Cognitive Behavioral Analysis System of Psychotherapy for treatment-resistant depression: Adaptation to a group modality

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Very little is known about treatment-resistant depression and studies researching this increasing clinical reality are quite new to the field (Rush, Thase, & Dube, 2003a). The World Health Organization (Greden, 2001) has predicted that unipolar depression alone will be the second most important contributor to disability by the year 2020 worldwide. The epidemiology of treatment-resistant depression however is not well known and varies according to the population studied (primary care, general population or secondary care), and most of all, according to the definition used.

Numerous patients (up to 15%) remain very depressed, even after multiple interventions with aggressive pharmacological and psychotherapeutic treatments (Berlim & Turecki, 2007a). Only about 20% to 40% of patients receiving their first treatment for a major depressive episode are expected to achieve a relatively asymptomatic state (Sackeim, 2001). Even then, there is often a lag until a full recovery of social and occupational functioning is achieved (Sackeim, 2001). Other authors report a 50% response (i.e. have a > or equal 50% reduction in baseline symptom severity) rate for outpatients with nonpsychotic major depressive disorder (MDD) initially treated with either a time-limited depression-targeted psychotherapy or a single antidepressant medication (Rush et al., 2004). Another 20% to 40% of patients in a major depressive episode (unipolar or bipolar) do not show substantial clinical improvement to the first treatment with antidepressant medication, with improvement defined as at least a 50% reduction in symptom scores (Sackeim, 2001), or they respond but have residual symptoms, therefore do not remit (Rush et al., 2004). About half of the patients who show symptom reduction have significant residual symptoms that are associated with continued functional disability and a worse prognosis (Fava, Ruini, & Belaise, 2007; Rush et al., 2004).

It is common to find that patients who respond with or without remission can continue to experience residual attenuated depressive symptoms and even symptoms not usually considered among the core symptoms of depression. These may include irritability, problems with depressive thinking, and problems with functioning socially at work (Fava et al., 2007). Some residual attenuated depressive symptoms may include insomnia, fatigue, anxiety, excessive reactivity to social stress and mild dysphoria. Patients may take time before

resuming an interest or motivation for pleasurable activities and feel that they have to “push themselves to do things”.

According to Nierenberg et al., (2001), no standard definition of nonresponse exists across studies. It can be defined as failing to achieve a minimal partial response of <25% decrease from baseline scores, or failing to achieve a response <50% decrease from baseline, or at the far end is the criterion of failing to achieve remission, that is a <7 score on the HAM-D. Defining nonresponse according to the first two categories includes patients who respond but have substantial residual symptoms or patients who don’t remit. This is a problem when the treatment goals include a return to “normal” functioning as the standard.

Failure of remission is the threshold used to define treatment failure, according to the National Institute of Mental Health. There is increasing evidence that remission is most often achieved with a combination of drug therapy as well as psychotherapy for the more severe cases of chronic depression (Nierenberg & DeCecco, 2001).

Definition of treatment-resistant and chronic depression

The World Psychiatric Association made one of the earliest definitions of resistant depression as ‘an absence of clinical response to treatment with a tricyclic antidepressant at a minimum dose of 150mg/day of imipramine (or equivalent drug) for 4 to 6 weeks’ (World Psychiatric Association, 1974) (Stimpson, Agrawal, & Lewis, 2002). This definition has been the one most often used in studies on treatment-resistant depression.

With increasing consensus in the literature, the following definition of treatment-resistant depression is suggested:

- **An individual’s failure to respond to two adequate trials of medication with different classes of antidepressant medication, with treatment response recorded prospectively, not retrospectively (McPherson et al., 2005).**
- **Treatment-resistant depression also applies when relapse/recurrence occurs while patients continue to adhere to the same medication regimen that produced response or remission (Sackeim, 2001).**

It is not known yet whether this definition identifies a group of patients that are clinically different from those with chronic depression, dysthymia or ‘pseudo-resistant’ depression (which refers to the under treatment of depression) (McPherson et al., 2005). Berlim and Turecki (2007a) suggest that treatment resistant depression (TRD) be considered along a continuum ranging from partial

response to complete treatment resistance and that depression subtypes also be considered in the evaluation and management of TRD.

Most studies in the literature refer to this difficult-to-treat population as being chronically depressed rather than treatment resistant. Chronic depression usually includes a major depressive disorder of at least two years' duration; dysthymic disorder ("pure" dysthymia); double depression, which is a major depression superimposed on dysthymia; and recurrent major depression with residual symptoms between episodes (Keller, Shapiro, Lavori, & Wolfe, 1982) or MDD in incomplete remission (Michalak & Lam, 2002). According to the NIMH Collaborative Depressive Study, about 20% of patients with major depressive disorder will develop a chronic course of the illness (Keller et al., 1984). Patients with recurrent depression are also at risk of developing a more chronic picture with each new episode of depression (Keller & Boland, 1998). Keller found that patients who have suffered from a chronic depression for many years often have not received adequate treatment. The category of treatment resistance requires that adequate treatment has been given but without success (Rush et al., 2003a).

Another characteristic of the more chronic patients is their slower response to medication. Keller et al. (1998) found that patients might respond up to 28 weeks after the acute phase of the illness. Thase (1997) makes an interesting distinction saying that while treatment-resistant patients have become chronically depressed after several trials have failed, most chronically depressed people are not treatment resistant. This is primarily due to the inadequacy of the pharmacotherapy.

A poor understanding of chronic depression as well as misdiagnosis and under treatment may contribute to treatment resistance (Berlim & Turecki, 2007b). In addition, co-morbid psychiatric conditions on axis I or II are also important to consider in the diagnostic profile (Kornstein & Schneider, 2001).

