006) and week 6 (13.4 vs. 16.2, P<0.001) (Mahmoud et al., 2007). Furthermore, remission rates (HAM-D17 ≤7) were significantly higher with risperidone augmentation compared to placebo at week 4 (13.6% vs. 6%, P=0.041) and at week 6 (24.5% vs. 10.7%, P=0.004) and the overall response to treatment (HAM-D17 reduction by ≥ 50%) was greater in the risperidone group compared to placebo at week 4 (35.6% vs. 18.8%, P=0.002) and week 6 (46.2% vs. 29.5%, P=0.004). Importantly, the study noted improvement on

patient-rated efficacy outcomes of quality of life with risperidone augmentation which is consistent with results from a recent meta-analysis (Zhou et al., 2015). However, the study also reported several AEs resulting in discontinuation of risperidone therapy, including somnolence, malaise, weight gain, attention disturbance, depression, insomnia, and panic attacks. Although the diversity of antidepressants used in combination with risperidone in the study make it difficult to draw a conclusion regarding superiority of one over the other, using a wide variety of antidepressants may reflect conditions pertaining to actual practice.

Data points to high efficacy for adjunct risperidone therapy in open label trials and RCTs, but its robustness in reducing depressive symptoms, especially in patients with a more sever profile of depression, remains questionable. Another weakness to open label and RCT trials reported about risperidone augmentation therapy is that they included only patients who have failed one course of antidepressants, rather than confining to the CANMAT guidelines which require failure (i.e., Lack of improvement, or <20% reduction in depression scores) to two or more adequate trials of antidepressants (Lam et al., 2009). Considering these limitations, as well as the serious metabolic AEs including prolactin elevation, weight gain and EPS; risperidone usefulness in TRD remains debatable.

1.5.2.5-Ziprasidone

A recently published, double-blind, placebo controlled-RCT including patients (n=139) with persistent symptoms of MDD found a significant improvement in mean HAM-D17 scores (-6.4 [SD=6.4] compared with -3.3 [SD=6.2] and a clinical response of 35.2% compared with 20.5% in ziprasidone plus escitalopram vs. escitalopram plus placebo after an 8-week open-label trial (G. I.

Papakostas et al., 2015). A smaller 8 week open-label trial comparing the effect of ziprasidone 80mg, ziprasidone 160mg or placebo as augmentation therapy patients (n=64) with unipolar MDD concluded that no significant differences were found between ziprasidone or placebo groups and that significantly more AEs were observed in the ziprasidone groups including: asthenia, agitation, insomnia and QTc prolongation (Dunner, Amsterdam, Shelton, Loebel, & Romano, 2007). All other reported data involves the use of ziprasidone in schizophrenia, bipolar disorder and anxiety disorders.

1.5.2.6-Clozapine

Clozapine has FDA approval for treatment resistant schizophrenia and prevention of suicide in patients with psychotic disorders. A case series investigating the effect of clozapine in five drug and ECT resistant depressive patients concluded that clozapine did not demonstrate favorable results and instead lead to serious AEs (neutropenia and flu like syndrome) in two patients (Quante, Zeugmann, Bajbouj, & Anghelescu, 2007). Moreover, clozapine is a diabetogenic antipsychotic, and the risk of developing diabetes due to continued therapy may persist even after weight reduction (Manu et al., 2013). All other reported data involves the use of clozapine in psychosis, bipolar depression and schizophrenia.

1.5.3 Therapeutic augmentation using mood stabilizers

1.5.3.1-Lithium

Augmentation of antidepressant therapy using lithium was first proposed in 1981 on the basis of a neurochemical rationale (De Montigny, Grunberg, Mayer, & Deschenes, 1981) where it was

believed that short-term lithium administration in TCA non responders could unveil the sensitization of their 5-HT receptors induced by chronic TCA administration.

Since then, many placebo-RCTs have been conducted to study lithium augmentation, all of which were included in a meta-analysis including all studies up to 2006 on the EMBASE, MEDLINE and The Cochrane Central Register of Controlled Trials (Crossley & Bauer, 2007). The review supported the use of lithium in antidepressant augmentation and found only modest evidence in favor of its ability to accelerate antidepressant response.

However, although the systematic review clearly underlined potential antidepressant properties of lithium in combination therapy in MDD, the overall value of lithium in TRD continues to be debatable. This is because the largest RCT included only 68 patients and all other studies were small with only 3 - 20 patients in each. In addition, only a few studies demonstrated a clear cut diagnosis of TRD. Indeed, according to the STAR*D project, patients entering level 3 after failure to respond to at least 2 adequate trials of antidepressants (the formal diagnosis of TRD according to the CANMAT guidelines) (Lam et al., 2009) who had their antidepressant therapy augmented using lithium experienced modest remission rates (15.9%), even less than patients who were randomized to augmentation using T-3 (24.7%) or were switched to nortriptyline (19.8%). Moreover, patients taking lithium were more likely to leave the study due to intolerance to AEs despite the use of moderate dosage.

The only study to exclusively assess the efficacy of lithium augmentation for TRD, included patients who had failed to respond to at least one, but no more than five, adequate trials of antidepressants as well as failure of prospective nortriptyline therapy for 6 weeks (Nierenberg et al., 2003). The study found no significant difference between Lithium (n=18) and placebo (n=17)

augmentation of nortriptyline with 12.5 % of subjects responding (defined as ≥ 50% decrease in HAM-D17 scores) to lithium vs. 20.0% to placebo. The study concluded that lithium had limited usefulness in TRD.

1.5.3.2-Lamotrigine

From a neurobiological prospective, lamotrigine acts on voltage gated sodium (Na+) and calcium (Ca+) ion channels thereby inhibiting presynaptic release of glutamate (Lees & Leach, 1993). This is believed to prevent excessive stimulation of serotonin dubbed "serotonin flooding" in the vicinity of the DRN which would secondarily impede the shutdown of DRN serotonin neuron firing (Coplan, Gopinath, Abdallah, & Berry, 2014).

The first evidence highlighting the importance of lamotrigine in TRD came from retrospective chart review studies (Gutierrez et al., 2005; F. L. Rocha & C. Hara, 2003) where reduction of depressive symptoms was noted after lamotrigine was added to patient's therapeutic regimen. More evidence was established from an open label descriptive study including 14 patients with TRD (Gabriel, 2006). 12 patients completed the study and lamotrigine adjunctive therapy resulted in a significant and rapid resolution in symptoms of depression from baseline in CGI-S and MADRS vs. 8 weeks (Study end-point). Moreover, a double-blinded placebo controlled-RCT including 23 patients with TRD with lack of response for at least 1 year found superiority in using fluoxetine plus lamotrigine over fluoxetine plus placebo on the CGI-S scale (2.15 ± 1.28 vs. 3.40 ± 1.17 respectively; p =.0308) (Barbosa, Berk, & Vorster, 2003). However, besides the relatively small sample size, the study also included both unipolar (n=15) and bipolar (n=8) depressed patients. In addition, lamotrigine failed to separate statistically from placebo on the HAM-D17 or

MADRS scales, which could be attributed to the small sample size and the resultant limited power of the study. Similar results were produced by another double-blinded placebo controlled-RCT also including a relatively small sample size (n=34) but pertaining to unipolar, nonpsychotic patients with a DSM-IV diagnosis of MDD and resistance to at least 2 antidepressants (Santos, Rocha Fá, & Hara, 2008). This demanded for larger double-blinded placebo controlled trials to rectify or deny the antidepressant efficacy of lamotrigine as an augmentation agent in TRD.

Indeed, a large multicenter double-blinded placebo-controlled RCT (n=183) failed to show significant difference on the MADRS, HAM-D17 or CGI-S scales between lamotrigine and placebo as augmentation to paroxetine in unipolar depression (Barbee et al., 2011). Interestingly, secondary post hoc analyses were suggestive of efficacy, particularly in those patients who completed the study (completer analysis) and in more severely ill patients (HAM-D17 $\geq$ 25).

A major setback with lamotrigine is the time required to raise its dose. This slow titration process could explain why data from the multicenter trial suggested a placebo and lamotrigine separation by the last visit with completers of 10 weeks treatment approaching significance (Barbee et al., 2011). Another setback is the wide range of AEs, including somnolence, headache, dizziness, nausea and malaise which can lead to discontinuation of treatment (F. L. Rocha & C. Hara, 2003). Altogether, it seems that evidence points to better results with using lamotrigine augmentation in well characterized patient subgroups where TRD is more severe, and patients are able to tolerate treatment for a longer period. On the downside, this makes it difficult to choose the right patient for this form of augmentation therapy.

1.5.3.3-Valproate (VPA)

In the late eighties and nineties several case reports and open labeled studies were published demonstrating the therapeutic potential of valproate (VPA) in unipolar depression, depression with anxiety and depression with atypical features (L. L. Davis, Ryan, Adinoff, & Petty, 2000), but no double-blinded studies have been so far conducted. Indeed, a study including 22 unipolar MDD participants who were enrolled in an 8 week open trial of VPA monotherapy (starting dose 500mg) after a period of washout (6 weeks for fluoxetine, 2 weeks for other antidepressants and 10 days for benzodiazepines), concluded that HAM-D17 scores were reduced by 48.8% by week 4 and the score was 7 ± 4 by week 8 (Lori L Davis et al., 1995).

Although the mechanism of action of VPA in unipolar depression is yet to be completely elucidated, its ability to modulate the GABAminergic system is already well established. Several studies have demonstrated a γ-aminobutyric acid (GABA) deficit in MDD patients (Petty, 1995). This data is consistent with results from tissue samples of rodent brain, studies involving brain tissue retrieved during psychosurgery for depression and post mortem brain specimens (Cross, Cheetham, Crompton, Katona, & Horton, 1988; Dennis, Beauchemin, & Lavoie, 1993; Honig, Bartlett, Bouras, & Bridges, 1988). VPA can potentiate the synthesis of GABA through enhancing GABAminergic activity and preventing GABA degradation through inhibition of GABA transaminase in the tricarboxylic acid cascade. This is achieved by increasing levels of succinate-semialdehyde and preventing its reduction by succinic-semialdehyde dehydrogenase enzyme, thus resulting in blockage of Na+ currents and repetitive firing in cortical neurons (Johannessen, 2000; McLean & Macdonald, 1986). This has been demonstrated in animal models by measurement of whole brain GABA levels which increased by 15±45% after acute administration of VPA as well

as regional changes in GABA levels in the cortex, striatum, hippocampus, and cerebellum of rat models (Chapman, Riley, Evans, & Meldrum, 1982; Hariton et al., 1984).

In contrast to the GABAminergic system which is largely inhibitory in nature, the glutamatergic system is excitatory and involves glutamate as its major neurotransmitter in the center nervous system (CNS). Glutamate binds to both ionotropic and metabotropic receptors in the brain. Ionotropic receptors are divided into three groups, N-methyl-D-aspartate receptor (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) and kinate receptors which are expressed mostly in the medial prefrontal cortex (mPFC), an area implicated in the pathophysiology of depression (H. E. Covington et al., 2010). Interestingly, inhibition of the glutamatergic pathway is believed to yield antidepressant properties (Papp & Moryl, 1994). VPA, by modulating the activity of excitatory amino acids (EAS) at the level of the mPFC pyramidal neurons, is able to block NMDA, AMPA and kinate excitatory response (Gabriella Gobbi & Luigi Janiri, 2006).

Moreover, many studies have highlighted the implication of an epigenetic mechanisms in major depression (Sun, Kennedy, & Nestler, 2013). Severe stress may trigger changes in chromatin structures of vulnerable individuals at particular genomic loci in the brains limbic regions resulting in changes in gene expression which may contribute to episodes of depression (Nestler, 2014). An experiment involving the exposure of mice to chronic social defeat stress to induce a depressive state, found that levels of acetylated histone H3 at the level of lysine residue 14 (acyH3K14) experienced a transient decrease, which was followed by a persistent increase in the nucleus accumbens, an important limbic brain region involved in depression, the cognitive process of addiction, motivation, reward, pleasure and an important part of the basal ganglia (H. E.

Covington, 3rd et al., 2009; Nestler et al., 2002; Nicola, 2007). In addition, infusion of MS-275, a specific HDAC2 inhibitor, mediated long lasting positive neuronal adaptations and exerted robust antidepressant-like effects in the social defeat paradigm and other behavioral assays. This was accompanied by reversal of the effects of the chronic social defeat stress on the global patterns of gene expression in the nucleus accumbens.

Recently, VPA has gained much attention due to novel research signifying its ability to induce widespread epigenetic reprogramming through the inhibition of histone deacetylases enzyme (HDAC) (Tremolizzo et al., 2002). VPA is able to inhibit HDAC class 1 enzymes (1, 2, 3 and 8) resulting in acylH3K14, which is implicated in the epigenetic mechanism of depression (Chiu, Wang, Hunsberger, & Chuang, 2013; Costa-Borges, Santaló, & Ibáñez, 2010). Consequently, it may be hypothesized that VPA could be a useful pharmacological intervention mitigating epigenetically induced vulnerability in patient with TRD (H. E. Covington, 3rd et al., 2009).

1.5.4 Augmentation using neuromodulation

Neuromodulation involves the use of various devices to alter electrical activity through brain stimulation (Janicak, Dowd, Rado, & Welch, 2010; Kosel, Frick, Lisanby, Fisch, & Schlaepfer, 2003). This concept is based on the fact that the brain is an organ with electrical activity and therefore this activity can be modulated through electrical and magnetic impulses. Various neuromodulatory devices impact areas of the brain implicated in the pathophysiology of depression, e.g. the use of rTMS on the dorsolateral Prefrontal Cortex (DLPFC) (Mark S George, Ketter, & Post, 1994; Sidney H Kennedy et al., 2009). Other modalities such as VNS and DBS are more invasive forms of neurostimulation which were approved for the treatment of neurological

disorders prior to being investigated for TRD (Sidney H Kennedy et al., 2009). In addition, ECT is another form of neuromodulation devices used in psychiatry practice and has been available for over 75 years.

1.5.4.1-Repetitive Magnetic Stimulation (rTMS)

Transcranial magnetic stimulation (TMS) is a relatively safe, noninvasive and painless technique which involves stimulation of the motor cortex in TRD patients, and is recommended as second line treatment in patients with refractory depression (R. Chen, 2000; Sidney H Kennedy et al., 2009).

