Psychological Characteristics and Treatment of Chronic Depression

Wiersma, J.E.

2011

8

Summary and General Discussion

Introduction

Chronic depression is among the most common psychiatric conditions seen in clinical settings, with up to 47% of outpatients meeting criteria for chronic depression.[1] Chronicity of depression is associated with increased comorbidity, greater service use, higher rates of suicidality, and poorer psychosocial functioning.[1-3] Chronic depression is difficult to treat, and misdiagnosis and undertreatment are common. A better understanding of the factors underlying chronicity and more knowlegde about optimal treatment approaches for chronic depression may help to improve the classification and treatment of chronic depression.

The aims of this thesis were, first, to examine several potentially important characteristics of chronic depression, such as developmental (e.g. childhood life events, childhood trauma) and psychological (e.g. neuroticism, extraversion, locus of control) characteristics. Second, to investigate the effectiveness of Cognitive Behavioral Analysis System of Psychotherapy (CBASP), a psychotherapy model that specifically focuses on these (pathological) developmental and psychological characteristics of chronically depressed patients. Finally, we wanted to explore whether a relatively new and promising line of treatment for depression, Internet-based Computerized Cognitive Behavioral Therapy (CCBT), can also be beneficial for patients with more chronic forms of depression.

Following our aims, we examined the importance of childhood trauma and psychological characteristics for chronicity of depression in large and representative samples. Subsequently, we conducted a randomized controlled trial comparing CBASP with Care as Usual (CAU) in 3 mental health care organizations. Finally, we investigated the prevalence and predictive value of chronicity of depression in patients treated with CCBT.

In this final chapter the findings from the previous chapters will be summarized and discussed. In addition, some notes will be given on methodological considerations relevant for this thesis and the possible implications for clinical practice will be portrayed. This chapter finishes with a few suggestions for future research and an overall conclusion.

Main findings

In chapter 2 we found that a reported history of childhood trauma is associated with a significant increased risk of chronicity of depression in adults with a MDD diagnosis in the past year. Emotional neglect, psychological abuse, physical abuse, and sexual abuse were all significantly associated with chronicity of depression, whereas a reported history of objective childhood life events such as parental loss, divorce of parents, and separation were not. There was a dose-response relationship between the frequency of childhood trauma and chronicity of depression. Subjects with the highest scores on the childhood trauma index (score 7-8) had a three-fold increase in chronicity of depression compared to those with no childhood trauma (score 0). A high score on the childhood trauma index was also associated with a significanty higher prevalence of comorbid anxiety, more severe depression and an earlier onset of the first depressive episode. However, after controlling for these characteristics, we found that the association between a high score on the childhood trauma index and chronicity of depression persisted. Consequently, even after considering that childhood trauma was also associated with comorbid anxiety, earlier age of onset and a more severe depression, childhood trauma was an independent determinant of chronicity of depression.

In chapter 3 we found that in depressed persons, chronicity is associated with higher levels of neuroticism, hopelessness, aggression, risk aversion, rumination, and external locus of control and lower levels of extraversion, agreeableness, and conscientiousness. No differences were found for openness to experience, acceptance and perfectionism. When testing these variables multivariably, the associations between extraversion, rumination and external locus of control with chronicity of depression remained significant and were not due to underlying differences between chronically depressed persons and non-chronically depressed persons in severity of depressive symptoms, age of onset, comorbidity with anxiety disorders, medical illnesses, and treatment status (use of antidepressants and/or receiving therapy/counselling).

In chapter 4 the treatment protocol of Cognitive Behavioral Analysis System of Psychotherapy (CBASP) was described. CBASP focuses on the pathological characteristics of the chronically depressed patient, such as extreme interpersonal fear and avoidance and an external locus of control, which often stem from a developmental history filled with psychological insults and trauma.[4] In CBASP, beside the regular behavioral, cognitive and interpersonal techniques, specific techniques are used to replace the interpersonal fear of the chronic patient with interpersonal safety, starting within the therapeutic relationship. Subsequently, the relationship with the therapist is used as a tool to help patients to become more aware of their impact on others and to distinguish between adaptive and maladaptive relationships. Finally, the patient learns how to assert him or herself and how to interact in a functional way, creating a more internal locus of control.[4, 5]