McCullough (2000) stresses the distinction between early-onset (depression before the age of 21) and late-onset patients (depression at or after the age of 21) that has been proposed by Akiskal et al (Akiskal, King, Rosenthal, Robinson, & Scott-Strauss, 1981; Akiskal et al., 1980). This distinction was substantiated by evidence that the majority (72%) of patients with dysthymic disorder have an early onset. These patients also have an earlier onset of major depressive disorder with a longer index of a major depressive episode, which suggests a more severe condition (Klein et al., 1999). McCullough describes the early-onset depressives as having experienced early childhood maltreatment or trauma. These patients respond more effectively to psychotherapy (CBASP) with or without medication, while late-onset patients without childhood maltreatment responded more to combination treatment (medication and CBASP) (Nemeroff et al., 2003).

Depressed patients with co-morbid anxiety are more severely depressed and are found to be at a greater risk for suicide and more functional impairment (Kornstein & Schneider, 2001; Sonawalla & Fava, 2001; Thase, 1997; Thase, Friedman, & Howland, 2001).

Depressive patients with personality disorders are less responsive to antidepressant medication (Kornstein & Schneider, 2001) and have a lower proficiency in learning a specific skill taught in the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) Manber et al. (2003) than patients without personality disorders. Early-onset depressives also have higher rates of depressive personality traits and disorder than late-onset depressives and had co-morbid personality disorders (Klein et al., 1999; Klein, Taylor, Dickstein, & Harding, 1988).

McCullough (2000) suggests that chronically depressed individuals have a primitive cognitive functioning that resembles the preoperational level of functioning found in children aged 2 to 7. That is, chronically depressed patients use global and pre-logical thinking; their thought processes are unaffected by the logical reasoning and reality-based views of others and are not amenable to critical-analytic cognitive techniques; they tend to be primarily egocentric in their views of self and others; their verbal communication is usually a monologue; authentic interpersonal empathy is difficult; there is poor emotional regulation under stress.

In addition, these patients most often perceive that the causal influences in their life are beyond their personal control. They have a poor ability to use a problem-focused coping style and problems are described in a global way, resulting in feelings of hopelessness and helplessness. These patients see their depression as going on forever and as affecting their life in a pervasive and global way, which contribute to feelings of hopelessness. They have maladaptive interpersonal styles often playing out a “victim lifestyle” when interacting with others. These patients often adopt a submissive style of interacting that makes it difficult for the therapist not to assume a more dominant role (J. P. McCullough, 2000).

McCullough (2000) observes that preoperational thinking dominates the interpersonal-social sphere of the chronically depressed person, while maturational impairment may not be observed in non-social areas of the person’s life such as work. This is why his treatment model targets the interpersonal-social sphere of functioning as the problematic area for both early and late onset chronic depressives.

McCullough’s description appears to be confirmed by findings that treatment-resistant, depressed patients tend to give very global descriptions of their psychosocial functioning, when asked by the clinician “how have you been feeling?” (they respond: “terrible”) In addition, they assign a lower rating to their

global functioning, but more varying ratings to specific areas of their psychosocial functioning (Petersen et al., 2004).

Cognitive Behavioral Analysis System of Psychotherapy (CBASP) for chronic depression

Cognitive Behavioral Analysis System of Psychotherapy, developed by James McCullough Jr., Ph.D. (2006; 2000), is the only psychotherapy model developed specifically to treat the chronically depressed patient. This model is based on contemporary learning theory with its primary goal being: (1) to connect the patient perceptually to others (the environment) so that others can begin to inform / influence the behaviour of the patient in positive ways – CBASP is based on a Person X Environment Causal Determinant Model of Behavior; (2) to acquire stimulus learning (through the therapeutic and other more adaptive relationships) and response learning (acquire more adaptive coping behaviours to reduce interpersonal avoidance and increase positive reinforcements) (J.P. McCullough, Jr., 2008). With regards to relapse prevention, McCullough insists that unless patients keep practicing the new learning, then the old pathological learning, in addition to the extinction of the new learning will greatly increase the risks of relapse or recurrence a depressive episode.

This highly structured, skills-oriented and interpersonal approach teaches concrete skills to help patients overcome their interpersonal problems and is a focused approach aimed at achieving tangible and attainable goals (J.P. McCullough, Jr., 2006). Keller et al. (2000) mounted a long-term, multi-site clinical trial showing the best-yet response rates for chronic depression when CBASP and pharmacotherapy are combined.

Keller et al (2000) report the first findings of this long-term multi-center study in which they compared the efficacy of nefazodone alone, the cognitive behavioural analysis system of psychotherapy (CBASP) alone or the combination of the two in the treatment of chronic major depression. The sample consisted of 681 adult patients randomized to the three conditions. Outpatients from 12 academic centers who received a diagnosis of chronic major depressive disorder (at least 2 years' duration), a current major depressive disorder superimposed on a pre-existing dysthymic disorder, or a recurrent major depressive disorder with incomplete remission between episodes in a patient with a current major depressive disorder (lasting at least two continuous years), were included in the study. Several other exclusion criteria were also specified. Severity of depression was determined by a score of more than 20 on the 24-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1967). The score on the HRSD was the primary outcome measure. Remission was defined as an HRSD score of no more than 8 at weeks 10 and 12 at completion or at time of withdrawal from the study. A satisfactory therapeutic response was defined as a reduction in the HRSD score by at least 50 percent from baseline to weeks 10 and 12, with a total

score of 15 or less at these times (but a HRSD greater than 8 at weeks 10 and/or 12).