However, being a fairly new neuromodulation machine used in treatment of depression, it is not without limitations. Although low-frequency rTMS stimulation appears to reduce seizure activity, high-frequency rTMS is considered a significant potential risk for seizure induction as it is liable to decrease seizure threshold in susceptible individuals (Wassermann, Cohen, Flitman, Chen, & Hallett, 1996). In addition, rTMS has been reported to contribute to the induction of mania (Sakkas et al., 2003) and manic switches have also been reported even with non-intensive rTMS protocols (Nahas et al., 1999; Nedjat & Folkerts, 1999). More recently, emerging evidence also points towards poor tolerance of chronic migraine patients to high frequency rTMS (Teo et al., 2014). Moreover, preliminary studies have shown that its effect is modest and less cost effective in comparison to ECT (Knapp et al., 2008). Therefore, further investigation is still required for rTMS adjustment and optimization in terms of key parameters such as frequency/intensity of stimulation and length of treatment.

1.5.4.2-Electroconvulsive Therapy (ECT)

Perhaps the oldest neuromodulation technique in psychiatry practice is ECT. It is often kept as method of last resort for patients with refractory depression unless patients displays signs of acute psychosis, suicidal ideation (level one evidence), catatonia, repeated intolerance to medication, rapidly deteriorating physical status or during pregnancy if any previously mentioned co-morbidity exists (level three evidence) in which case it may be considered as first line therapy (Sidney H Kennedy et al., 2009). Indeed, ECT has shown to be effective in patients who have failed to respond to a full course of rTMS (Dannon & Grunhaus, 2001). It works by inducing a brief electrical current over the scalp in order to induce a grand mal seizure. During this process, the patient is briefly sedated under general anesthesia and muscle relaxant. ECT requires 6 to 12 separate sessions over the course of several weeks to alleviate depressive symptoms and can either be applied to one hemisphere (unilaterally) or to both hemispheres (bilaterally).

However, the use of ECT is limited due to the lack of access in many areas, substantial relapse rates after successful acute treatment, and a negative public image (Janicak, Marder, & Pavuluri, 2011). Moreover, due to its nature, it is usually reserved for the most severely ill patients encountered in clinical practice. The result of this is that a substantial proportion of patients who inadequately respond to one or two adequate trials of antidepressants refuse to consider ECT as an option or are not considered as ideal candidates for ECT. Furthermore, ECT is commonly associated with post-ictal confusion, anterograde and retrograde memory impairment (Payne & Prudic, 2009); although Ultrabrief-Pulse (0.25 millisecond) ECT is becoming more popular over Brief-Pulse (0.50 millisecond) ECT due to association with less cognitive deficit and less memory

impairment (Niemantsverdriet, Birkenhäger, & van den Broek, 2011). In addition, patients who have responded well to ECT are often required to take additional ECT sessions on a weekly or monthly basis as a form of maintenance therapy in order to prevent relapse after treatment stops as these patients are less likely to respond to an antidepressant maintenance therapy (Harold A Sackeim et al., 1990).

1.5.4.3-Vagus Nerve Stimulation (VNS)

VNS is typically indicated as adjunctive therapy upon failure to respond to four or more adequate antidepressant treatments (Conway, 2005; R. C. Shelton, Osuntokun, Heinloth, & Corya, 2010). VNS was not initially designed for treatment of depressed patients; indeed, using VNS for treatment of clinically depressed patients was first based on observation of improved cognition and mood during studies of patients with epilepsy upon which VNS was approved by Health Canada for management of TRD in 2001 (Handforth et al., 1998; Sidney H Kennedy et al., 2009). Although a plausible explanation for improved mood may be due to reduced seizure frequency, patients with little or no seizure improvement also reported substantial enhancement in mood (Harden, Pulver, Nikolov, Halper, & Labar, 1999). Although failure to respond to ECT is not a prerequisite for VNS, the CANMAT guidelines recommend its use as third line treatment in TRD after ECT (Sidney H Kennedy et al., 2009). Stimulation of the left Vagus nerve is achieved by implantation of a bipolar electrode accessed through an incision in the lower neck producing intermittent electrical signals which activates limbic structures (Sidney H Kennedy et al., 2009).

However, the invasive nature of VNS results in several acute side effects, most prominent of which is voice hoarseness due to stimulation of the recurrent laryngeal nerve which may lead to treatment intolerance (Gerson et al., 2011). Other side effects include neck pain related to site of incision, neck infection, headache, cough, dysphagia and dyspnea (Sidney H Kennedy et al., 2009; Nahas et al., 2005). In addition, first manic episodes with psychotic features have also been reported in the context of first use of VNS in unipolar depressed patients (Gerson et al., 2011); similar to the phenomenon of *organic mania* reported with the use of antiepileptic treatments (Mula & Monaco, 2006). Moreover, upon following patients for up to two years, the response rates of VNS adjunctive therapy only ranged from 27% to 46% and remission rates from 16% to 29% (M. S. George et al., 2005; Marangell et al., 2002; A John Rush et al., 2005). Although it is believed that VNS may deliver a delayed antidepressant effect with increased clinical improvement, antidepressant adjustments cannot be excluded as a plausible explanation for the increased rates of response and remission. Given the lack of concrete evidence in support of VNS as adjunctive therapy, it is difficult to determine its place in the treatment algorithm for TRD.

1.5.4.4-Deep Brain Stimulation (DBS)

DBS is regarded as the most invasive neuromodulatory procedure for stimulating deep brain structure. It involves the insertion of a thin electrode directly into the brain and the application of different currents at varying depths until the desired effect is eventually produced. Indeed, DBS is regarded as treatment of last resort, after failure of ECT and there are no large enough RCTs on which its efficacy can be judge; nor is there sufficient evidence to recommend DBS in the absence or presence of pharmacotherapy (Sidney H Kennedy et al., 2009). DBS is also associated with

significant morbidity and mortality and is only considered when all pharmacotherapy and neuromodulatory options have been taken into consideration (Mark S George et al., 2000). In addition, two large randomized control trials examining the use of DBS in TRD by stimulation of the ventral striatum failed to demonstrate a significant difference in response between the active and control groups at the end of the 16-week controlled phase (Dougherty et al., 2015). At the moment, CANMAT does not have a formal set of guidelines for DBS, instead it is under *investigational* neurostimulation therapies (Sidney H Kennedy et al., 2009).

1.5.5 New treatment options-ongoing research

Various techniques, involving the use of novel medication or neuromodulation devices are emerging for the management of TRD. Recently Ketamine, a well-known dissociative general anesthetic, is emerging as an unexpected pharmacotherapeutic agent with potent antidepressant properties (Kwak, Tiller, & Tucker, 2015). In addition, ketamine is now being validated for superior efficay against ECT and rTMS therapy, although results have so far been negative (Gosek, Chojnacka, Bienkowski, & Swiecicki, 2014). More recently, emerging evidence supports the superiority of ketamine combination with rTMS over TMS monotherapy (Best & Griffin, 2015). Magnetic seizure therapy (MST) has also surfaced as a novel neuromodulation technique with compelling antidepressant properties for TRD patients with a benign cognitive side effect profile (Kosel et al., 2003).

CHAPTER 2 – TREATMENT RESISTANT DEPRESSION: PSYCHOPATHOLOGICAL PROFILES AND TREATMENT OUTCOMES

2.1 Introduction

TRD typically refers to inadequate response following adequate antidepressant therapy among patients suffering from MDD (Maurizio Fava, 2003). According to the STAR*D project, approximately half of depressed patients had an inadequate response to antidepressant monotherapy, and as many as 20% had resistant depression despite up to four aggressive pharmacotherapeutic switch and augmentation strategies (Trivedi, Rush, et al., 2006; Wisniewski et al., 2007).

In addition, the lack of a universally accepted TRD definition has influenced clinical research negatively, in terms of detecting sociodemographic and clinical comorbidities, leading to conflicting results (Martina Balestri et al., 2016). On the other hand, several switch and augmentation strategies using antidepressants and neuromodulation in the context of TRD staging models (Marcelo T Berlim & Gustavo Turecki, 2007) and mood stabilizers (De Montigny et al., 1981; Fabio Lopes Rocha & Claudia Hara, 2003) have been suggested for patients with TRD. More recently, MST surfaced as a novel neuromodulation technique with compelling antidepressant properties for TRD patients and a benign cognitive side effect profile (Kosel et al., 2003), yet remission rates only range from 30% to 40% (Cretaz, Brunoni, & Lafer, 2015).

Since the early nineties, several studies were published demonstrating therapeutic efficacy of atypical antipsychotics eventually leading to FDA approval of multiple antipsychotics in unipolar-TRD (Bobo & Shelton, 2010; Nelson et al., 2008; Šagud et al., 2011). In addition, multiple studies

have been published demonstrating the therapeutic potential of using adjunct mood stabilizers in TRD (Barbosa et al., 2003). However, no studies have examined treatment outcome of adjunct antipsychotics or mood stabilizers in a homogenous TRD patient population. In the present study, we report treatment outcomes and clinical characteristics, including sociodemographic, psychopathological features and comorbidities in patients who have failed to respond to two or more antidepressant trials and/or combinations, therefore suffering from TRD according to CANMAT clinical guidelines (Lam et al., 2009). Patients were treated with antipsychotics, and/or mood stabilizers in combination with antidepressants.

2.2 Materials and Methods

Data from seventy eight patients aged 19-75 years old was collected from the Mood Disorder Clinic (MDC) register of McGill University Health Center (MUHC), a university clinic mostly treating TRD and bipolar disorder patients. The study was approved by the Institutional Review Board (IRB) of McGill University (13-375-PSY). The Register 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, Spitzer, Gibbon, & Williams, 2002) carried out by skilled professional or by psychiatrists. All participants met DSM-IV criteria for MDD and were currently in a major depressive episode without hypomanic or manic symptoms (Association & DSM-IV., 1994). Seventy two patients included in the study have previously failed to fully or partially respond and/or achieve remission following at least two adequate trial (at least 4-6 weeks) of an antidepressant medication used as mono or in combination. Four had no documented information

asserting failure of previous pharmacotherapy, but had previous history of depressive episodes in the past. Two patients refused to try more than one antidepressant trial in mono or combination and were referred by their treating psychiatrist for TRD. Patients received treatment as usual by their treating psychiatrist, and the study retrieved data on depression scales without randomization. Patients were evaluated at baseline/before beginning (T-0) and after 3 month ± 8 week (T-3) of pharmacotherapy.

2.2.1 Patients Sociodemographic characteristics

The following socio-demographic characteristics of patients are collected in the Register: Age, race, gender, marital status, employment, level of education and living arrangement as well as 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, 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. Duration of illness was calculated by subtracting age of most recent/current psychiatric consultation from age of first psychiatric consultation. Sociodemographic data from the entire database is presented in *Table 1* followed by a comparison between various treatment groups. The number of patients and specific pharmacotherapy combinations are described in details in *Table 2*.

2.2.2 Patient rating and assessment Scales

Patients were assessed by three raters (two psychiatrists and a General Practitioner) using the following scales:

1. The 17-item HAM-D17 from the beginning of therapy and 3 months thereafter in order to assess the rate of remission and/or response of depressive symptoms. The HAM-D17 (Hamilton, 1960) is a 17-item questionnaire and is the most universally used scale in assessing depressive symptoms, generally regarded as the "gold standard" (Riedel et al., 2010). Each item (or question asked) on the 17-item HAM-D17 is rated according to a 5-point likert-scale and is an indication of symptom severity; where 0 = absent, 1 = mild, 2 = moderate, 3 = moderate-to-severe, and 4 = severe. Total HAM-D17 scores reflect the severity of depressive symptoms and range from 0 – 52. Total scores were evaluated as follows: 0 – 7, normal; 8 – 13, mild; 14 – 19, moderate; 20 – 25, severe; 26 – 52, very severe (Hamilton, 1960).
2. The 10-item MARDS score report from the beginning of therapy and 3 months thereafter in order to assess the rate of remission and/or response of depressive (S. A. Montgomery & Asberg, 1979). The MADRS is a 10 item rating scale used to assess the severity of depression. Each item (or question asked) on the 10-item MADRS is rated according to a 5-point likert-scale and is an indication of symptom severity; where 0 = absent, 1 = mild, 2 = moderate, 3 = moderate-to-severe, 4 = severe and 5 = very severe. Total MADRS scores reflect the severity of depressive symptoms and range from 0 – 60. Total scores were evaluated as follows: 0 – 6, normal; 7 – 19, mild; 14 – 19, moderate; 20 – 34, severe; 26 – 60, very severe (S. A. Montgomery & Asberg, 1979)
3. The 16-item clinician rating Quick Inventory of Depressive Symptomatology (QIDS-C16) from the beginning of therapy and 3 months thereafter in order to assess the rate of remission and/or response of depressive symptoms. The Quick Inventory of Depressive

Symptomatology (QIDS-C16) (A. J. Rush et al., 2003) is a 16-item rating scale used to assess the severity of depressive symptoms. Each item (or question asked) on the 16-item QIDS-C16 is rated according to a likert-scale (with scores ranging from 0 – 3). The total score of the QIDS-C16 ranges from 0 to 27 and reflects the severity of depressive symptoms. A score 0 – 5 = normal, 6 – 10 = mild, 11 – 15 = moderate, 16 – 20 = severe, 21 – 27 = very severe (A. J. Rush et al., 2003).

4. The CGI-S score report and a 3-month Clinical Global Impression: Improvement scale (CGI-I) score report in order to assess the rate of remission and/or response of depressive symptoms Both CGI-S and CGI-I are 7-point scales. The severity of the patient's illness at the beginning and end of treatment was ranked as follows: 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill for the CGI-S. Patients were assessed 3 months from the beginning of antidepressant combination treatment (baseline) using the CGI-I for the severity of the patient's symptoms to determine if symptom severity has improved or diminished. 3-month symptom improvement scores from baseline were scored as follows: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

The study was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice.

2.2.3 Three-month trial and mental status stabilization

All *pharmacological trials* for each patient were evaluated. Multiple patients had several trials before identifying the best combinations. Only the last trial, when the patient responded to

treatment and remained stable for more than 6 weeks (mean 12.5±5.90, T-3), and the treating psychiatrist kept the treatment unchanged, was included in this study for statistical analysis. Evaluation was done at time T-0 (before starting the combination therapy X), at time T-3 (30-90 days after the combination). The number of failed pharmacotherapeutic trials were calculated in the number of failed antidepressant/combination trials.