In a large study (N=681), the efficacy of CBASP for chronic depression was established.[6] In order to examine the effectiveness of CBASP, we designed a multisite randomized controlled trial, in which CBASP was compared to Care As Usual (CAU) in 3 mental health care organizations in the Netherlands (chapter 5). The results described in chapter 6 showed no significant main effect between the two groups on the IDS (t = -1.10, *P*= .27), however, there was a significant treatment X time interaction (t = -2.51, *P*= .01), indicating that patients assigned to CBASP had a greater reduction of depressive symptoms towards the end of the trial compared to patients assigned to CAU. Moreover, CBASP completers were more likely to respond (CBASP: 45.8% versus CAU: 15.4%, *P*=.001) and to remit (CBASP: 27.1% versus CAU:

7.7%, *P* =.01) and less likely to fulfill DSM-IV criteria for major depression compared to CAU completers (CBASP: 25.5% versus CAU: 65.3%, *P* <.001) at week 52.

Finally, in chapter 7 we examined the prevalence and predictive value of chronicity of depression in a relatively new and promising line of treatment for depression, Internet-based Computerized Cognitive Behavioral Therapy (CCBT). Our findings indicate that the majority of patients that applied for CCBT reported previous mental health treatment (82%) and suffered from chronic symptoms of depression (72%). In addition, we found that chronicity of depression did not predict treatment outcome. Moreover, regarding reliable change (pre- to post-treatment), patients with chronic symptoms of depression benefited as much from CCBT as patients without chronic symptoms of depression (64.6% vs 70.0%, *P*=.59). However, regarding full recovery, patients with chronic symptoms of depression did not benefit as much from CCBT as patients without chronic symptoms of depression (22.8% vs 53.3%, *P* =.002).

Possible explanations of these findings

Our findings in chapter 2 that childhood trauma can be seen as a potential risk factor for a chronic course of depression, but childhood life events not, are in line with the findings of prior studies on the role of childhood trauma[7-12] and childhood life events [13-16] in chronicity of depression. Our results support the assumption that the most important factor is not the life event per se, but rather the quality of the childhood home environment.[17] Dose-response relationships between childhood trauma and chronic depression have also been reported by Bifulco and colleagues.[7] The greater the number of childhood trauma the individual reported, the higher the probability of lifetime chronic or recurrent depression.

Our findings in chapter 3 suggest that extraversion, rumination and external locus of control, but not neuroticism, are differentiating psychological characteristics for chronicity of depression. This finding is new since prior studies on chronicity of depression and neuroticism[18,19] did not consider other psychological characteristics such as rumination and locus of control in their models, which might explain why they did find neuroticism to differentiate between chronic- and nonchronic depression and we did not. Instead of a differentiating characteristic, we propose that neuroticism is rather a distal vulnerability factor for chronic depression[20-23], with external locus of control and rumination serving as mediating mechanisms. Rumination has been conceptualized as a cognitive and behavioral expression of neuroticism [24] and prior studies have found that rumination mediates the association between neuroticism and depression.[25,26] External locus of control might consolidate this mediation: it is suggested that the stronger the belief that fate controls the outcomes of personal events, the greater the stimulation of worry and guilt, and the deeper the depression that is manifested.[27,28]

Our findings in chapter 6 showed that the added effect of CBASP over CAU became evident after the acute treatment phase ended suggesting that the added effects of CBASP over the other 3 commonly used treatments for depression took time to emerge. This could be due to its explicit focus on the pathological characteristics of chronically depressed patients, such as extreme interpersonal fear and avoidance, and their developmental history, often filled with trauma (69% of our sample reported experiences of childhood trauma). Since chronic patients, more often than not, disclose a lifelong history of interpersonal fear and avoidance, changing these patterns takes time.[4,5] Furthermore, it has been found before that the patients treated with CBASP kept improving during the maintenance phase of treatment.[29] It is therefore tempting to speculate that acute phase CBASP has long-term effects that persist when treatment becomes less intensive or even terminates.