The analyses of the rates of improvement in HRSD scores as a regression slope were significantly larger for patients in the combined-treatment group than the rate of improvement in scores for patients in the nefazodone group ($P<0.001$). The overall rate of response was significantly higher in the combined-treatment group than in the nefazodone or in the psychotherapy groups in both the modified intention-to-treat sample and the group of patients who completed the study ($P<0.001$ for all comparisons).The overall rates of response for the entire sample, at the last follow-up visit, were 73% for the combined-treatment group and 48% for each of the other monotherapies. Among the patients who completed the 12 weeks of treatment, the overall rates of response were 85% in the combined-treatment group, 55% of patients in the nefazodone group and 52% of patients in the psychotherapy group. In both samples (modified intention-to-treat and completers) of patients, significantly ($P<0.001$ for all comparisons) more patients had a remission in the combined treatment group than in the other two monotherapy groups. Among those who completed the study, remission rates were 24% for the psychotherapy group, 22% for the nefazodone group and 42% for the combined-treatment group.

There were no significant differences at endpoint in the effect sizes for the final HRSD scores, between the nefazodone group and the psychotherapy group, calculated for both samples. The combined-treatment scores were significantly higher than either psychotherapy alone or nefazodone alone ($P<0.001$ for all comparisons) (M. B. Keller et al., 2000).

The second phase of this study involved crossing over the nonresponders in each of the monotherapy conditions for a 12-week trial of the other monotherapy. This was the first prospective controlled trial evidence to examine switching from nefazodone therapy to psychotherapy (CBASP), or switching from CBASP to nefazodone therapy following completion with nonresponse to a 12-week trial of the alternative treatment (Schatzberg et al., 2005). Results suggest that a switch strategy for nonresponders is beneficial for chronically depressed patients whether it is from CBASP to nefazodone or vice versa. Although 50% of patients who completed the crossover treatment improved, only about 1 in 4 patients achieved full remission and still had significant residual symptoms at the end of the crossover phase. Unfortunately, residual symptoms put the patient at a high risk of relapse and recurrence for depression (Reesal & Lam, 2001). This risk is even greater than the well-known risk for relapse associated with having had 3 or more previous depressive episodes (Keller, 2003).

Thase et al. (2001) recommend that treatment duration be from 4 to 6 months for treatment-resistant depression or until the symptoms have remitted. They suggest that the frequency of sessions be at least biweekly until the patient has achieved a 50% reduction in symptom severity and weekly sessions afterwards.

Continuation or Maintenance therapy is also recommended for 6 to 9 months after the reduction of symptoms, particularly for patients who still have residual symptoms.

The third phase of the same study using the sample described by Keller et al, involves a 16-week continuation phase of the treatment (total of 6 session), with the same intervention that was responded to, for patients in each of the three acute treatment conditions with remission or a partial response and for responders in the two crossover conditions (Kocsis et al., 2003). This study is the first to report on continuation phase psychotherapy for chronic forms of major depressive disorders.

The results for the group of patients who entered continuation phase treatment directly after the 12 weeks of acute-phase treatment were analysed separately from the group who entered continuation after the cross-over phase of treatment. This is because the length of treatment is different for the two groups as well as the type of treatment received. Results show that 73% of patients in full remission at entry into the continuation phase maintained their remission at endpoint with only 6.5% experiencing an MDD relapse. More than half (53%) of patients entering continuation with a partial remission, ended in full remission. There is also confirmation for a lower rate of deterioration for the combined treatment group by the end of the continuation phase. Overall, more than 85% of patients who responded partially or with remission to an acute phase of treatment maintained that response by the end of continuation. The use of combined treatment is clearly superior to monotherapies in preventing relapse in patients with chronic forms of MDD.

Patients who maintained their response through the continuation phase were directed to either the pharmacotherapy or the psychotherapy (CBASP) arm of the maintenance phase (phase four), according to which treatment they had responded to in the continuation phase (Klein et al., 2004).

Patients, who were randomized to continue CBASP as opposed to assessment only (no treatment given), received the 52-week maintenance phase, at the rate of 1 session every 4 weeks, for a total of 13 sessions of CBASP. Results show that compared to the assessment only condition, patients in the maintenance CBASP condition had a 3 to 10 time lower rate of recurrence. The CBASP and assessment only conditions differed significantly on the direction of change of depressive symptoms. Patients receiving assessment only experienced a small increase in symptoms over time, while patients receiving CBASP showed a small reduction in symptoms over time.

Klein et al (2004) suggest that the benefits of maintenance CBASP go beyond preventing recurrence and seem to contribute to continued reduction of sub threshold symptoms for patients with chronic forms of major depressive disorders. Continuation and maintenance therapy with antidepressant medication

beyond six months after recovery has been shown to prevent relapse, particularly for patients who have had multiple recurrences, and is now accepted as the standard of care (Keller, 2003). This study was the first to examine the efficacy of maintenance psychotherapy for chronic forms of major depression and the first using an approach other than Interpersonal Psychotherapy (Klein et al., 2004).

The same long-term multicenter study described earlier (M. B. Keller et al., 2000) examined whether changes in psychosocial functioning occur independent of documented changes in depressive symptoms, and whether combined treatment is superior to monotherapy once the relationship between psychosocial functioning and depressive symptoms has been controlled statistically. Additional aims were also to compare improvement rates in depressive symptoms relative to psychosocial / work functioning for the three treatments (Hirschfeld et al., 2002). McPherson et al. (2005) found that none of the treatment-resistance studies they reviewed used outcome measures of the patients' functioning, disability or quality of life.

This study demonstrated for the first time that improvements in psychosocial functioning are greater for the combined nefazodone and CBASP treatment group than for either monotherapy groups alone. According to the authors, the results suggest that combined treatment may have an independent effect on psychosocial functioning above and beyond its effects on depressive symptoms. They speculate that medication seems to work on improving depressive symptoms, which in turn improves psychosocial functioning. However, improvements in depressive symptoms have less influence over changes in psychosocial functioning for CBASP, suggesting, according to the authors, that this therapy has a direct effect on psychosocial functioning through the social skills learned. Even at the endpoint assessment, the study group remained one standard deviation worse than the community norm for overall social functioning.