2.2.4 Patient classification, Grouping and Comparison

Patients were classified into three *pharmacotherapy groups*:

- **Group-A:** *patients treated with antidepressant mono or combination therapy* (n=21).
- **Group-B:** *patients treated with mood stabilizers for augmentation, plus antidepressants* (n=16).
- **Group-C:** *patients treated with antipsychotics (typical and atypical) and/or mood stabilizers plus antidepressants* (n=41).

I. Patients in **Group-A** (*antidepressant mono or combination therapy*) were compared to patients in **Group-B** + **Group-C** (*augmentation therapy*).

II. Patients in **Group-A** (*antidepressant mono or combination therapy*) were compared to patients in **Group-B** (*mood stabilizer augmentation*) and patients in **Group-C** (*antipsychotic ± mood stabilizer augmentation*).

Given that patients in **Groups-B and C** responded only to *antipsychotic or mood stabilizer augmentation of antidepressant therapy*, we decided to cluster both groups together and compare them against patients in **Group-A** who responded to *antidepressants without augmentation*. Following this, we decided to compare patients in **Group-A** vs. **Groups-B** vs. **Group-C** to detect

possible differences in psychopathological features, socio-demographics and clinical characteristics between **Groups-B** and **Group-C** while considering **Group-A** patients as control. In addition, the triple group comparison allowed us to evaluate clinical response and appraise efficacy of atypical antipsychotics versus mood stabilizers.

2.2.5 Statistical Analysis

The statistical analysis was conducted using SigmaPlot 13 and SPSS 23. Data are presented as mean ± standard error of the mean (S.E.M.), mean ± Standard deviation (SD) and delta score (Δ score) end-point change. Group comparison on demographic and clinical characteristics was performed using one-way analysis of variance (one way-ANOVA) for continuous variables and chi-square test or χ^2-distribution for categorical variables to test for balance and compare means between groups. In addition, inter-rater reliability for individual scales was calculated using Cohen's kappa (Cohen, 1968). For comparisons for all scales between antidepressants and augmentation groups, score changes between treatments and time were evaluated using the two-way ANOVA (factors treatment and time) followed by Newman-Keuls post-hoc test for multiple comparisons. For comparison for all scales between antidepressant group, mood stabilizer augmentation group and antipsychotics augmentation group, score changes between treatments and time were evaluated using two-way ANOVA (factors treatment and time) followed by Dunnett's post-hoc test for multiple comparisons considering the antidepressant group as a control. Statistical significance was set at an alpha of 0.05 (two-sided).

2.3 Results

2.3.1 - Table 1. Clinical characteristics and demographics of participants.

Age (Years) (Mean±SD)		48.5±13.67
Ratio of Males : Females		32:46
Patients≤65 years of age		69 (88.4%)
Age of first psychiatric consultation (Years) (Mean±SD)		36.7±15
Race	**White:**	53 (67.9%)
	Hispanic:	8 (10.3%)
	Black:	3 (3.8%)
	Oriental:	6 (7.7%)
	Other:	8 (10.3%)
Education Level	**High School:**	14
	College:	28
	Bachelor's:	19
	Master's:	6
	Doctorate:	8
	Vocational:	3
Patients diagnosed with Unipolar-TRD without psychotic features		63 (80.8%)
Patients living alone at baseline		22 (28.2%)
Number of patients with 1st degree family history of mental illness		50 (64.1%)
Number of failed pharmacotherapy in mono or combination (Mean±SD)		3.9±3
Duration of illness-current episode (years) (Mean±SD)		11.8±11.9

Number of patients with comorbid anxiety disorder	**Agoraphobia:**	4 (5.1%)
	GAD:	38 (48.7%)
	OCD:	2 (2.6%)
	Panic Disorder:	17 (21.8%)
	PTSD:	5 (6.4%)
	Social phobia:	2 (2.6%)
	Anxiety Disorder NOS:	1 (1.3%)
Number of patients with other psychiatric illnesses (Anorexia, Bulimia, Eating disorder NOS, Circadian Rhythm Sleep Disorder, Trichotillomania, ADHD)		14 (17.9%)
Patients with history of substance abuse		14 (17.9%)
Number of patients with suicide attempts		17 (21.8%)
Number of patients with a diagnosed personality disorder		4 (5.1%)
Number of patients with prominent axis II features but no formal diagnosis		11 (14.1%)
Axis II Traits	**Cluster A (Odd)** (Paranoid, Schizoid, Schizotypal):	6 (7.7%)
	Cluster B (Dramatic) (Antisocial, Borderline, Histrionic, Narcissistic):	17 (21.8%)
	Cluster C (Anxious) (Avoidant, Dependant, Obsessive-Compulsive):	23 (29.5%)
	Cluster B + C traits:	9 (11.5%)
	N/A:	23 (29.5%)

Number of patients with axis III (Medical condition potentially relevant to treatment)	54 (69.2%)
Patients with chronic pain disorder or back problems (Plantar fasciitis, Fibromyalgia, Herniated disc, Gastroplasty with repeated fistulas, migraines, spinal stenosis, multiple fractures, diverticulitis, shingles, fractures post-car accident)	20 (25.6%)
Patients with history of cancer or inflammatory/autoimmune conditions (Asthma, arthritis, Lupus, ankylosing spondylitis, Vogt-koyanogi-harada syndrome)	11 (14.1%)
Patients with neurological conditions (meningioma, TBI, craniostenosis, Lewy body dementia)	9 (11.5%)
Patients with Type I or Type II diabetes	4 (5.1%)
Patients with dyslipidemia, hypertension and related cardiac disease	17 (21.8%)
Number of patients with axis IV (Psychosocial and Environmental problems (Support system, Personal losses, Education, Occupation, Access to health care, etc.)	68 (87.2%)

GAD: Generalized Anxiety Disorder. PTSD: Post Traumatic Stress Disorder. OCD: Obsessive Compulsive Disorder. 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. SEM: Standard Error Measurement. TBI: Traumatic Brain Injury

2.3.2 - Table 2. Pharmacotherapy of participants in each treatment group.

<table>
<tr><th></th><th>Antidepressant mono or combination therapy (N=21)</th><th>Antidepressant + Mood Stabilizer (N=16)</th><th colspan="2">Antidepressant + Antipsychotic (Typical/ Atypical) ± Mood Stabilizer (N=41)</th></tr>
<tr><td rowspan="8">Augmentation agents or antidepressant combination used per group</td><td>SSRI/TCA + Wellbutrin: 6</td><td rowspan="2">Valproic acid: 5</td><td>Quetiapine: 23</td><td rowspan="8">Valproic acid: 8

Lamotrigine: 2

Gabapentin: 2

Valproic acid + Gabapentin : 1

Valproic acid + Lamotrigine + Lithium: 1

Topiramate ± Valproic acid: 2</td></tr>
<tr><td>SSRI + Mirtazapine: 5</td><td>Olanzapine: 5</td></tr>
<tr><td>SNRI + Wellbutrin: 2</td><td>Lamotrigine: 7</td><td>Aripiprazole: 6</td></tr>
<tr><td>SNRI + Mirtazapine: 2</td><td>Lithium: 2</td><td>Aripiprazole + Quetiapine: 2</td></tr>
<tr><td>SNRI + SNRI: 1</td><td>Valproic acid + Topiramate: 1</td><td>Risperidone: 3</td></tr>
<tr><td>SSRI + TCA/Trazodone: 3</td><td rowspan="2">Valproic acid + Lamotrigine: 1</td><td rowspan="2">Typical agents (Haldol/ Fluphenazine): 2</td></tr>
<tr><td>SSRI/SNRI monotherapy: 2</td></tr>
</table>

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

NOTE: This database represents a longitudinal study. Therefore only 14 individuals were included in the VPA results published in the World Journal of Biological Psychiatry since at time of manuscript preparation we had a total of 45 patients in the database and 14 patients on VPA adjunctive therapy rather than 18 at current date as demonstrated above.

2.3.3 - Table 3. Clinical psychopathological characteristics and demographics of participants in antidepressant mono/combination therapy and participants using adjunctive Atypical/Typical antipsychotics and/or Mood stabilizers for therapeutic augmentation.

	Antidepressant Mono or combination therapy (N=21)	**Augmentation group (Antipsychotic and/or Mood stabilizer) (N=57)**
Age (Years) (Mean±SD)	49.9±15.1	48±13.2
Ratio of Males: Females	9:12	23:34
Patients≤65 years of age	*16 (76.2%)*	*53 (93%)*[1]
Age at first episode of MDD (Mean±SD)	40.9±16.7	35.2±14.1
Duration of illness-current episode (years) (Mean±SD)	9.1±10.3	12.8±12.4
Patients diagnosed with Unipolar-TRD without psychotic features	*20 (95.2%)*	*43 (75.4%)*[2]
Patients with history of substance abuse	*1 (4.8%)*	*14 (24.6%)*[3]
Number of patients with suicide attempts	3 (14.3%)	14 (24.6%)
Number of failed pharmacotherapies in mono or combination (Mean±SD)	*2.7±2*	*4.3±3.2*[4]
Number of patients with 1st degree family history of mental illness	13 (61.9%)	37 (64.9%)
Unemployed/Disability sick leave before treatment	13 (61.9%)	37 (64.9%)
Unemployed/Disability sick leave after treatment	12 (57.1%)	31 (54.4%)
Patients returning to work after treatment	1 patient	6 patients
Patients with comorbid anxiety disorders (PTSD, GAD, Agoraphobia, phobia, OCD, panic disorder, social phobia, anxiety disorder NOS)	12 (57.1%)	38 (66.7%)
Patients living alone at baseline	7 (33.3%)	15 (26.3%)
Patients living alone after 4-20 weeks	6 (28.6%)	14 (24.6%)

Number of hospitalizations for depression since first episode		
None	12 (57.1%)	35 (61.4%)
One	8 (38.1%)	11 (19.3%)
>one	1 (4.8%)	12 (21.1%)

GAD: Generalized Anxiety Disorder. PTSD: Post Traumatic Stress Disorder. OCD: Obsessive Compulsive Disorder. Anxiety Disorder NOS: Anxiety Disorder Non-otherwise specified. Unipolar-TRD: Unipolar-Treatment Resistant Depression. MDD: Major Depressive Disorder. SD: Standard Deviation.

1 χ^2=4.24, df = 1, *P*=0.04; Fisher's exact test, *P*=0.04; significantly higher MDD patients ≤65 in the antidepressant comb/solo group.

2 χ^2=3.9, df = 1, *P*=0.05; Fisher's exact test, *P*=0.04; significantly higher MDD patients with psychotic features in augmentation group.

2 χ^2=3.9, df = 1, *P*=0.05; Fisher's exact test, *P*=0.057; significantly higher incidence of substance abuse in augmentation group.

4 One-way ANOVA, number of failed pharmacotherapy in antidepressant vs. augmentation group, $F_{1, 75}$=4.27, *P*=0.04.

2.3.4 - Table 4. Treatment outcomes of participants in antidepressant mono/combination therapy and participants using adjunctive Atypical/Typical antipsychotics and/or Mood stabilizers for therapeutic augmentation.

	Antidepressant Mono or combination therapy (N=21)	**Augmentation group (Antipsychotic and/or Mood stabilizer) (N=57)**	**Two-way ANOVA Factor A (Treatment) Factor B (Time) Factor A x Factor B (Interaction)**
MADRS TOTAL (Mean ± SEM)			
Baseline Score	*29±2.1*	*33.5±1.1*[1]	Factor A (Treatment): $F_{1, 152}$=2.22, P=0.138 Factor B (Time): $F_{1, 152}$=66.1, P<0.001 Factor A x Factor B (interaction): $F_{1, 152}$=2.16, P=0.14
End-Point Score	18.8±2.1	18.8±1	
Δ change	-10.2	-14.7	
Number of patients in remission (<10)	5 (23.8%)	7 (12.3%)	
HAM-D17 TOTAL (Mean ± SEM)			
Baseline Score	*21.3±1.5*	*24.9±0.8*[2]	Factor A (Treatment): $F_{1, 152}$=2.89, p=0.09 Factor B (Time): $F_{1, 152}$=59.3, P<0.001 Factor A x Factor B (interaction): $F_{1, 152}$=2.28, P=0.13
End-Point Score	14.3±1.6	14.5±0.8	
Δ change	*-7*	*-10.4*[3]	
Number of patients in remission (≤7)	5 (23.8%)	7 (12.3%)	
QIDS-C16 TOTAL (Mean ± SEM)			
Baseline Score	*14.5±1*	*16.7±0.6*[4]	Factor A (Treatment): $F_{1, 152}$=2.33, P=0.128 Factor B (Time): $F_{1, 152}$=59.9, P<0.001 Factor A x Factor B (interaction): $F_{1, 152}$=2.43, P=0.12
End-Point Score	10±1	9.9±0.5	
Δ change	-4.5	-6.8	
CGI-Severity of illness Scores (Mean ± SEM)			
Baseline Score	*4.6±0.3*	*5.3±0.2*[5]	Factor A (Treatment): $F_{1, 152}$=3.55, P=0.06 Factor B (Time): $F_{1, 152}$=56.4, P<0.001 Factor A x Factor B (interaction): $F_{1, 152}$=1.47, P=0.23
End-Point Score	3.2±0.4	3.4±0.1	
Δ change	-1.4	-1.9	

CGI-Global Improvement (Mean ± SEM)		
End-Point Score	2.6±0.3	2.2±0.1

MADRS: Montgomery-Asberg Depression Rating Scale. HAM-D17: Hamilton Rating Scale for Depression. QIDS-C16: Quick Inventory of Depressive Symptomatology. CGI: Clinical Global Impression. SEM: Standard Error Measurement. Δ change: baseline to end point change.

1 Two-way ANOVA, $F_{1, 152}$=2.22, P=0.138; comparing MADRS-T-0 of antidepressant vs. augmentation group, Newman-Keuls's post-hoc analysis, P=0.03.

2 Two-way ANOVA, $F_{1, 152}$=2.89, P=0.09; comparing HAM-D17-T-0 of antidepressant vs. augmentation group, Newman-Keuls's post-hoc analysis, P=0.023.

3 One-way ANOVA, HAM-D17 Δ change of antidepressant vs. augmentation group, $F_{1, 76}$=5.01, P=0.028.

4 Two-way ANOVA, $F_{1, 152}$=2.33, P=0.13; comparing QIDS-C16-T-0 of antidepressant vs. augmentation group, Newman-Keuls's post-hoc analysis, P=0.03.

5 Two-way ANOVA, $F_{1, 152}$=3.56, P=0.06; comparing CGI-S-T-0 of antidepressant vs. augmentation group, Newman-Keuls's post-hoc analysis, P=0.028.