Our findings in chapter 7 indicate that the majority of patients that applied for CCBT reported previous mental health treatment (82%) and suffered from chronic symptoms of depression (72%). Convenience (no need to travel, less time consuming and no costs) was the main reason why patients had applied for CCBT. Privacy and anonymity were also important reasons. Furthermore, they reported that face-to-face treatment did not help, was too confronting or was not available. In addition, our findings showed that these patients can benefit from CCBT. Learmonth and Rai[30] found similar results in their (pilot) study on CCBT for anxiety and depression in secondary care in a chronic sample (a median period of problem duration of 5-10 years and only 5% of these patients had no prior treatment history). Furthermore, the results obtained in CCBT are comparable to those associated with face to face treatment for depression.[31-35] It could be that this is also the case in chronic depression, since the remission rates found in our studies described in chapter 6 and 7 are comparable; 22.8% for CCBT versus 27.1% for CBASP, with CAU being clearly the underdog (7.7%). However, comparing the chronically depressed patients in the CCBT sample with the chronically depressed patients in the CBASP/CAU sample, it appears that the patients in the CCBT sample belong to a different population (highly motivated, with a preference for Internet-based treatment and rather favourable social demographic characteristics) and/or were in a different stage of their illness (mildly to moderately depressed) than the patients in the CBASP/CAU sample. Therefore, comparisons cannot be made. Nonetheless, the remission rates found in both chapter 6 and 7 do show that residual symptoms of depression often remain. It is frequently the case that chronically depressed patients do not fully recover after treatment[1] and these residual symptoms might explain their chronic course of depression, since residual symptoms are known to be a strong predictor of relapse and chronicity.[36,37]

Methodological considerations

For the studies described in chapter 2 and 3 data were drawn from the Netherlands Study of Depression and Anxiety (NESDA), an ongoing 8-year longitudinal cohort study aimed at examining the long-term course of depressive and anxiety disorders in different health care settings and phases of illness. A total of 2981 respondents were recruited from the community, primary care, and specialized mental health care, including healthy controls, respondents with subtreshold symptoms, and those with an anxiety and/or depressive disorder.[38] All 2981 respondents were administered a baseline assessment, which lasted on average 4 hours and included assessment of psychopathology, demographic and personal characteristics, psychosocial functioning, and biomarkers. Further details about NESDA are provided elsewhere.[38]

Participants with a current diagnosis of MDD in the past year were selected in both studies. The diagnosis of MDD in the past year was established with the Composite Interview Diagnostic Instrument (CIDI) (WHO version 2.1) which classifies diagnoses according to DSM-IV criteria.[39] However, in both studies chronicity of depression was not defined according to DSM-IV criteria.[39] Chronicity was defined as being depressed for 24 months or more in the past 4 years instead of being depressed for 24 consecutive months. Therefore, it could be that some of the participants in the chronically depressed group did not strictly fulfill a diagnosis of chronic MDD, but rather a diagnosis of recurrent MDD according to DSM-IV criteria.[39] Nonetheless, the mean number of months depressed in the past 4 years was 40.7 for the chronically depressed group (versus 10.3 months for the nonchronic ally depressed group), indicating that many chronically depressed participants also would fulfill DSM-IV criteria.[39] Furthermore, some persons in the nonchronic depression group may have had a chronic depression in the past. However, this would have led to a weakening of the association between chronicity of depression, childhood trauma, and psychological characteristics.

Another methodological issue in both studies was that the findings are based on a cross-sectional survey. Hence, the specific pathways by which childhood trauma and psychological characteristics may be related to chronicity of depression are unknown. Data from NESDA will give us the opportunity to repeat these studies using prospective methods. These longitudinal analyses should confirm the relationship between childhood trauma, psychological characteristics and chronicity of depression and will help us to determine factors mediating the relationships between these characteristics and chronicity of depression. However, to provide definite evidence for cautial relationships studies using a birth cohort, in which subjects are followed up from childhood into adulthood, are needed.

In chapter 6 a significant proportion of participants did not complete treatment (30%) which, unfortunately, is a phenomenon prevalent among chronically depressed patients.[1] Although we used data analytic techniques that made use of all data up to the point of drop-out, we could not rule out the possibility that our findings were biased in unknown ways by early attrition; however, no differences on baseline demographic and clinical variables between the completers and noncompleters were obtained and the number of drop-out was the same in both groups. Secondly, a longer follow-up period would have been necessary to determine if the long-term effects of CBASP treatment will survive over an extended time period.

The study in chapter 7 is a post-hoc analysis that made use of the sample of a recent Randomized Controlled Trial (RCT) on the efficacy of Internet-based CCBT for depression.[35] The fact that chronicity of depression did not predict treatment outcome could be explained by a lack of power due to our relatively small sample size (n=112, of which 81 reported chronic symptoms and 31 reported no chronic symptoms). In addition, we did not consider a follow-up period. An RCT with an enlarged sample size and follow-up data is required to substantiate our findings. The results of the current study should therefore be viewed as tentative, pending a more methodologically rigorous replication.