For all three groups, psychosocial functioning improved more slowly than for depressive symptoms at the end of the 12-week acute phase treatment period. This finding, in addition to the remaining psychosocial impairment in the sample compared to a nondepressed community sample, confirm other findings of persisting psychosocial impairments and hence a worse prognosis in about half of the patients, even after symptomatic improvements (Rush et al., 2004). Sackeim (2001) also reports a lag until a full recovery of social and occupational functioning is achieved after symptomatic relief.

Manber et al (2003) demonstrated that the subsample of participants (N-431), from the large multi-center depression study (M. B. Keller et al., 2000), who received CBASP alone or in combination with nefazodone, also benefited from learning the main skill taught in psychotherapy independently of medication. In fact, all patients who responded to treatment learned the social skill taught better than non-responders. Furthermore, there is evidence that both the therapeutic alliance and the ability to perform the skill learned in psychotherapy made unique

and additive contributions to promoting change and improvement in depressive symptoms (Santiago et al., 2005).

Although CBASP has demonstrated effectiveness in treating chronic depression (Keller et al., 2000), strong early results have been tempered by more recent results (Kocsis et al., 2009b) in which it was found that neither CBASP nor Supportive Psychotherapy was more effective than medication alone for chronically depressed treatment resistant patients. The lack of positive findings in that study were hypothesized to be related to the small number of CBASP sessions (*M* = 12.5) and the effect of an aspect of the study design which focused on pharmacological switching and augmentation that may have had a negative impact on participants' interest in and expectation of, psychotherapy. Kocsis et al. (2009a) reported elsewhere significantly higher remission rates for patients with MDD who received their preferred treatment, psychotherapy or medication monotherapy, rather than the alternate combination treatment (nefazodone and CBASP). Remission rates were even higher for those who preferred and received psychotherapy (CBASP) as a monotherapy than for those who received a combination of CBASP and nefazodone treatment. CBASP has been used more recently to treat chronically depressed pregnant smokers and was found to be more effective than standard treatment at increasing abstinence and decreasing depressive symptoms 6 months post-treatment. Indeed, CBASP was more effective in women with higher levels of baseline depressive symptoms (Cinciripini et al., 2010).

CBASP has been shown to be effective when used in individual therapy. It is very pertinent to ask whether CBASP can be equally effective in a group therapy modality for chronically depressed patients. Treating chronically depressed patients in group therapy would have the added benefit of being cost-effective and of providing an interpersonal context in which patients can practice some social skills and face some previously avoided interpersonal situations.

Group therapy for chronic depression

Very few studies have been published using a group approach to treat chronic or treatment-resistant depression and none using CBASP with a comparison group. A meta-analysis of 48 studies evaluating the effectiveness of group psychotherapy for adults with unipolar, non-psychotic depression revealed that 93.5% of studies demonstrated that group psychotherapy significantly decreases depressive symptoms following treatment (McDermut, Miller, & Brown, 2001). The authors point out that these findings cannot be generalized to severe depression since the data collected was on moderate depression.

Harley et al. (2008) examined the effectiveness of a 16-week Dialectic behaviour therapy-based skills training group for adult outpatients with treatment resistant depressive symptoms, compared to a waiting-list control group. Treatment

resistance was defined as patients with major depressive disorder who were symptomatic at baseline despite stable, adequate doses of antidepressant medication. Results revealed that participants in the skills training group improved significantly more than the waiting-list control group, although they still had mild levels of depressive symptoms. The authors suggest that a second skills cycle be given to consolidate and generalize the learning acquired.

Swan et al. (2004) reported on an uncontrolled group case series, which evaluated the effectiveness of the Coping With Depression course by Lewinson et al. (1984) with moderate to severely depressed adult outpatients who had not responded to initial treatment. Although the authors report that a structured clinical assessment was not used to determine the diagnosis, results reveal significant symptomatic improvement for those who completed the treatment with sustained rates of remission and changes in self-reported quality of life.

Bristow and Bright (1995) compared five patients suffering from depression of more than one year's duration, given group cognitive therapy for depression, to a wait-list control group with similar characteristics and size. The treatment group was followed for one year. Result showed that the treatment group improved markedly in depressive symptoms, over the control group, at the end of the group and maintained this improvement at one-year follow-up. However, the hopelessness and irritability measures were not sustained as well at the one-year follow-up.

Oei and Dingle (2008) carried out a review of 34 papers with the goal of evaluating the effectiveness of Group Cognitive Behavioral Therapy (GCBT) as an intervention for unipolar depressive disorders. They assessed GCBT versus controls and GCBT versus other treatment interventions. Contrary to other previous meta-analyses, which were done on studies using a single outcome, usually a measure of mood symptoms, this study included measures of mood, cognitions, behaviours and general health. Of the 34 studies reviewed, 13 included a no-treatment control condition and 21 studies did not include a control condition. The majority of the studies used the Beck Depression Inventory (BDI) or the Hamilton Depression Rating Scale (HAM-D) to measure mood. In comparison with other treatment modalities, GCBT yielded larger effect sizes (ES) than many other group modalities and some individual treatment modalities. No differences in ES were found between individual and group CBT. The results also revealed that studies in which only mood was measured, produced greater ES than studies in which behavioural or cognitive outcomes were measured. The authors propose as an explanation: "it is difficult to obtain effect sizes in behaviours or dysfunctional attitudes of the same magnitude as symptom improvement, at least during the treatment phase".

The findings in this study suggest that an adaptive level of social functioning, which is a measure of relapse prevention, may be more difficult to attain during the course of treatment, particularly when this treatment (GCBT) is not designed

to deal with interpersonal difficulties but rather with cognitive and behavioural restructuring. This may provide support for the present study, which aims to assess CBASP, a treatment which focuses on social functioning.