2.3.5 - Table 5. Clinical psychopathological characteristics and demographics of participants in antidepressant mono/combination therapy, participants using adjunctive mood stabilizers and participants using adjunctive Atypical/Typical antipsychotics ± Mood stabilizers for therapeutic augmentation.

	Group-A Antidepressant Mono or combination therapy (N=21)	**Group-B Antidepressant + Mood Stabilizer (N=16)**	**Group-C Antidepressant + Typical/ Atypical antipsychotic ± Mood Stabilizer (N=41)**
Age (Years) (Mean±SD)	49.9±15.1	47.0±15.6	46.8±12.5
Ratio of Males: Females	9:12	5:11	18:23
Patients≤65 years of age	*16 (76.2%*	15 (93.8%)	38 (92.7%)
Age at first episode of MDD (Mean±SD)	40.9±16.7	36.6±13.7	34.7±14.4
Duration of illness-current episode (years) (Mean±SD)	9.1±10.3	10.4±7	13.7±13.9
Patients diagnosed with Unipolar-TRD without psychotic features	*20 (95.2%)*	*16 (100%)*	*27 (65.9%)*[1]
Patients with history of substance abuse	*1 (4.8%)*	*6 (37.5%)*	*8 (19.5%)*[2]
Number of patients with suicide attempts	3 (14.3%)	2 (12.5%)	12 (29.3%)
Number of failed pharmacotherapies in mono or combination (Mean±SD)	2.7±2	4.6±4	4.2±2.9
Number of patients with 1st degree family history of mental illness	13 (61.9%)	13 (81.3%)	24 (58.5%)
Unemployed/Disability sick leave/retired before treatment	13 (61.9%)	7 (43.7%)	30 (73.2%)
Unemployed/Disability sick leave/retired after treatment	12 (57.1%)	5 (31.3%)	25 (61%)
Patients returning to work after treatment	1 patient	2 patient	5 patients
Patients with comorbid anxiety disorders (PTSD, GAD, Agoraphobia, phobia, OCD, panic disorder, social phobia, anxiety disorder NOS)	12 (57.1%)	10 (62.5%)	28 (68.3%)
Patients living alone at baseline	7 (33.3%)	4 (25%)	11 (26.8%)
Patients living alone after 4-12 weeks	6 (28.6%)	4 (25%)	10 (24.4%)

Number of hospitalizations for depression since first episode			
None	12 (57.1%)	13 (81.3%)	22 (53.7%)
One	8 (38.1%)	3 (18.8%)	7 (17.1%)
>one	1 (4.8%)	0 (0%)	12 (29.3%)

GAD: Generalized Anxiety Disorder. PTSD: Post Traumatic Stress Disorder. OCD: Obsessive Compulsive Disorder. Anxiety Disorder NOS: Anxiety Disorder Non-otherwise specified. Unipolar-TRD: Unipolar-Treatment Resistant Depression. MDD: Major Depressive Disorder. SD: Standard Deviation.

[1] χ^2=12.5, df = 2, P=0.002

[2] χ^2=6.3, df = 2, P=0.04

2.3.6 - Table 6. Treatment outcomes of participants in antidepressant mono/combination therapy, participants using adjunctive mood stabilizers and participants using adjunctive Atypical/Typical antipsychotics ± Mood stabilizers for therapeutic augmentation.

	Group-A Antidepressant Mono or combination therapy (N=21)	**Group-B Antidepressant + Mood Stabilizer (N=16)**	**Group-C Antidepressant + Typical/ Atypical antipsychotic ± Mood Stabilizer (N=41)**	**Two-way ANOVA Factor A (Treatment) Factor B (Time) Factor A x Factor B (Interaction)**
MADRS TOTAL (Mean ± SEM)				
Baseline Score	*29±2.1*	*31.3±1.7*	*34.4±1.4*[1]	Factor A (Treatment): $F_{2, 150}$=2.16, P=0.12 Factor B (Time): $F_{1, 150}$=79.25, P<0.001 Factor A x Factor B (interaction): $F_{2, 150}$=1.12, P=0.33
End-Point Score	18.8±2.1	17.4±1.8	19.4±1.2	
Δ change	-10.2	-13.9	-15	
Number of patients in remission (<10)	5 (23.8%)	3 (18.8%)	4 (9.8%)	
HAM-D17 TOTAL (Mean ± SEM)				
Baseline Score	21.3±1.5	*22.9±1.1*	*25.7±1*[2]	Factor A (Treatment): $F_{2, 150}$=3.05, P=0.05 Factor B (Time): $F_{1, 150}$=72.1, P<0.001 Factor A x Factor B (interaction): $F_{2, 150}$=1.21, P=0.30
End-Point Score	14.3±1.6	13.2±1.1	15.1±0.9	
Δ change	*-7*	*-9.7*	*-10.6*[3]	
Number of patients in remission (≤7)	5 (23.8%)	2 (12.5%)	5 (12.2%)	
QIDS-C16 TOTAL (Mean ± SEM)				
Baseline Score	*14.5±1*	*15.8±0.8*	*17.1±0.7*[4]	Factor A (Treatment): $F_{2, 150}$=2.1, P=0.125 Factor B (Time): $F_{1, 150}$=73.36, P<0.001 Factor A x Factor B (interaction): $F_{2, 150}$=1.23, P=0.3
End-Point Score	10±1	9.2±0.8	10.2±0.6	
Δ change	-4.5	-6.6	-6.9	

CGI-Severity of illness Scores (Mean ± SEM)				
Baseline Score	4.6±0.3	*4.9±0.26*	*5.4±0.2*[5]	Factor A (Treatment): $F_{2, 150}$=3.59, P=0.03 Factor B (Time): $F_{1, 150}$=66.48, P<0.001 Factor A x Factor B (interaction): $F_{2, 150}$=0.84, P=0.43
End-Point Score	3.2±0.4	3.1±0.26	3.5±0.2	
Δ change	-1.4	-1.8	-1.9	
CGI-Global Improvement (Mean ± SEM)				
End-Point Score	2.6±0.3	2.2±0.2	2.2±0.1	

MADRS: Montgomery-Asberg Depression Rating Scale. HAM-D17: Hamilton Rating Scale for Depression. QIDS-C16: Quick Inventory of Depressive Symptomatology. CGI: Clinical Global Impression. SD: Standard Deviation. SEM: Standard Error Measurement. Δ change: baseline to end point change.

[1] Two-way ANOVA, $F_{2, 150}$=2.16 P=0.12; comparing MADRS-T-0 of Group A vs. Group C, Dunnett's post-hoc analysis, P=0.035.

[2] Two-way ANOVA $F_{2, 150}$=3.05, P=0.05; comparing HAM-D17-T-0 of Group A vs. Group C, Dunnett's post-hoc analysis, P=0.02.

[3] One-way ANOVA $F_{2, 75}$=2.60, P=0.08; HAM-D17 Δ change of Group A vs. Group C, Dunnett's post-hoc analysis, P=0.05.

[4] Two-way ANOVA $F_{2, 150}$=2.10, P=0.12; comparing QIDS-C16-T-0 of Group A vs. Group C, Dunnett's post-hoc analysis, P=0.032.

[5] Two-way ANOVA $F_{2, 150}$=3.58, P=0.03; comparing CGI-S-T-0 of Group A vs. Group C, Dunnett's post-hoc analysis, P=0.02.

2.3.7 Figure 1. Treatment outcome of participants in antidepressant mono/combination therapy and participants using augmentation therapy (adjunctive Atypical/Typical antipsychotics and/or Mood stabilizers).

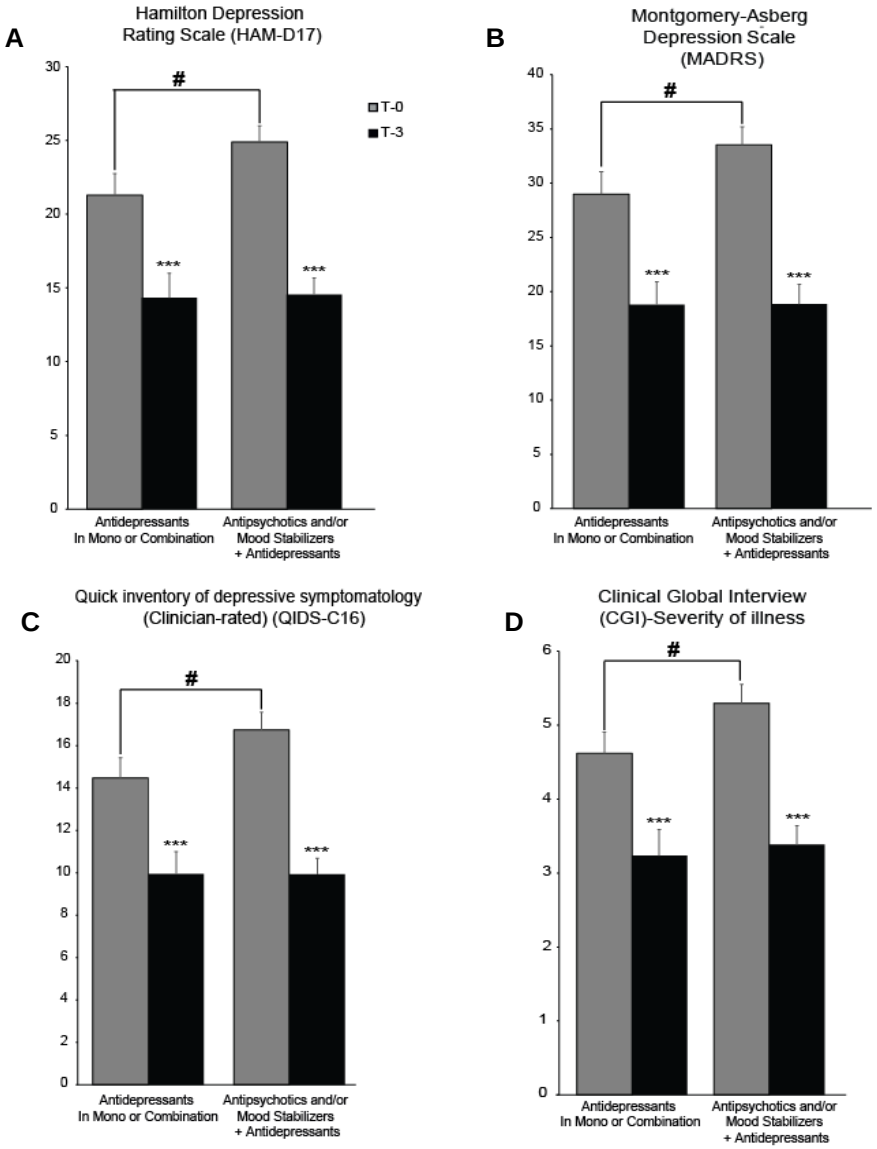

Figure 1. Effects of antidepressant mono/combination therapy versus augmentation agents (adjunctive mood stabilizers and/or Atypical/Typical antipsychotics) on HAM-D17, MADRS, QIDS-C16 and CGI scales. (A) HAM-D17. (B) MADRS. (C) QIDS-C16. (D) CGI-Severity of illness score. Data are expressed as mean ± SEM; ***$P \leq 0.001$, compared to T-0; #$P \leq 0.05$, comparing T-0 across treatment groups, two-way analysis of variance followed by Newman-keuls post-hoc test for multiple comparisons. HAM-D17: Hamilton Rating Scale for Depression. QIDS-C16: Quick Inventory of Depressive Symptomatology. MADRS, Montgomery–Asberg Depression Rating Scale; CGI, Clinical Global Impression Scale.

2.3.8 Figure 2. Treatment outcome of participants in antidepressant mono/combination therapy, participants using adjunctive mood stabilizers and participants using adjunctive Atypical/Typical antipsychotics ± Mood stabilizers.

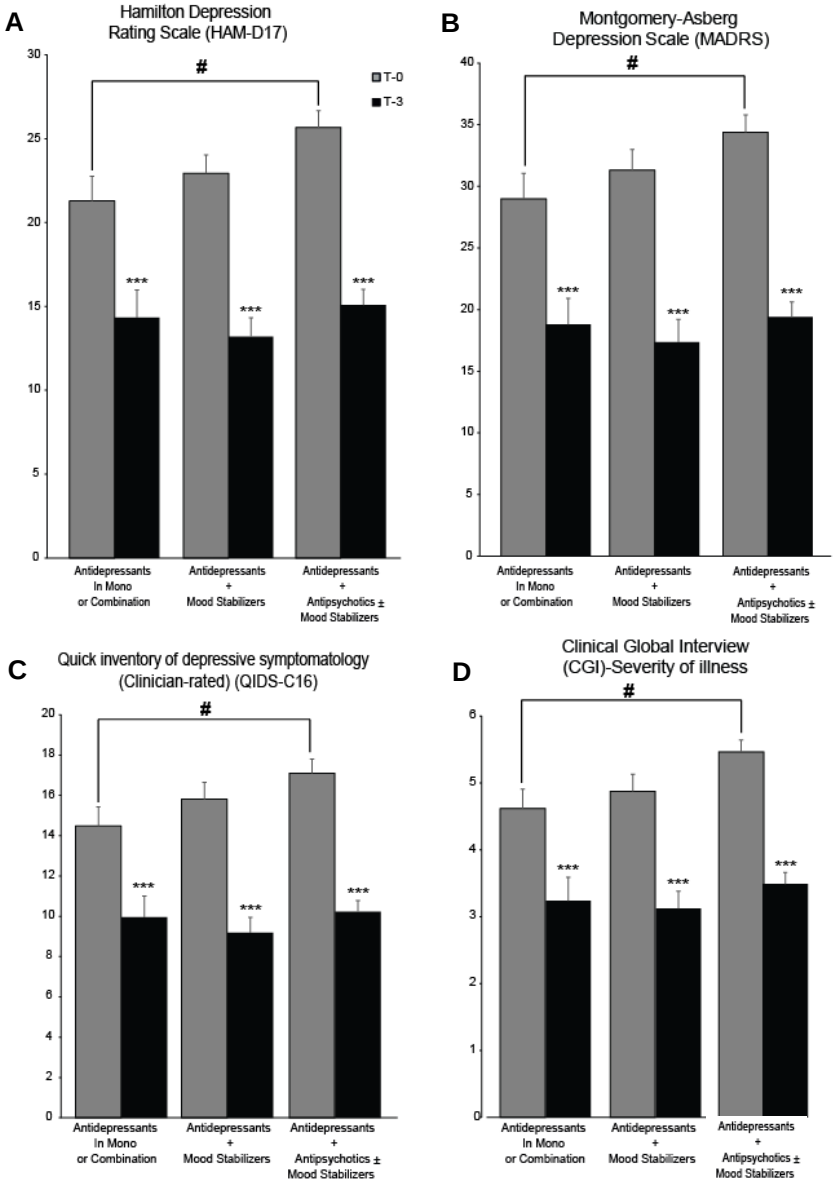

Figure 2. Effects of antidepressant mono/combination therapy versus adjunctive mood stabilizers versus adjunctive Atypical/Typical antipsychotics ± Mood stabilizers on HAM-D17, MADRS, QIDS-C16 and CGI scales. (A) Total HAM-D17. (B) MADRS. (C) QIDS-C16. (D) CGI-Severity of illness score. Data are expressed as mean ± SEM; ***$P \leq 0.001$, compared to T-0; #$P \leq 0.05$, comparing T-0 across treatment groups, two-way analysis of variance followed by Dunnett's post-hoc test for multiple comparisons. HAM-D17: Hamilton Rating Scale for Depression. QIDS-C16: Quick Inventory of Depressive Symptomatology. MADRS, Montgomery–Asberg Depression Rating Scale; CGI, Clinical Global Impression Scale.