Clinical Implications of these findings

Concerning our findings in chapter 2 on the importance of childhood trauma for chronicity of depression, there are several implications for clinical practice. First, clinicians in mental health care should be aware that the presence of childhood trauma, and especially the presence of multiple childhood trauma may imply a more chronic course of depression. Thus, childhood trauma provides prognostic information beyond that available from clinical information of the current depressive episode. Second, the presence of childhood trauma may also be of importance in the subsequent management of chronic depression. In a study by Nemeroff et al.[40] a retrospective analytical technique was used to examine the influence of childhood trauma on the effect of the treatment in a large group of chronically depressed patients (n=681). Their analysis showed that chronically depressed patients who had experienced childhood trauma benefitted significantly more from CBASP (on its own or in combination with Nefazodone) than from Nefazodone on its own. For patients who had experienced childhood trauma, the combination of CBASP and Nefazodone was no more effective than CBASP alone.

CBASP uses specific techniques that focus on the pathological characteristics of chronically depressed patients, such as extreme interpersonal fear and avoidance, which often stem from a developmental history filled with trauma.[4,5] The findings by Nemeroff and colleagues[40] suggest that in chronically depressed patients who have experienced childhood trauma, interventions that focus on childhood trauma lead to a better treatment outcome.

The findings in chapter 3 suggest that there might be important psychological differences between chronically depressed persons and nonchronically depressed persons. This has the following implications for clinical practice: First, clinicians should be aware that low levels of extraversion (denoting introversion and poor sociability patterns), and high levels of rumination (denoting ineffective reasoning skills) and external locus of control in depressed persons (denoting helplessness and hopelessness) might imply a more chronic course of depression. Second, psychological treatment of chronic depression that puts greater emphasis on combating hopelessness and helplessness, and that focuses on poor sociability patterns and ineffective reasoning skills might improve treatment outcome.[4,40-43]

In sum, the presence of childhood trauma (especially multiple childhood trauma), and certain psychological characteristics such as low levels of extraversion, high levels of rumination and external locus of control in depressed persons might imply a more chronic course of depression. Interventions that focus on these characteristics could potentially lead to a better treatment outcome.

Our findings in chapter 2 and 3 seem to provide support for the theory of CBASP that chronically depressed patients often have a developmental history filled with psychological insults and/or trauma, low levels of extraversion, and an external locus of control. This could be one of the explanations of our finding in chapter 6 that CBASP is more effective than standard evidence based treatments for chronic depression. The fact that CBASP explicitly focuses on these pathological characteristics may have lead to a better treatment outcome, which became especially evident after the acute treatment phase. The results are important as this is the first time CBASP has been tested rigorously with predominantly treatment-resistant patients who were referred to mental health care centers and comparatively tested against a “high standard” active treatment control condition. Our results suggest that CBASP can be a welcome addition to the range of treatments currently available for chronically depressed patients in mental health care.

Internet-based Computerized Cognitive Behavioral Therapy (CCBT) is considered a low-intensity intervention, recommended as a first step treatment for mild to moderate depression.[41] Our findings suggest that CCBT can also be of value for patients with a prior treatment history of depression and chronic symptoms of depression. Considering the increasing demands of managed health care to improve cost-effectiveness of treatment in combination with the likelihood that chronically depressed patients need longer periods of intervention, CCBT could be a welcome and useful addition to the range of treatments currently available for chronically depressed patients.

To prevent or alternate a chronic course of depression, patients should continue treatment until they are fully recovered from their depression.[36,45-46] For the studies discussed in chapter 6 and 7 this means that most of the participating chronically depressed patients should continue treatment or seek additional treatment until they are fully recovered from their depression to minimize the risk of a relapsing or a continuing chronic course.

Future research

This thesis aimed to provide a further insight into the psychological characteristics and treatment of chronic depression. This could give rise to more studies examining these features. Research on psychological characteristics and other potential risk factors for chronic depression using prospective data can be informative. Progress in understanding the etiology and development of chronic depression could help maximizing treatment efficacy.