Saulsman, Coall and Nathan (2006) examined the effect of depressive personality traits on treatment outcome after a standardized group cognitive-behavioural treatment for unipolar depression. They compared two groups with high or low depressive personality scores using the Millon Clinical Multiaxial Inventory – III; MCMI-III, (Millon, 1994) at intake, post-treatment and at one-month follow-up. Depressive symptomatology was the primary measure of treatment outcome. In addition, anxiety symptomatology, dysfunctional cognitions and quality of life were also measured at outcome. The MINI PLUS, a structured interview for Axis I diagnosis, was used to include patients with a primary diagnosis of major depressive disorder. Results revealed that the rate of improvement between the two groups did not differ and both groups maintained this gain at one-month follow-up. Patients improved on all measures from pre to post treatment, according to the authors, with the high depressive group generally showing poorer scores and more residual symptoms than the low depressive group. The authors also report that depressive personality did not contribute any predictive value regarding treatment outcome for depression. The authors also found that depressive personality was not correlated with severity of depression at the end of treatment and not correlated with treatment gain. The authors conclude that those with a depressive personality and a more severe symptomatology require longer time in treatment to reach the same end-state functioning as patients without a depressive personality. This study provides more evidence that group psychotherapy can be beneficial for severely depressed patients. It is however also evident that social functioning is rarely assessed as an outcome measure of improvement after group psychotherapy for major depression.

Proposed study

The primary objective of this study is to evaluate the effectiveness of a CBASP approach adapted to group therapy for treatment-resistant, depressed, psychiatric outpatients. CBASP has been shown to be an effective treatment for chronic depression using an individual treatment modality but has not yet been tested using a group modality with a comparison group, for treatment-resistant major depression.

A secondary objective is to assess whether Group-CBASP also improves the psychosocial functioning and decreases the social isolation and avoidance of these patients and helps them develop more adaptive social skills, which becomes a protective factor against relapse into depression.

The comparison group is a behavioural activation therapy group, which will carry out the same behavioural activation exercises also used in the CBASP group.

The aim is to show that CBASP is superior to behavioural activation alone in helping chronically depressed patients break their social isolation and reintegrate back into their community.

Hypotheses:

The group undergoing therapy using a CBASP approach is expected to show a greater improvement in psychosocial integration, as indicated by increased social functioning, decreased social avoidance or emotional coping as the primary coping strategies, and a greater relief from the depressive symptomatology, than the comparison group. This is considered to be the generalization of treatment effects to the patient's life outside of therapy and is essential for remission, as indicated in the literature review. The level of satisfaction with the group modality is also assessed.

A second hypothesis states that the CBASP group is expected to improve in their level of "perceived functionality", which reveals the acquisition-learning that has taken place in therapy on the patients' part. "Perceived functionality" is defined by McCullough (2000) as "a general cognitive set in which an individual perceives that his/her behaviour has specific consequences in the environment". This will be assessed using the therapist-rated Patient Performance Rating Form (J. P. McCullough, 2000), which assesses the ability to self-administer a Situational Analysis.

A third hypothesis predicts that the experimental and comparison groups will be equivalent with regard to the degree of behavioural activation that has been attained by the end of therapy. Although an improved level of behavioural activation is beneficial, it is not sufficient to improve psychosocial functioning or to prevent relapse in chronic depression if psychosocial functioning is not also improved, as described by the CBASP model.

The characteristics of patients who respond well to CBASP will be examined to provide a better understanding of the new application of this approach.

Methodology:

Patient selection:

Participants for this study will be recruited through the Depressive Disorders Program (DDP) at the Douglas Mental Health University Institute (DMHUI) in Montreal, Quebec, Canada. This specialized outpatient clinic serves adults aged 18 to 65 suffering from MDD, and is responsible for servicing a catchment area of more than 500,000 individuals.

The patients included in this study will have a diagnosis of treatment resistant major depression (TRD), unipolar, as a primary diagnosis (according to DSM-IV-

TR), as defined by two adequate trials of antidepressants that have failed, as well as a score of at least 32 or more, at baseline, on the Inventory of Depressive Symptomatology (IDS-C, clinician rated) and a score of at least 18 or more on the Hamilton Rating scale for Depression-21. These patients will undergo a comprehensive psychiatric evaluation before admission to the Depressive Disorders Program of the DMHUI, which includes structured and semi-structured interviews for Axis I and II diagnoses, Hamilton interviews for depression and anxiety, interviews for suicidal ideation, behaviours and intent, and for levels of aggressivity. In addition, there are self-report questionnaires to be completed at intake into the program.

The primary diagnosis of major depressive disorder may be accompanied by an additional co-morbid diagnosis on axis one or two; however, the following diagnostic criteria comprise exclusion criteria for participation in the study: bipolar disorders, cyclothymic disorder, psychosis, a primary diagnosis for any anxiety disorder, schizophrenia, substance abuse disorder as a primary diagnosis, eating disorder as a primary diagnosis. Patients with a debilitating medical diagnosis will also be excluded, as the depression may be secondary to this physical condition. Patients who are at high risk for suicide, as defined by a score greater than or equal to 6 on the Suicide Ideation Scale, will be excluded. This constitutes a high-risk group who need a different form of intervention at that time. Patients who come to treatment under the influence of substances, who are noncompliant to the medical treatment, or who are engaged in disruptive acting-out behaviours (including missing sessions regularly, self-destructive behaviours, aggressive physical or verbal outbursts in therapy or outside, and those with secondary gains from being ill), will not be included in the study as they are not considered to be ready to work on their interpersonal difficulties. All patients in both groups receive the same pharmacological treatment. This involves routine clinical management appointments examining the symptomatology and tolerance of medication and the use of standard antidepressants.