2.3.9 Figure 3. Comparing Δ change for HAM-D17 scores for antidepressant mono/combination therapy and augmentation (antipsychotics and/or mood stabilizers).

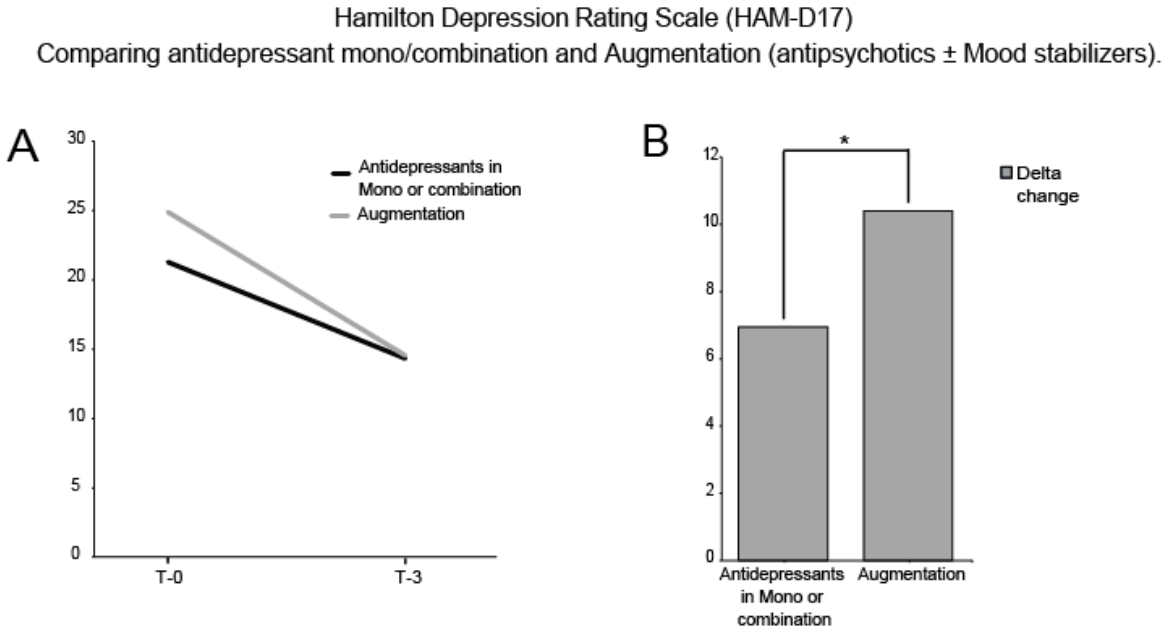

Figure 3. Effects of antidepressant mono/combination therapy versus augmentation agents (adjunctive mood stabilizers and/or Atypical/Typical antipsychotics) on HAM-D17 scale (A) Total HAM-D17 at T-0 and T-3. (B) HAM-D17 Δ change. Data are expressed as mean ± SEM; *$P \leq 0.05$ comparing overall Δ change, one-way analysis of variance. HAM-D17: Hamilton Rating Scale for Depression.

2.3.10 Figure 4. Comparing Δ change for HAM-D17 scores for antidepressant mono/combination therapy, antidepressant + mood stabilizers and antidepressants + antipsychotics ± mood stabilizers.

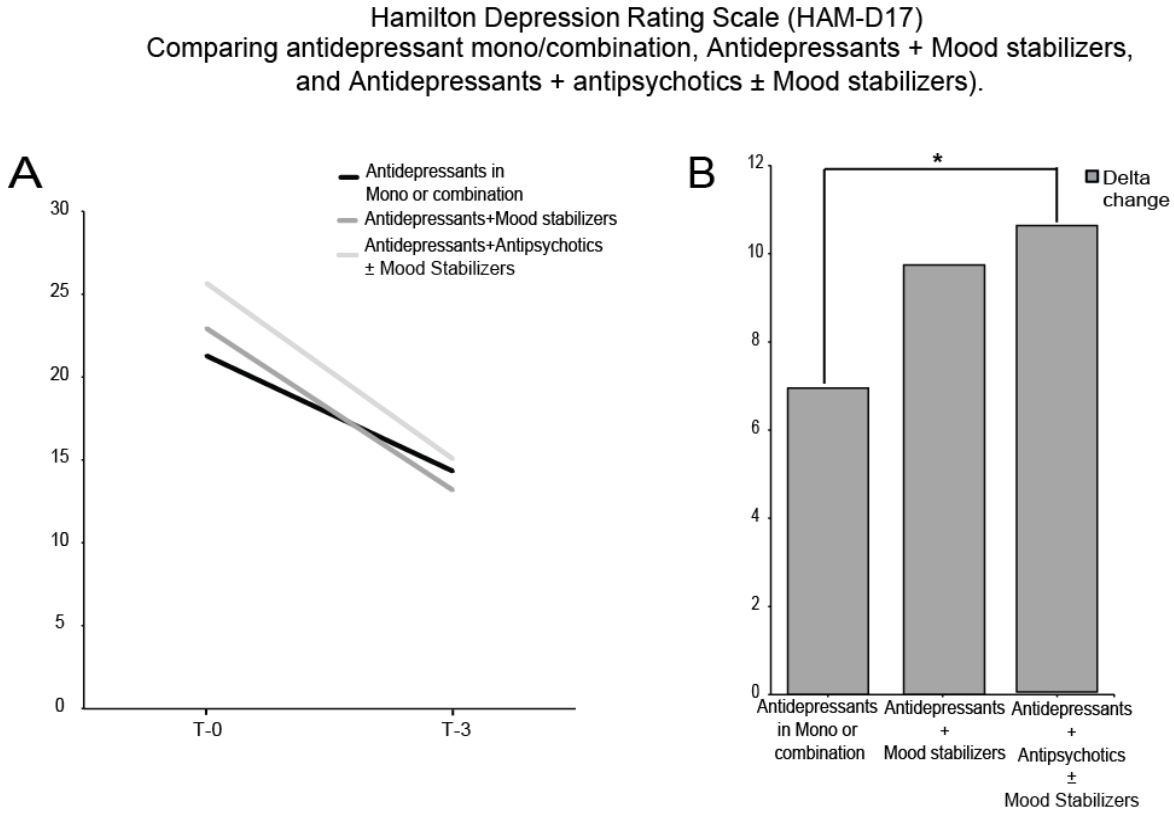

Figure 4. Effects of antidepressant mono/combination therapy versus antidepressant + mood stabilizers, versus antidepressants + antipsychotics ± mood stabilizers on HAM-D17 scale (A) Total HAM-D17 at T-0 and T-3. (B) HAM-D17 Δ change. Data are expressed as mean ± SEM; *$P \leq 0.05$ comparing overall Δ change, one-way analysis of variance followed by Dunnett's post-hoc test for multiple comparisons. HAM-D17: Hamilton Rating Scale for Depression.

2.3.11 Socio-demographic and clinical characteristics

The demographic and clinical characteristics of the study population are reported in *Table 1*. The mean (SD) age of this sub-population was 48.5 (13.67) years. The group included 32 male and 46 female patients; 53 patients were Caucasian, 8 patients were Hispanic, 6 patients were oriental and 11 patients were of other racial origins. 69 patients were ≤65 years of age and the mean age of 1st psychiatric consultation was 36.7 years old. All patients received a diagnosis of Major Depressive Disorder and recurrent episodes of depression of moderate to severe intensity following the DSM-IV criteria. None of the patients were current alcohol or substance abusers, 11 were past alcohol abusers and the rest were either social drinkers or reported not drinking. 4 patients abused cocaine, 5 patients abused cannabis prior to the study and one patient was dependent on opioids. 22 patients were living alone at baseline (T-0) and 50 patients reported at least one first degree family member (Siblings, children or parents) suffering from mental illness in the past. 50 patients also suffered from a comorbid anxiety disorder (PTSD, GAD, Agoraphobia, phobia, OCD, panic disorder, social phobia, anxiety disorder NOS) and 14 patients suffered from other psychiatric illnesses (Anorexia, Bulimia, Eating disorder NOS, Circadian Rhythm Sleep Disorder, Trichotillomania, ADHD and Lewy Body dementia). 17 patients attempted suicide and 45 patients reported ideation but have never displayed aggressive or suicidal behaviour. 7 patients were unemployed or on sick leave before therapy and were able to return to work after treatment. 4 patients had a formal diagnosis of axis II personality disorder diagnosed according to DSM-IV guidelines prior to the study. Furthermore, 11 patients displayed prominent axis II features but did not have a formal diagnosis. 23 patients were in the (Anxious) Cluster C, 17 patients were in the (Dramatic) Cluster B, 6 patients were in the (odd) Cluster A and 9 patients had both Cluster B + C traits. Finally, 54 patients

reported a comorbid axis III medical condition potentially relevant to illness and 68 patients reported a comorbid axis IV psychosocial or environmental problem.

2.3.12 Inter-rater Agreement

Inter-rater reliability was tested on a sample of 52 patients (67%) who were typical of the population. Patients were assessed by three raters (two psychiatrists and a General Practitioner). We found substantial to moderate agreement across all scales (Range: 0.53-0.87) (Viera & Garrett, 2005). The inter-rater coefficient for each behavioral scale is provided in *table 7* below.

*2.3.12.1-**Table 7**. Inter-reliability of depression scales (n=52)**

Scales	***Kappa***
MADRS	0.77
HAM-D17	0.53
QIDS-C16	0.56
CGI-S	0.87
CGI-Global Improvement	0.71

* The inter-rater reliability was moderate to substantial.

2.3.13 Antidepressants solo/combination versus augmentation (adjunct antipsychotics and/or mood stabilizers) group

At T-0, all patients in the augmentation group had moderate to severe depression (MADRS score of 33.5 ± 1.1; HAM-D17 score of 24.9 ± 0.8; QIDS-C16 score of 16.7 ± 0.6 and CGI-S score of 5.3 ± 0.2) in spite of previous antidepressant trials and all patients in the antidepressant group had

mild to moderate depression (MADRS score of 29 ± 2.1; HAM-D17 score of 21.3 ± 1.5; QIDS-C16 score of 14.5 ± 1 and CGI-S score of 4.6 ± 0.3) in spite of previous antidepressant trials (*Table 4*).

Two way-ANOVA revealed a significant effect of time for scores on the MADRS ($F_{1, 152}$=66.1, P<0.001), HAM-D17 ($F_{1, 152}$=59.3, P<0.001), QIDS-C16 ($F_{1, 152}$=59.9, P<0.001) and CGI-S scales ($F_{1, 152}$=56.4, P<0.001) but not of treatment and no time x treatment interaction, meaning that the two treatment groups (both antidepressants and augmentation groups) produced a similar decrease in depressive symptoms (*Table 4; figure 1*).

Two way-ANOVA followed by Newman-Keuls's post-hoc test for multiple comparisons, revealed a significantly higher baseline (T-0) score for the augmentation group vs. the antidepressant group across all scales (MADRS P=0.03; HAM-D17 P=0.02; QIDS-C16 P=0.03; CGI-S P=0.028); while we found no significant difference between treatment groups at study endpoint (T-3) (MADRS P=0.99; HAM-D17 P=0.90; QIDS-C16 P=0.98; CGI-S P=0.63). This means that although patients in the augmentation treatment group were significantly more depressed as compared to patients in the antidepressant group, both groups achieved a similar treatment response or outcome (*Table 4; figure 1; figure 3*).

Finally, we chose to analyze both the ANOVA and the change in score (Δ) to demonstrate superiority of augmentation group in reducing depressive symptomatology vs. antidepressant group since both treatments end at similar T-3 values on all scales yet T-0 is significantly higher in augmentation group compared to the antidepressant group (*Table 4*). Augmentation treatment significantly decreased the Δ change between both groups on the HAM-D17 scale (one way-ANOVA, $F_{1, 76}$=5.01, P=0.028) but not for other scales; although MADRS and QIDS-C16

demonstrated a trend or near significance (P=0.055 and P=0.067 respectively) (*Table 4; figure 3*). Noteworthy, although the Δ change comparing both treatment groups on the HAM-D17 scale was significant, the within factor of the ANOVA was unable to capture this aspect of change (factor A, treatment; $F_{1, 152}$=2.89, p=0.09). This is possibly because delta scores do not account for sphericity assumption meaning that score changes are more liberal than repeated measures as it does not take into account variance of the individual time points.

2.3.14 Antidepressants solo/combination versus adjunct mood stabilizers group versus adjunctive antipsychotics ± mood stabilizers) group.

At T-0, all patients in the adjunct antipsychotics group had moderate to severe depression (MADRS score of 34.4 ± 1.4; HAM-D17 score of 25.7 ± 1; QIDS-C16 score of 17.1 ± 0.7 and CGI-S score of 5.4 ± 0.2) in spite of previous antidepressant trials and all patients in the antidepressant group had mild to moderate depression (MADRS score of 29 ± 2.1; HAM-D17 score of 21.3 ± 1.5; QIDS-C16 score of 14.5 ± 1 and CGI-S score of 4.6 ± 0.3) in spite of previous antidepressant trials. Moreover, baseline scores for all patients in the adjunct mood stabilizer treatment group were also in the moderate to severe depressive range but were less than adjunct antipsychotics and more than the antidepressant group (MADRS score of 31.3 ± 1.7; HAM-D17 score of 22.9 ± 1.1; QIDS-C16 score of 15.8 ± 0.8 and CGI-S score of 4.9 ± 0.26) (*Table 6).*

Two way-ANOVA revealed a significant effect of time for scores on the MADRS ($F_{1, 150}$=79.25, P<0.001), HAM-D17 ($F_{1, 150}$=72.1, P<0.001), QIDS-C16 ($F_{1, 150}$=73.36, P<0.001) and CGI-S scales ($F_{1, 150}$=66.48, P<0.001). Of note, for HAM-D17 and CGI-S scales we found a significant effect of treatment ($F_{2, 150}$=3.05, *P=0.05; and* $F_{2, 150}$=3.59, *P=0.03 respectively*); while we found

no effect of treatment on the MADRS or QIDS-C16 ($F_{2, 150}$=2.16, *P=0.12; and* $F_{2, 150}$=2.11, *P=0.13 respectively*) and no time x treatment interaction for all scales (*Table 6; figure 2*).

Using two way- ANOVA followed by Dunnett's post-hoc test for multiple comparisons, we looked at possible differences between treatments for all scales. We found no significant effect for treatment except on the HAM-D17 (*P*=0.05) and CGI-S (*P*=0.03) scales comparing the antidepressant group versus the adjunct antipsychotics group (*Table 6*).

Furthermore, comparing baseline scores on MADRS, HAM-D17, QIDS-C16 and CGI-S across all groups we found a significantly higher T-0 for the adjunct antipsychotics group (*P*=0.035, *P*=0.02, *P*=0.032 and *P*=0.02 respectively), but not for the mood stabilizer augmentation group (*P*=0.62, *P*=0.63, *P*=0.50, *P*=0.74 respectively) compared to the antidepressant group. Noteworthy, we found no significant differences between treatment groups at study endpoint (data not shown). This means that although patients in the antipsychotic augmentation group were considerably depressed compared to patients in the antidepressant group, all groups- including the mood stabilizer augmentation group- achieved a similar treatment response or outcome (*Table 6; figure 2; figure 4*). In addition, using one way-ANOVA followed by Dunnett's post-hoc test for multiple comparisons, adjunct antipsychotics significantly decreased Δ change on the HAM-D17 scale (*P*=0.05) compared to the antidepressant group, but not for other scales (*Table 6; figure 4*).

2.4 Discussion

2.4.1 Patients Sociodemographic and psychopathological characteristics

The present study compared three pharmacotherapeutic strategies; namely adjunct antipsychotics, adjunct mood stabilizers and antidepressants (TCA's, SSRI's, SNRI's, NDRI's and TeCA etc.) in

patients who have failed to respond to two or more antidepressants in solo or combination in a population of unipolar-TRD patients. The mean age of the study population was 48.5 and 88.4% of patients were ≤ 65 years of age. The ratio of male to female patients identified was approximately 40:60, which is in line with current literature suggesting higher prevalence of depression amongst female patients (Ronald C Kessler et al., 1993). In addition, the incidence of a 1st degree family member suffering from depression was around 64.1%; and the mean age of 1st psychiatric consultation was 36.7 years old. This is important because the literature points towards a common link between early onset depression and positive family history in TRD patients (Klein, Schatzberg, McCullough, Dowling, et al., 1999). Furthermore, multiple studies have reported increased risk of non-remission in MDD in unmarried or individuals living alone (Chou, Ho, & Chi, 2006; Maurizio Fava et al., 2002). In agreement with our sample, 28.2% of the study population lived alone at baseline. Comorbid anxiety disorders were also common, with around 48.7% of patients suffering from GAD and 21.8% suffering from panic attacks. In fact, in two large samples of MDD patients who failed to respond to at least one antidepressant trial, anxious symptoms were associated with higher rates of non-remission in MDD (Russell et al., 2001). Similarly, current or lifetime GAD were considered as predictors of non-response in TRD (Petersen et al., 2001); while in panic disorders it was associated with poor treatment outcome and chronicity (Flint & Rifat, 1997). However, this lack of response could also be related to antidepressant dose or duration of treatment (M. T. Berlim & G. Turecki, 2007b). We also identified 21.8% of patients amongst our study population who had previous history of suicide attempts which may be considered as a predictor of non-response in TRD patients (Sagud et al., 2013). Indeed, patients with comorbid anxiety tend to have greater risk for suicide and more

functional impairment (S. G. Kornstein & Schneider, 2001). Moreover, the literature suggests higher incidence of suicide attempts in patients with treatment resistance (Nelsen & Dunner, 1995).

Interestingly, several patients in our sample reported a pre-existing axis II diagnosis of personality disorder or displayed prominent axis II features. As previously mentioned, given their current depressive state, it is almost impossible to elucidate the existence of an axis II disorder in MDD patients unless a diagnosis was established prior to current episode of depression (Thase, 1996). This is mainly due to overlap of several depressive symptoms with symptoms of personality disorders. For example, borderline personality disorder is characterized by marked difficulties in interpersonal relationships, suicidal or self-harming behaviour, negative thinking and emotional instability; many of which overlap with symptoms experienced by currently depressed patients (Beatson & Rao, 2013). This makes it difficult to determine whether the patient has MDD co-occurring with borderline personality disorder, or whether depressive symptoms are part of the borderline paradigm itself (Beatson & Rao, 2013). In addition, while chronic depression has often been thought to be most frequent in association with borderline personality disorders, it is actually more common in cluster C personality disorders (Points, 2005). Indeed, personality disorders most frequently reported as comorbid with depression are in the anxious-fearful cluster C, followed by the dramatic-unstable cluster B (Keller et al., 1998; S. G. Kornstein & Schneider, 2001). This is important because although we were unable to establish a concrete axis II personality disorder diagnosis for the reasons described earlier, we identified 23 patients in the (Anxious) Cluster C, 17 patients in the (Dramatic) Cluster B and 9 patients displaying both Cluster B + C traits; meaning that 49 (62.8%) of our patient population displayed either cluster B and/or Cluster C traits suggesting the possibility of an underlying axis II personality disorder.

The literature also points towards an association between comorbid axis III pathology and treatment resistance (R. C. Hall et al., 1981). Indeed, the study identified 54 patients with a comorbid axis III medical condition potentially relevant to illness including 20 patients with chronic pain associated disorder or back problems (plantar fasciitis, Fibromyalgia, Herniated disc, Gastroplasty complicated with multiple fistulas, migraines, spinal stenosis, multiple fractures, diverticulitis, shingles, fractures post-car accident), 11 patients with history of cancer or inflammatory/autoimmune conditions (Asthma, arthritis, Lupus, ankylosing spondylitis, Vogt-koyanogi-harada syndrome), 9 patients with neurological conditions (meningioma, TBI, craniostenosis, Lewy body dementia) and 21 patients with Type I or Type II diabetes, dyslipidemia, hypertension and related cardiac disease. As previously mentioned, patients suffering from a serious medical illness in association with depression are more likely to develop treatment resistance due to lower response rate to antidepressant pharmacotherapy (Popkin et al., 1985).

Noteworthy, although not significant, several key differences were noticed when comparing patients receiving antidepressants and patients receiving augmentation therapy (*Table 3*). First, the age of first episode MDD was 35.2 years for the augmentation group compared to 40.9 years for the antidepressant group; while the duration of illness was longer for the augmentation group (12.8 vs. 9.1 years). In addition, the number of failed pharmacotherapies was 4.3 for the augmentation group and 2.7 for the antidepressant group. Similarly, multiple important clinical similarities were found comparing **Group-B** versus **Group-C**, but not between **Group-A** versus **Group-B and/or Group-C** (*Table 5*). First, the current mean age of patients in Group-A was 49.9 years old, while the mean age for Groups-B and C patients was 47 and 46.8 years old respectively. In addition, the

mean age of first episode MDD in Group-A was 40.9 versus 36.6 and 34.7 years of age in Groups-B and C respectively; while the duration of illness was also longer in Groups-B and C patients compared to Group A (10.4 and 13.7 vs. 9.1 respectively). Importantly, the mean number of failed pharmacotherapies in mono or in combination for Groups-B and C patients was 4.6 and 4.3 respectively, while for Group-A, it was 2.7. Taken all together, patients in Groups-B and C are similar in terms of important clinical characteristics, especially, age of first episode MDD, course of illness and number of failed pharmacotherapies. While patients in Group-A, are older and less chronic. In addition, patients in Group-A were not as severely depressed as patients in Group-B or C (*Table 6*) at T-0. Therefore it is safe to assume homogeneity between Groups-B and C in terms of severity of TRD and important clinical predictors, including number of failed pharmacotherapies. Current literature also suggests that early onset/longer duration and higher severity MDD episodes are associated with TRD (M. Balestri et al., 2016). This is important because patients using adjunct antipsychotics had the lowest mean age of first episode MDD as compared to patients using adjunct mood stabilizers or antidepressants and the longest duration of illness while the population of patients receiving adjunct antipsychotics were significantly more depressed at T-0 on the HAM-D17 and CGI-S scales (P=0.02).

2.4.2 Patients Pharmacotherapy

When the sample was divided and analyzed into 3 groups, in **Group-C** *(adjunctive antipsychotics)*, we found 36/41 (87.8%) patients using one of three antipsychotic agents for augmentation. A total of 23 patients received quetiapine, 6 patients received aripiprazole, 2 patients received quetiapine and aripiprazole, and 5 patients received olanzapine for adjunctive therapy. We were also able to

identify 3 patients using risperidone and 2 patients using typical agents off label for augmentation therapy (*Table 2*).

Typical agents exert their effects mainly through DA2 antagonism, while most atypical agents are relatively weak DA2 antagonists (Richard C Shelton & Papakostas, 2008). For this reason, typical agents are associated with high incidence of EPS (Robertson & Trimble, 1982) unlike atypical antipsychotics which do not carry the same risk of EPS, hence the use of atypical agents for non-psychotic depressed adults increased over the past decade from 4.6 % in 2000, to 12.5% in 2010 (Gerhard et al., 2014).

Quetiapine is a 5HT1A receptor agonist and exerts 5HT2A and 5HT7 antagonism which contributes to its overall antidepressant efficacy (Jensen et al., 2008). In two large double-blinded RCTs including over 850 patients suffering from MDD who had their current antidepressant therapy maintained and were randomized to augmentation using either quetiapine-XR 150mg, quetiapine-XR 300mg or placebo, mean MADRS scores were significantly reduced in both augmentation groups (Michael Bauer et al., 2009; El-Khalili et al., 2010). This eventually lead to FDA approval of quetiapine-XR as adjunct treatment to antidepressants in MDD at a dose of 150-300mg (Šagud et al., 2011).

Aripiprazole is unique where unlike most atypical antipsychotics which are weak DA2 antagonists, aripiprazole is a partial DA2 and DA3 agonist with 30% intrinsic dopaminergic activity (Gründer, Carlsson, & Wong, 2003). This helps manage negative affect and poor cognitive function common in chronically depressed patients (T.-Y. Chen & Tzeng, 2013). Indeed, aripiprazole is the first atypical antipsychotic to receive approval by the FDA as an adjunct treatment in unipolar MDD (Nelson et al., 2008). Its efficacy in TRD was demonstrated in three placebo controlled-RCTs

including over 1000 patients using adjunct aripiprazole at doses ranging from 2-20mg after failure of at least two adequate trails of standard antidepressants (Berman et al., 2009; Berman et al., 2007; Marcus et al., 2008).

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 (P. Blier & Szabo, 2005). A recently published meta-analysis including pooled data from five outpatient studies (n=1446) comparing OFC (n=462), fluoxetine (n=342) and olanzapine monotherapy (n=342) found a significant reduction in MADRS scores in the OFC group and the 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®; olanzapine and fluoxetine HCl capsules) (Bobo & Shelton, 2010).

Finally, although studies highlighted the superiority of adjunct risperidone in patients with MDD (Mahmoud et al., 2007), an open label trial (n=386) examining the effect of risperidone vs. placebo in citalopram monotherapy found that risperidone has limited usefulness in severe TRD (Rapaport et al., 2006). That being said, and in light of our results, we are unable to affirm or refute risperidone's efficacy in TRD given the limited number of patients in our sample (n=3).

In **Group-B** *(adjunctive mood stabilizers)*, 5 patients received VPA, 7 patients received lamotrigine, 2 patients received lithium, 1 patient received VPA + lamotrigine and 1 patient received VPA + Topiramate. Noteworthy, in **Group-C** *(adjunctive antipsychotics)*, we also identified 8 patients who received VPA, 2 patients who received lamotrigine, 2 patients who received gabapentin, 1 patient who received VPA + lamotrigine + lithium, 1 patient who received

VPA + gabapentin and 2 patient who received Topiramate. In both **Group-B** and **Group-C**, VPA was the most commonly used mood stabilizer, followed by lamotrigine.

Multiple studies and case reports have been published since the eighties and nineties demonstrating the therapeutic potential of VPA in unipolar depression (L. L. Davis et al., 2000), but no double-blinded studies have been conducted thus far. Indeed, a study including 22 unipolar MDD participants who were enrolled in an 8 week open trial of VPA monotherapy concluded that HAM-D17 scores were reduced by 48.8% by week 4 and the score was 7 ± 4 by week 8 (Lori L Davis et al., 1995). Although the mechanism of action of VPA in unipolar depression is yet to be completely elucidated, its ability to modulate the GABAminergic and glutamatergic systems is already well established (Gabriella Gobbi & Luigi Janiri, 2006). Recently, VPA gained much attention due to its ability to induce epigenetic reprogramming through inhibition of HDAC (Tremolizzo et al., 2002). VPA is able to inhibit HDAC class 1 enzymes (1, 2, 3 and 8) resulting in acylH3K14, which is implicated in epigenetic mechanism of depression (Chiu et al., 2013; Costa-Borges et al., 2010).

Augmentation using lithium was first proposed in 1981 on the basis of a neurochemical rationale (De Montigny et al., 1981) where it was believed that short-term lithium administration in TCA non responders could unveil the sensitization of their 5-HT receptors induced by chronic TCA administration. A recent meta-analysis including all trials up to 2007 using adjunct lithium therapy supported the use of lithium in antidepressant augmentation yet found only modest evidence in favor of its ability to accelerate antidepressant response (Crossley & Bauer, 2007).