Procedure:

Patients will be randomly assigned to either treatment or comparison group after the psychiatric intake and admission to the study. All patients will have two individual sessions to complete preliminary information required for participation in each group. Each of the two groups will run for 20 sessions of two-hour duration each week. Both CBASP and Behavioral Activation (B.A.) groups will use a manualized treatment. A certified CBASP senior psychologist will run the CBASP group with a graduate student in psychology, trained in using the CBASP model, as a co-therapist. A senior psychologist will run the behavioural activation group, also with a graduate student in psychology as co-therapist.

The group leader will be blind to the assignment of cases to each group and will conduct behavioural activation similarly in each group for the first three group

sessions. Then, the group leader will be informed as to which group to carry on CBASP with and which to continue with B.A.

CBASP is a model based on contemporary learning theory as described earlier (J.P. McCullough, Jr., 2008). The group-CBASP manual has been developed at the Depressive Disorders Program of the Douglas Mental Health University Institute, using the basic learning paradigm of the model and has been approved by Dr. McCullough and his team. The group-CBASP model is comprised of two modules. The first module introduces the behavioural activation program along with an activity calendar and graded task assignments (the same B.A. program is used in the two therapy groups). The second module introduces the CBASP model, which uses the Interpersonal Circumplex to demonstrate how complementary interpersonal behaviours result in satisfactory exchanges and how interpersonal motives and goals drive our interpersonal interactions. The Situational Analysis (SA) is used to teach participants to take note of the consequences of their interpersonal behaviours. Social skills are also practiced during the SA with participants carrying out role plays together.

The Behavioral Activation manual to be used is the one developed by Lejuez, Hopko DR and Hopko SD (C. W. Lejuez, Hopko, & Hopko, 2001; C. W. Lejuez, Hopko, D.R., LePage, J.P.,Hopko, S.D., McNeil, D.W., 2001). This therapeutic model is based on behavioural principles, which examine the mechanisms of behavioural change. The goal of this treatment is to gradually increase the frequency of targeted healthy behaviour by increasing the relative value of such behaviour. This model uses the theory of the Matching Law applied to depression, stating that the relative frequency of depressed behaviour, compared to non-depressed behaviour (that is all other types of behaviours), is proportional to the relative value of reinforcement obtained for depressed behaviour compared to non-depressed behaviour (C. W. Lejuez et al., 2001). The initial stage of treatment consists in assessing the function of depressed behaviour. That is, is the depressed behaviour maintained by (a) an absence of reinforcement for non-depressed behaviour, (b) reinforcement for depressed behaviour, or (c) some combination of the two? This model was chosen because it is relatively simple to use and is reasonable to add onto the already extensive CBASP protocol for group therapy.

Statistical analyses:

Repeated-measures analysis of variance will be used to compare the base-line demographic and clinical characteristics of the sample with the data obtained at the start of the group, at mid-point, at the end of the group and at a 6-month follow-up. No further data will be collected from patients who withdraw from treatment.

Remission from depressive symptoms is defined as a score of 11 or less on the Inventory of Depressed Symptomatology (IDS-C, clinician rated) and of 8 or less

on the HAM-D-21 at week 20, for those who completed all group sessions or at drop-out for those who only attended one mid-point assessment. A satisfactory therapeutic response for depressive symptoms is defined as a reduction in the IDS-C and HAM-D scores by at least 50 percent from baseline to week 20. Patients in either the remission or the response categories will be combined to constitute the response group and all other patients will be considered to have had no response regarding depressive symptoms.

For patients who will have attended at least half of the total amount of sessions and then drop out at least after the mid-point assessment, this data will be carried forward and used as an end of treatment assessment. Therefore, patients who are randomized but who do not attend at least one assessment period after this will not be included in the analyses.

The Keller et al. (2000) long-term multi-center study (N=681) comparing the efficacy of Nefazodone alone, CBASP alone or the combination of the two, in the treatment of chronic depression using an individual mode of therapy, was used to determine the sample size for this study. The response rate for the Nefazodone group and for the Nefazodone and CBASP group were 48% and 73%, respectively, using the Hamilton Rating Scale for Depression-24. Using an alpha of .05 and a power of 80%, a sample size of 27 patients for each group was found to be necessary in order to obtain a difference of 25% between the two groups as was found in the Keller et al. study.

Assessment measures:

Patients will be assessed before group begins, half way through the group (week 10), at the end of treatment (week 20) and at a 6-month follow-up with the following instruments.

Scales used to assess depressive symptomatology include the Inventory of Depressive Symptomatology (IDS clinician rated and self-report) (Trivedi et al., 2004) and the Hamilton Rating Scale for Depression –21 items (Hamilton, 1960).

The Inventory of Depressive Symptomatology:
The Inventory of Depressive Symptomatology is a 30-item, clinician-rated and self-rated forms designed to assess the severity of depressive symptoms. The IDS assesses all the criterion symptom domains of the DSMIV to diagnose a major depressive episode. The IDS also includes commonly associated symptoms such as anxiety and irritability and items relevant to melancholic or atypical symptom features. Items on the ICD-C (clinician-rated) and ICD-SR (self-report) rate identical symptoms with equivalent anchors.

Criterion validity was demonstrated with Pearson product moment correlations of 0.95 between the IDS-C and the Hamilton Rating Scale for Depression ($HRSD_{17}$)

and 0.88 between the IDS-SR and the $HRSD_{17}$. The correlation coefficient between the IDS-C and the IDS-SR was 0.91. The correlation between the BDI_{21} and the IDS-C was 0.86, while it was 0.93 between the BDI_{21} and the IDS-SR (Rush, Gullion, Basco, Jarrett, & Trivedi, 1996).

The IDS has been used to distinguish response from remission (Trivedi et al., 2004). The IDS assessments have demonstrated sensitivity and specificity as good as or better than the HRSD (Rush et al. 1996, 2000, 2003b), the BDI (Rush et al., 1996) and other scales.