The overall efficacy of lamotrigine in TRD remains subject of debate. Indeed, a large multicenter double-blinded placebo-controlled RCT including over 180 patients failed to show significant difference on the MADRS, HAM-D17 or CGI-S scales between lamotrigine and placebo as

augmentation to paroxetine in unipolar depression (Barbee et al., 2011). Interestingly, secondary post hoc analyses were suggestive of efficacy, particularly in those patients who completed the study (completer analysis) and in more severely ill patients (HAM-D17 $\geq$ 25). This suggests that lamotrigine augmentation in a well characterized patient subgroups where TRD is more severe, and patients are able to tolerate treatment for a longer period, may yield a better response. On the downside, this makes it difficult to choose the right patient for this form of augmentation therapy. The literature provides abundant information regarding the efficacy and/or superiority of various mood stabilizers, antidepressants and antipsychotics in TRD. However, to the best of our knowledge, no previous studies were conducted providing a comparison between all three treatment modalities in a population of patients with unipolar-TRD.

In addition, a diagnostic re-evaluation is essential for the proper management of TRD patients. In particular, the potential role of several contributing factors, such as medical and psychiatric comorbidity, needs to be taken into account (Maurizio Fava, 2003). The literature contains information regarding comorbid axis I and associated axis II, III or IV in TRD. However, there are no studies examining clinical features as well as treatment outcomes in the same population of TRD patients. We believe that this is the first study to examine both clinical characteristics and treatment outcomes in one population of TRD patients.

Finally, while analyzing both clinical characteristics and treatment outcomes of all treatment groups, we were able to identify treatment response and appraise the most superior pharmacotherapy in TRD patients. Moreover, we were able to characterize a subpopulation of patients with significantly more severe TRD who were able to benefit from antipsychotic

augmentation as demonstrated by the Δ change on the HAM-D17, and we were able to demonstrate the superiority of antipsychotics over mood stabilizers in this population.

INTERM DISCUSSION

In the previous chapter, we have clearly demonstrated the superiority of antipsychotic augmentation (Group C) in TRD by highlighting the Δ change on the HAM-D17 scale and compared it to other treatment groups (*figure 4*, *Table 6*). We were also able to highlight the severity of TRD at baseline and compare it across treatment groups thereby demonstrating that patients in Group C were significantly more depressed at T-0 compared to patients receiving antidepressant mono or combination therapy in Group A (*figure 2*, *Table 6*). Moreover, we were able to demonstrate key clinical differences between patient populations across treatment groups, where the number of failed pharmacotherapy was 4.3 in the augmentation groups B and C versus 2.7 in the antidepressant group (*Table 3*). In addition, patients in the augmentation groups developed MDD at an earlier age (35.2 vs. 40.9) and had a more chronic course of illness (12.8 vs. 9.1) compared to patients in Group A. This demonstrates homogeneity between groups B and C in terms of severity of TRD and important clinical predictors, importantly, number of failed pharmacotherapies.

During the study, we noticed that several patients in groups B and C achieved substantial clinical improvement using Valproic acid (VPA). Given that current literature focuses exclusively on the use of Lithium in TRD, but not VPA; we decided to better analyze this subgroup of patients and publish the first report about VPA augmentation in TRD. In the next chapter, we will examine the use of VPA as augmentation therapy in 14 patients with TRD using the MADRS, CGI-S and YMRS (to exclude the element of bipolarity) over the course of 6-8 months.

CHAPTER 3 – VALPROATE AUGMENTATION IN A SUBGROUP OF PATIENTS WITH TREATMENT-RESISTANT UNIPOLAR DEPRESSION

3.1 Introduction

TRD remains one of the most important challenges in the treatment of depression. Following the STAR*D project, the largest clinical study on the treatment outcome for depression, only 50% of more than 2800 patients who received an adequate course of citalopram therapy responded - as defined by a 50% reduction in HAM-D17; about 60% of patients entered in the level 2, opted for switch strategies with another antidepressants, and among them 18-25% reached the remission. (Trivedi, Rush, et al., 2006; Wisniewski et al., 2007).

Several strategies with antidepressant switches or combinations (Trivedi, Fava, et al., 2006) as well as with atypical antipsychotics (Nelson & Papakostas, 2009) have been suggested for patients with TRD. Ketamine has been introduced for the management of TRD, but its effects are still conflicting and most importantly, they are short-term (Machado-Vieira, Salvadore, Diazgranados, & Zarate, 2009). More invasive treatment options such as DBS have also been tested in patients suffering with TRD, but the rate of recovery is however around 50% (S. H. Kennedy et al., 2011).

In the late eighties and nineties several case reports and open labeled studies were published demonstrating the therapeutic potential of VPA in unipolar depression, depression with anxiety and depression with atypical features (L. L. Davis et al., 2000), but no double-blinded studies have been so far conducted. The therapeutic potential of VPA in depression has recently gained much attention due to recent research showing the involvement of epigenetic mechanisms in major depression (Sun et al., 2013) and the fact that VPA induces widespread epigenetic reprogramming through the inhibition of histone deacetylases enzyme (HDAC) (Tremolizzo et al., 2002).

Consequently, it may be hypothesized that VPA could be a useful pharmacological intervention mitigating epigenetically induced vulnerability in patient with TRD (H. E. Covington, 3rd et al., 2009). In the present study, we report the effects of VPA in fourteen patients with severe TRD not responding to at least two antidepressant trials and various combinations. VPA was added to antidepressants and patients were followed for 6-8 months.

3.2 Materials and methods

3.2.1 Patients and recruitment

We will also present data from a sub-group of patients (*Table 5)* who were treated off label with VPA. We found fourteen patients aged 19–59 years in which VPA was added as an "off label drug" and were collected from the MDC Register of MUHC, as part of an ongoing study database at McGill University (IRB-13-375-PSY). Participants' diagnoses are once again ascertained by the SCID (First et al., 2002) carried out by skilled professional or by psychiatrists. All participants in this sub-group met DSM-IV criteria for MDD and were currently in a major depressive episode without psychotic features and without hypomanic or manic symptoms (American Psychiatric, 1994).

This specific sub-population of patients had a current major depressive episode lasting more than 2 years; a detailed past history of lack of response to at least two adequate antidepressant combination trials operationally defined using the Antidepressant Treatment History Form (H. A. Sackeim, 2001). None of these 14 patients had a DSM-IV diagnosis of alcohol and/or substance abuse or dependence, serious, unstable medical illness, or uncorrected hypo- or hyperthyroidism within the previous 3 months. Only this group of patients were evaluated before the beginning (T-0) and after 1 month ±1 week (T-1), 4 months ±1 month (T-4) and 7 month ±1 month (T-7) of

VPA adjunct treatment. The socio-demographic characteristics collected for patients in this study are the same as that pertaining to the database socio-demographics mentioned above.

We will present their response to VPA augmentation using the following scales:

1. MADRS (S. A. Montgomery & Asberg, 1979).
2. CGI-S (Guy, 1976).
3. The 11-item YMRS (Young, Biggs, Ziegler, & Meyer, 1978). The YMRS is an 11-item multiple choice diagnostic questionnaire which psychiatrists use to measure the severity of manic episodes in children and young adults (Young et al., 1978). The YMRS was used to exclude symptoms of bipolarity in the group of patients using VPA for augmentation therapy.

The study was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice.

3.2.2 Statistical Analysis

The statistical analysis was conducted using SigmaPlot 13 and SPSS 23. Data are presented as mean ± standard error of the mean (S.E.M.). For the VPA augmentation sub-group one-way analysis of variance for repeated measures (RM-ANOVA) followed by Bonferroni corrected *post hoc* comparisons was used to examine the effects of VPA at the different time points.

3.3 Results

3.3.1 - Table 8. Clinical characteristics and demographics of participants in the VPA augmentation group.

no.	Age	Sex	History of 1st degree relatives	Illness years	Failed pharmacotherapies used alone or in combination	Psychotherapy	Pharmacotherapies combined to VPA	VPA dose (mg/day)	VPA level (mol/L)
1	32	M	Father-Anxiety	9	Sertraline, Quetiapine, Bupropion SR, Venlafaxine	No	Escitalopram 10mg Ariprazole 2mg Alprazolam 0.75mg	625	336
2	45	F	No	20	Clonazepam, Zopiclone, Duloxetine, Fluoxetine, Aripiprazole	Psychodynamic in the past	Venlafaxine XR 50mg Quetiapine 12.5mg Lisdexamfetamine 70mg	375	397
3	40	M	Father-Anxiety Mother-MDD Sister-Anorexia	5	Citalopram + Trazodone	Psychodynamic in the past, CBT during VPA	Amitriptyline 25mg	625	344
4	55	M	Father-MDD	2	Venlafaxine, Paroxetine, Mirtazapine, Bupropion, Olanzapine	No	Duloxetine 60mg Quetiapine 100mg	500	130
5	54	M	Sister-MDD/Suicide attempt	21	Venlafaxine, Bupropion XR, Zopiclone, Citalopram, mirtazapine, Lorazepam, Quetiapine XR.	Psychoanalysis in the past	Duloxetine 30mg Quetiapine 150mg Zopiclone 7.5mg	500	371
6	48	F	Mother-MDD+Alcohol Abuse Sister#1-MDD Sister#2-Alcohol Abuse	7	Duloxetine, Fluoxetine, Bupropion XL, Citalopram, Paroxetine, Escitalopram, Venlafaxine XR, Lithium, Moclobemide, Zopiclone, Clonazepam, Gabapentin, Respiridone, Modafinil, Aripiprazole, Sertraline, Light Therapy	CBT in the past	Clomipramine 75mg Bupropion XL 150mg Gabapentin 300mg Zopiclone 7.5mg	625	441
7	52	F	Father-MDD Sister-MDD	35	Reboxetine, Citalopram, Mirtazapine, Paroxetine, Fluoxetine, Moclobemide, Amitriptyline	CBT and Psychodynamic in the past	Reboxetine 8mg Citalopram 10mg Quetiapine 25mg	1000	454

8	27	M	No	10	Bupropion SR, Quetiapine, Carbamazepine, Olanzapine, Venlafaxine, Methylphenidate, Oxazepam, Respiridol, Gabapentin	No	Bupropion SR 150mg Clonazepam 0.5mg Olanzapine 5mg	750	408
9	52	F	No	47	Bupropion, Venlafaxine XR, Olanzapine, Quetiapine, Fluoxetine, Tegaserod	No	Venlafaxine XR 150mg Mirtazapine 30mg	750	272
10	59	F	Father-Alcohol Abuse	20	Venlafaxine, Respiridone, Citalopram	CBT during VPA	Citalopram 60mg Zopiclone 15mg	1000	492
11	46	F	Father-Alcohol Abuse Mother-MDD Sister#1-MDD Sister#2-Cocaine Brother-Alcohol	38	Paroxetine, Lithium, Alprazolam, Clonazepam, Venlafaxine	Psychodynamic In the past	Olanzapine 5mg Citalopram 60mg Lorazepam 1mg	500	Not available
12	19	M	No	2	Quetiapine , Citalopram	No	Quetiapine 100mg Citalopram 20mg	500	300
13	36	F	Father-Bipolar, Suicide attempt. Brother-Substance ab	7	Venlafaxine, Lithium, Lamotrigine, Alprazolam, Quetiapine, Topiramate, Ariprazole	CBT during VPA	Duloxetine 60mg Alprazolam 0.5mg	625	432
14	22	M	Father-MDD	2	Lithium, Atomoxetine, Citalopram, Quetiapine, Clonazepam, Sativex 2 puffs twice daily	No	Lamotrigine150mg Duloxetine 60mg Amitriptyline 25mg Alprazolam 1.5mg	500	281

M: Male. F: Female. CBT: Cognitive Behavioral Therapy. MDD: major depression disorder VPA: Valproic acid.

3.3.2 Figure 5. Treatment outcome of participants in the VPA augmentation group

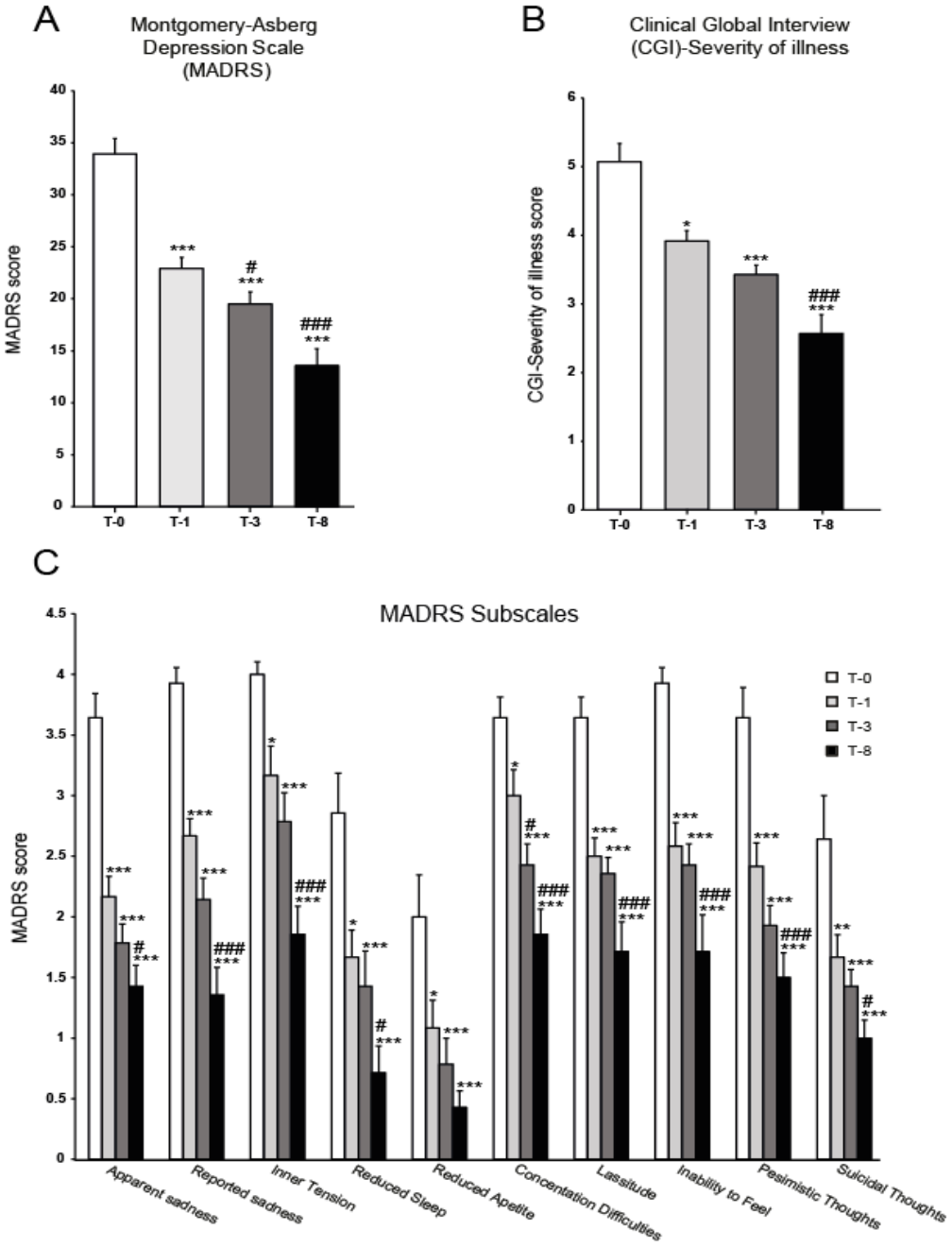

Figure 5. Effects of VPA on MADRS and CGI-S scales. (A) Total MADRS score. (B) CGI-S score. (C) MADRS subscale score. Data are expressed as mean ± SEM; * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$ when compared to T-0; # $P \leq 0.05$, ## $P \leq 0.01$ and ### $P \leq 0.001$ when compared to T-1; one-way ANOVA for repeated measures followed by Bonferroni post-hoc test for multiple comparisons. MADRS, Montgomery–Asberg Depression Rating Scale; CGI, Clinical Global Impression Scale.

3.3.3 Socio-demographic and clinical characteristics of the VPA study group

The demographic and clinical characteristics of the study population using VPA for augmentation are reported in *Table 5*. The mean (SD) age of this sub-population was 42 (12.88) years. The group included 7 male and 7 female patients all of which were Caucasian. All patients received a diagnosis of Major Depressive Disorder and recurrent episodes of depression of moderate to severe intensity following the DSM-IV criteria. None of the patients were current alcohol or substance abusers, four were past alcohol abusers, four were social drinkers, six reported not drinking, one patient abused cocaine and three patients abused cannabis prior to the study and one patient used to abuse cannabis and mushrooms throughout his teenage years and is currently 54 years old *(Table 1)*. Three patients attempted suicide, one at age 19, one at age 58 and one tried to commit suicide 7 times within a 10 year time frame. All other patients have reported ideation but have never displayed aggressive or suicidal behaviour. Five patients were on sick leave before therapy and were able to return to work after treatment.

3.3.3.1-Valproate regimen and plasmatic levels

Patients received a regimen of VPA ranging between 375 and 1000 mg/day, and the mean plasmatic level of VPA was 358±98 □mol/L (mean± standard deviation). Four participants were slightly under the therapeutic plasmatic concentration recommended for epileptic and bipolar patients.

3.3.3.2-MADRS Total score

Before starting VPA treatment, patients had moderate to severe depression (MADRS score of 33.9 ± 1.5) in spite of previous antidepressant trials. As shown in Figure 3A, VPA significantly decreased total MADRS score (one way RM-ANOVA, $F_{3,36}$=74, $P < 0.001$) at T-1 (23.5±1.0; *P*

< 0.001), T-4 (18.6±1.3; *P*<0.001) and T-7 (13.6±1.6; *P*<0.001) compared to T-0 (33.9±1.5), with a large effect size (partial η^2=0.86). Moreover, MADRS score was significantly lower comparing T-1 to T-4 (*P*<0.001) and to T-7 (*P*<0.001), and T4- to T-7 (*P*=0.008), implying that longevity of treatment provides a better outcome. None of the patients relapsed during the observational period. Importantly, MADRS mean score at T-7 was closer to the reported value of remission (MADRS<10).

3.3.3.3-MADRS sub-items

The mean average for each item of the MADRS is reported in Figure 3C. VPA significantly reduced all MADRS items when comparing T-0 to T-4 (*P*<0.001) and to T-7 (*P*<0.001). However, MADRS items were already significantly reduced at T-1 (*P*<0.05) with the exception of reduced sleep and reduced appetite.

3.3.3.4-CGI-Severity of illness

As illustrated in Figure 3B, VPA significantly reduced CGI-S score ($F_{3, 36}$=33.9, *P*<0.001; partial η^2=0.74). Post-hoc Bonferroni procedure showed that CGI-S score at T-1 (4.0±0.1), T-4 (3.3±0.2) and T-7 (2.6±0.3) was significantly lower than at T-0 (5.1±0.3) (*P*=0.03, *P*<0.001 and *P*<0.001 respectively).

3.3.3.5-YMRS: Bipolarity

No sign of mania/hypomania were observed at any assessment point during the study. The mean value of the YMRS was 1.6±0.6 at T-0, 0.9±0.4 at T-1, 0.4±0.3 at T-4 and 0±0 at T-7. Considering that remission of mania/hypomania occurs at a YMRS score of ≤12, we exclude the possibility of a miss diagnosis and the element of bipolarity (Data not shown).

3.4 Discussion

The present pilot study showed that VPA is a valid promising treatment for severe TRD patients, producing a significant clinical improvement after one month of treatment and more importantly, bringing severely ill patients close to remission after seven months, without relapse. Although the sample size was relatively small, the observed large effect sizes highlight the clinical relevance of VPA treatment in the decrease of depressive symptoms in TRD patients.

One study previously conducted in 33 patients with recurrent MDD and no history of hypomanic or manic disorders (L. L. Davis et al., 1996) reported that monotherapy with VPA decreased HAM-D17 scores by 48.8% in 4 weeks; unfortunately, this research was not followed by any large double-blinded study.

The exact mechanism of action of VPA in depression is still unknown, but its efficacy is very likely due to its effects on the glutamate system, in particular on NMDA/AMPA receptors (G. Gobbi & L. Janiri, 2006) which are involved in depression, or to its epigenetic effects including the induction of a dose-related brain histone H3 hyperacetylation (Tremolizzo et al., 2002), or the capacity to alter DNA methylation steady-state (Milutinovic, D'Alessio, Detich, & Szyf, 2006).
This study paves the way for the hypothesis that a subgroup of TRD patients should be treated in a similar way than bipolar spectrum patients. For example, DSM-5 (Page-149) recognizes that depressed patients with a familiarity for bipolar disorders should be considered and treated as Bipolar type V (Thase, 2006) even if they don't show any symptoms of hypomania or mania. Our patients had a family history of mental disease, a long history of major depression and non-response to antidepressants *(see Table 1)*, but no history of maniac or hypomanic episodes, and

thus they likely should be classified as part of the bipolar spectrum and treated with the association of antidepressants and mood stabilizers. Notably, several clinical trials have indeed indicated that the combination of mood stabilizers such as lithium (M. Bauer & Dopfmer, 1999) or lamotrigine (Schindler & Anghelescu, 2007) with antidepressants is an effective treatment for TRD.

Despite these open questions, our results suggest that further studies deserve to be undertaken to examine and validate VPA as add-on treatment for patients non-responding to antidepressants. In addition, more psychopathological and biological researches are needed to better classify this sub-type of patients responding to VPA.

CHAPTER 4 - GENERAL DISCUSSION

In this work, for the first time, we studied a selective population of TRD. We successfully replicated several socio-demographic and psychopathological features already reported in current literature regarding TRD, namely increased prevalence in female patients, early onset depression, positive family history, increased prevalence in individuals living alone, higher rates of comorbid anxiety disorders, higher rates of suicide attempts, increased prevalence of a pre-existing axis II diagnosis and higher prevalence of associated axis III and axis IV comorbidities (S. G. Kornstein & Schneider, 2001).

We were also able to identify a sub-population of severe and chronic TRD patients who responded well to augmentation using antipsychotics and/or mood-stabilizers reaching a HAM-D17 score of 14.5±0.8 after 3 months. Importantly, patients receiving augmentation in our sub-population not only responded to pharmacotherapy, but they also remained stable and well maintained over a period of 30-90 days (mean duration of therapy = 68.5 days). Furthermore, we were also able to demonstrate the clinical relevance of VPA treatment in decreasing depressive symptoms in TRD patients; where VPA augmentation resulted in significant clinical improvement after one month, and patients were close to remission after seven months without relapse. In this sub-population, we were also able to highlight prevalence of family history of mental disease, severity and chronicity of depression as well as high number of unsuccessful pharmacotherapies used in mono or combination prior to VPA augmentation. Although clinical improvement was only noticed after addition of VPA, it is also worth noting that 8 (57.1%) patients were using an antipsychotic agent adjunct to VPA therapy.

As previously noted, the study retrieved data on depression scales without randomization and patients received treatment as usual. An important confounder to be considered is potential placebo-effect which may contribute to misrepresentation of some of our results (Shapiro & Morris, 1978). This is particularly important for the VPA study sample, given its limited size (n=14). However, the chronicity and morbidity of our TRD patient sample in general, and the severity of treatment resistance in the patient population receiving VPA should be noted considering that placebo-effect is less likely to influence the outcome in patient populations with severe psychopathology or treatment resistance (A John Rush, 2000). In addition, the inter-rater agreement was substantial to moderate across all scales (Range: 0.53-0.87) (Viera & Garrett, 2005).

The population of patients using augmentation (antipsychotic and/or mood stabilizers) in our sample had an early mean age of first MDD episode (35.2yrs) compared to patients treated with antidepressants (40.9yrs) and a longer duration of illness (12.8yrs vs. 9.1yrs). Indeed, most recent literature suggests that early onset/longer duration of MDD are associated with higher severity of MDD episodes and TRD (M. Balestri et al., 2016). This provides as added evidence that patients receiving augmentation therapy in our study had a very severe and chronic profile of treatment resistance. Finally, the mean number of failed pharmacotherapies for this population was 4.3 trials in mono or in combination versus 2.7 for patients treated with antidepressants. Our results demonstrate that early identification of MDD patients at high risk for treatment resistance using psychopathological features; such as early age of onset, comorbid anxiety disorder, associated axis II, III or IV, could guide clinicians in selecting optimal setting and intensity of care. Indeed, individuals with high TRD risk could benefit from an early and more aggressive treatment. Our

results suggest that first line of therapy for severe TRD patients should include adjunct atypical agents; and adjunct VPA should also be considered.

In contrast, a Cochrane review published in 2012 including 28 placebo controlled clinical trial and over 8000 participants using one of five atypical agents; amisulpride, aripiprazole, olanzapine, quetiapine and risperidone as mono or add-on therapy concluded that only quetiapine was beneficial in mono or combination when compared to placebo, amisulpride was not effective in depression and only limited evidence supported additional benefit of risperidone, olanzapine and aripiprazole in combination with antidepressants (Komossa, Depping, Gaudchau, Kissling, & Leucht, 2012). Furthermore, the review found that treatment with antipsychotic medication was generally associated with worse tolerability when compared to antidepressants, mainly due to sedation (quetiapine), weight gain (aripiprazole, olanzapine, risperidone), EPS (aripiprazole) or increase in levels of prolactin (olanzapine, risperidone). In addition, according to data from the U.S. National Ambulatory Medical Care Survey, atypical antipsychotics were less likely to be prescribed in patients older than 65 years of age (adjusted OR 0.51 vs. ages 18-44years), and patients who were receiving psychotherapy (adjusted OR 0.68) due to their AE profile (Gerhard et al., 2014). A recent study demonstrated that only 10 % of Canadian clinicians opted for augmentation mostly using bupropion and lithium in TRD (Mischoulon et al., 2000) neither of which are atypical antipsychotics.

The results obtained from our TRD population showed better tolerability of atypical antipsychotics. A possible explanation for this is lower doses of atypical agents used in our study. In addition, patients in our samples demonstrated good compliance to treatment due to strict follow

up and care. Furthermore, we identified 9 (11.5%) patients in our study sample who were 65 years of age or older. 4 patients within this age group responded to augmentation therapy using antipsychotics ± mood stabilizers at subnormal doses. This demands for further investigation regarding the use of atypical agents in older patients at a lower dose in large double blinded RCTs targeting geriatric depressed patients belonging to the TRD paradigm. The dosage of atypical agents should be individualized and their safety and efficacy should be frequently reassessed to provide the highest benefit and least adversity for patients (Wright et al., 2013).

Finally, patients in the augmentation group receiving antipsychotics and/or mood stabilizers had a significantly higher TRD profile as noted by MADRS, HAM-D17, QIDS-C16 and CGI-S scores at baseline *(Table 4; figure 1)*, and shared common psychopathological features documented in bipolar patients; including early age of onset, positive family history, higher rates of substance abuse, suicide attempts and high incidence of comorbid axis I or anxiety disorders *(Table 3)* (Kauer-Sant Anna et al., 2007; Perlis, Brown, Baker, & Nierenberg, 2006; Pini et al., 1999). Overlapping comorbid features and subtle differences in presentation between bipolar and unipolar depression were reported in previous studies (Perlis et al., 2006); while other studies called for reevaluation of DSM criteria and even support the inclusion of sub-threshold bipolar disorder in the diagnostic classification of MDD (Angst et al., 2010). Similarly, patients in the augmentation group receiving antipsychotics and/or mood stabilizers responded well to therapy and experienced a significant reduction in depressive symptomatology as noted by the overall Δ change on the HAM-D17 scale *(Table 4; figure 3)* comparing both treatment groups (augmentation vs. antidepressant only groups) and remained stable for 30-90 days. This treatment is similar to that of patients with bipolar disorder (Gao, Gajwani, Elhaj, & Calabrese, 2005; Hirschfeld, 2002; Maj,

Tortorella, & Bartoli, 2000). Given this psychopathological resemblance and pharmacotherapeutic efficacy of augmentation therapy using atypical antipsychotics and/or mood stabilizers in severe TRD and bipolar disorders, our study opens the question if severe TRD patients should be classified and treated in the context of bipolar spectrum rather than unipolar depression. Our study indeed highlights that augmentation strategy using atypical antipsychotics and/or mood stabilizers should be considered as first line management of severe TRD since this pharmacotherapeutic approach would reduce depressive fluctuations commonly observed in TRD (Vergunst et al., 2013) and results in a superior clinical outcome compared to conventional antidepressant pharmacotherapy. Further ongoing studies in our laboratory are tailored to address these questions regarding TRD management through long-term longitudinal research and bigger sample.

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