With regards to internal consistency, Cronbach's alpha was 0.94 for both the IDS-C and IDS-SR for a complete sample of adult outpatients and normal controls (n=456, Rush et al., 1996), and 0.67 and 0.77 for the IDS-C and IDS-SR, respectively, for the sample of MDD patients (n=338). Trivedi et al. (2004) found alpha coefficients of 0.90 and 0.92 for the IDS-C and IDS-SR, respectively, for a sample of MDD patients (n=544).

Hamilton Rating Scale for Depression:
The Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) measures the severity of depressive symptoms in patients with a primary depressive illness. The HAM-D is perhaps the most commonly used, clinician-rated depressive symptom rating scale, which allows an estimate of symptom severity before treatment and may help assess the effectiveness of treatment or the presence of a relapse or recurrence of the illness. The 17-item scale is ranked on a scale from 0-4 or 0-2. Internal consistency was found to be 0.76 in a study of 140 subjects (Rehm & O'Hara, 1985) and 0.92 in a study of more than 300 patients and 0.89 in a study of 582 outpatients with MDD (Rush et al., 2006). The test-retest reliability was .96 with about a one-week interval (Reynolds & Kobak, 1995). The validity of the scale has also been demonstrated with correlations with global measures of depressive severity ranging between 0.65 and 0.90 (Rehm & O'Hara, 1985).

Social Adjustment Scale – Self-report:
The Social Adjustment Scale – Self-report (SAS-SR) (Weissman, 1999) is a 54-item self-report questionnaire which assesses instrumental and expressive role performance over the past two weeks. Six major areas of functioning are covered: work, either as paid worker, unpaid homemaker, or student; social and leisure activities; relationships with extended family; role as a marital partner; parental role; and role within the family unit, including perceptions about economic functioning. Four categories are covered within each area: (1) performance at expected tasks; (2) the amount of friction with people; (3) finer aspects of interpersonal relations; and (4) feelings and satisfaction. The SAS-SR contains skip-out questions that may not be relevant to a respondent. Each question is rated on a 5-point scale with higher scores indicating more impairment. A mean for each role is obtained as well as an overall adjustment score.

The SAS-SR has good test-retest coefficients over a period of two weeks (mean r=.78). A mean internal consistency of .74 has been demonstrated. There is also evidence of the scale's validity in a study comparing the Overall Adjustment score obtained from the patient, an informant and the clinician-rated interview. Significant correlations between patients' and interviewer ratings (r=.70, p<.01), between informant and interviewer ratings (r=.54, p<.05) and between patient and informant ratings (r=.74, p<.01) were found (Weissman & Bothwell, 1976). Discriminant validity has also been demonstrated showing that the SAS-SR discriminates between a sample of nonpatients, depressed, schizophrenics and alcoholic samples. The depressed sample demonstrates the most impairment in Overall Adjustment and in role-area performance scores. Furthermore, patient means were significantly higher than non-patient means on the Overall Adjustment Score (p<.001).

Inventory of Interpersonal Problems (IIP):

The IIP (Horowitz, Alden, Wiggins, & Pincus, 2000) is a 64-item self-report instrument that identifies a person's most salient interpersonal difficulties. A brief version containing 32 items (IIP-32) has been developed and is used in this study. This short version was based on a stratified community sample. This version preserves the scale structure of the 64-item version and retains the four items of each scale with the highest item-total correlations.

The internal consistency for the IIP-32 scale is high with reliability coefficients ranging from .68 to .93. Good test-retest reliabilities which compare to the ones obtained for the longer 64-item scale. Correlations between the scale scores of the IIP-64 and IIP-32 range from .88 to .98 and are all significant, suggesting that the IIP-32 scales, particularly the total score, are a good estimate of the IIP-64 scores.

The Coping Inventory for Stressful Situations:

The Coping Inventory for Stressful Situations (CISS) (Endler, 1999) is a 48-item, self-report questionnaire using a 5-point Likert-type rating scale ranging from (1) "not at all" to (5) "very much". This multidimensional assessment of coping with stressful situations is comprised of three coping dimensions: Task, Emotion and Avoidance-oriented coping strategies. There are two subscales for the Avoidance-Oriented scale: Distraction and Social Diversion.

The adult CISS form contains information about percentile scores and standard scores for all raw scores. These scores are presented for both non-psychiatric and psychiatric normative groups on the form.

High alpha reliability coefficients for internal consistency for the psychiatric normative group range from .69 to .91 and for the non-psychiatric group range from .72 to .90. Test-retest reliabilities were moderate to high for the Task and Emotion scales (.68 to .73) and moderate for the Avoidance scale (.51 to .60).

The 48 items were factor analyzed using a principle component analysis with varimax rotation (separately for each sample). The 3-factor solution obtained included Task-Oriented coping, Emotion-Oriented coping and Avoidance-Oriented coping. In addition, separate factor analyses for each subscale revealed one factor only for each of the Task and Emotion scales and two factors for the Avoidance scale, including Distraction and Social Diversion coping.

Good construct validity was found when comparing the CISS with the Ways of Coping Questionnaire (WCQ) (S. Folkman & Lazarus, 1985; S. Folkman, Lazarus, R.S., 1988), in the directions predicted.

Circumplex Scales of Interpersonal Values and Efficacy

The Circumplex scale of Interpersonal Values (CSIV) (K. D. Locke, 2000) is a 64-item self-report measure of the value or preferences that individuals place on certain interpersonal outcomes or modes of conduct associated with each octant of the Interpersonal Circumplex. Respondents are asked to rate (on a scale from 1 to 4) the importance of various interpersonal outcomes or modes of conduct. The scale demonstrates very good internal consistency for the eight scales of the circumplex, with a Cronbach's alpha ranging from .76 to .86. Also, the intercorrelations of the eight CSIV scales reveal the expected positive correlations between adjacent octants and high negative correlations between polar opposite octants. Overall, the pattern of correlations showed a circular ordering with no reversals. The CSIV shows good convergence with a measure of adaptive interpersonal traits, the Bem Sex Role Inventory (Bem, 1974), and with a measure of maladaptive interpersonal traits, the Inventory of Interpersonal Problems-Circumplex (IIP-C) (Alden, Wiggins, & Pincus, 1990) as well as with a measure of implicit interpersonal motives, the Thematic Apperception Test (TAT) (Atkinson, 1958) and explicit interpersonal motives, the Interpersonal Goals Inventory (IGI) (Dryer & Horowitz, 1997).

The Circumplex Scales of Interpersonal Efficacy (CSIE) (K. D. Locke, Sadler, P., 2007) is a 32-item self-report measure of individuals' confidence in their ability to perform interpersonal behaviours successfully associated with each of the 8 octants of the Interpersonal Circumplex (such as giving orders or following orders). Respondents rate on a scale from 0 to 10 how confident or sure they are that they can do certain specific behaviors. Higher scores indicate greater self-efficacy. The scales of the CSIE have been shown to have internal consistency (Cronbach alphas ranging from .66 to .83 for each of the 8 scales), they conform to a circumpplex structure and show good convergent validity with the scales of the IIP and CSIV.

There is evidence supporting the findings that both self-efficacy and values, as described above, have shared variance regarding the prediction of interpersonal behaviour, although self-efficacy alone explains unique variance in interpersonal behaviour that is not explained by values (K. D. Locke, Sadler, P., 2007). Locke and Sadler explain that this follows Bandura's (1997) hypotheses that "people will

not attempt a behaviour if they do not believe that they can complete it successfully".

Perceived Stress Scale

The Perceived Stress Scale (PSS) (S. Cohen, Kamarck, & Mermelstein, 1983) is originally a 14-item scale designed to measure the degree to which situations in one's life are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable and overloaded respondents find their lives. The authors present the scale as being one which assesses a state that places people at risk of developing a psychiatric disorder, rather than being a measure of psychological symptomatology. The 10-item version of this scale is used in the present study as it was found to be equal, if not slightly better, than the 14-item version as far as psychometric quality. The PSS does not tie appraisal to particular situations but is sensitive to ongoing life circumstances and to stress resulting from events occurring in the lives of friends and relatives as well as to expectations concerning future events.

The alpha coefficient of reliability for the 10-item scale is .85. In spite of a high correlation between the PSS and a measure of depressive symptomatology, the PSS independently predicts physical, psychological symptoms and utilization of health services and it is a better predictor of these than a life-events scale. All 10 items of the shorter version have a positive loading (.42 or above) on the first factor which regroups items with a negative wording (eg. been upset, unable to control things, felt nervous and stressed). After a principle components analysis of this scale, the total explained variance was at 48.9% for both factors combined, with an internal reliability coefficient of .78 (S. Cohen, Williamson, G.M., 1988).

The Client Satisfaction Questionnaire:

The Client Satisfaction Questionnaire (Larsen, Attkisson, Hargreaves, & Nguyen, 1979) is an 8-item questionnaire which measures the patients' general satisfaction with services. The questionnaire has been adapted to the group setting in order to assess general satisfaction with group therapy. The alpha coefficient of reliability for this scale is .93, revealing a high degree of internal consistency.

In addition, a scale measuring the patients' perception of the treatment received at the clinic (Perreault et al., 2010) was also administered as an indicator of the patients' satisfaction with their present situation regarding their symptoms. Patients rate on a 4-point rating scale, ranging from "worse than before" to "much better than before", the extent to which they perceive improvement in 20 areas of their life, since the beginning of group therapy. In a study with 232 participants in a methadone maintenance program, a factor analysis of this scale generated three main factors, accounting for 60.1% of the variance, including emotional health, social relations and physical health (Perreault et al. 2010). The internal consistency for the overall scale .91 and Alpha coefficients for the three

subscales were .91 for “emotional health”, .79 for “social relations”, and .79 for “physical health”.

LIFE-RIFT:

The LIFE-RIFT (Leon et al., 1999) is a brief semi-structured interview which is designed to assess functional impairment. It is derived from the Longitudinal Interval Follow-up Evaluation (LIFE) (Keller et al., 1987) and tested with a sample of subjects who were treated for Major Depressive Disorder. The LIFE-RIFT can be administered by either trained clinical or lay interviewers and takes no more than 5 minutes to administer. Each item assesses the level of functioning in four areas: work, interpersonal relations, recreation and global satisfaction. The score ranges from high level role functioning to severely impaired role functioning. The total score is a sum of the four items.

The scale has good construct validity and concurrent validity using the Global Assessment Scale (GAS) (Endicott, Spitzer, Fleiss, & Cohen, 1976) as a comparison. The inter-rater reliability from a mixed-effect linear regression model was 0.94, using ratings on 24 subjects with two raters. The results of the longitudinal study provide empirical support for the reliability and validity of the LIFE-RIFT. The four items comprising the scale are highly correlated and the factor analyses indicate that they are all measures of one construct, namely functional impairment.

The Patient Performance Rating Scale (PPRF):

The Patient Performance Rating Scale (J. P. McCullough, 2000), used to measure the ability to perform the Situational Analyses at each of the five steps involved, is a 5-item scale that will be scored by the treating therapist and by an independent rater, in order to obtain inter-rater agreement. The inter-rater agreement of the PPRF was found to be 0.62, in a sample of 162 therapy sessions of 162 participants in a multi-center study (J. P. McCullough, 2000), between the site supervisor and the site therapist. The correlation coefficient was 0.65 for inter-rater agreement between the study coordinator and the site supervisor. McCullough suggests that this scale can be scored reliably.

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