In addition, to make therapy, such as CBASP, for chronic depression more effective, it is important to determine why it works and for whom it works best, for example by studying the different techniques of CBASP separately and by examining the mediating and moderating processes of treatment outcome. Finally, research on Internet-based treatments for depression should also focus on chronic depression, for example by examining its use as an addition to face to face treatment in mental health care or as relapse prevention after face to face treatment.

In conclusion

The presence of childhood trauma (especially multiple childhood trauma), and certain psychological characteristics such as low levels of extraversion, high levels of rumination and external locus of control in depressed persons might imply a more chronic course of depression. Cognitive Behavioral Analysis System of Psychotherapy (CBASP), a psychotherapy that specifically focuses on these characteristics appears to lead to a better treatment outcome compared to standard evidence based treatments for chronic depression. Furthermore, a relatively new and promising line of treatment for depression, Internet-based Computerized Cognitive Behavioral Therapy (CCBT), can also be beneficial for patients with more chronic forms of depression. Our results suggest that CBASP and CCBT can both be a welcome addition to the range of treatments currently available for chronically depressed patients in mental health care in the Netherlands.

References

1.Torpey DC, Klein DN. Chronic depression: update on classification and treatment. Curr Psychiatry Rep 2008 December;10(6):458-64.

2.Arnow BA, Constantino MJ. Effectiveness of psychotherapy and combination treatment for chronic depression. J Clin Psychol 2003 August;59(8):893-905.

3.Arnow BA, Blasey C, Manber R et al. Dropouts versus completers among chronically depressed outpatients. J Affect Disord 2007 January;97(1-3):197-202.

4.McCullough JP. Treatment for Chronic Depression. Cognitive Behavioral Analysis System of Psychotherapy. New York: The Guilford Press; 2000.

5.McCullough JP, Lord BD, Conley KA, Martin AM. A method for conducting intensive psychological studies with early-onset chronically depressed patients. *Am J of Psychotherapy* 2010 December; 64(4), 317-337.

6.Keller MB, McCullough JP, Klein DN et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 2000 May 18;342(20):1462-70.

7.Bifulco A, Moran PM, Ball C, Lillie A. Adult attachment style. II: Its relationship to psychosocial depressive-vulnerability. Soc Psychiatry Psychiatr Epidemiol 2002 February;37(2):60-7.

8.Brown GW, Moran P. Clinical and psychosocial origins of chronic depressive episodes. I: A community survey. Br J Psychiatry 1994 October;165(4):447-56.

9.Brown GW, Harris TO, Hepworth C, Robinson R. Clinical and psychosocial origins of chronic depressive episodes. II. A patient enquiry. Br J Psychiatry 1994 October;165(4):457-65.

10.Brown GW, Craig TK, Harris TO, Handley RV, Harvey AL. Development of a retrospective interview measure of parental maltreatment using the Childhood Experience of Care and Abuse (CECA) instrument -- A life-course study of adult chronic depression - 1. J Affect Disord 2007 November;103(1-3):205-15.

11.Lizardi H, Klein DN, Ouimette PC, Riso LP, Anderson RL, Donaldson SK. Reports of the childhood home environment in early-onset dysthymia and episodic major depression. J Abnorm Psychol 1995 February;104(1):132-9.

12.Durbin CE, Klein DN, Schwartz JE. Predicting the 2 1/2-year outcome of dysthymic disorder: the roles of childhood adversity and family history of psychopathology. J Consult Clin Psychol 2000 February;68(1):57-63.

13.Akiskal HS. Factors associated with incomplete recovery in primary depressive illness. J Clin Psychiatry 1982 July;43(7):266-71.

14.Weissman MM, Klerman GL. The chronic depressive in the community: unrecognized and poorly treated. Compr Psychiatry 1977 November;18(6):523-32.

15.Kessler RC, Magee WJ. Childhood family violence and adult recurrent depression. J Health Soc Behav 1994;35: 13-27

16.Kessler RC, Davis CG, Kendler KS. Childhood adversity and adult psychiatric disorder in the US National Comorbidity Survey. Psychol Med 1997;27: 1101-1119

17.Tennant C. Parental loss in childhood. Its effect in adult life. Arch Gen Psychiatry 1988 November;45(11):1045-50.

18.Hirschfeld RMA. Personality and dysthymia. In: Burton SW, Akiskal HS, Editors, Dysthymic disorder, Gaskell, London (1990).

19.Klein DN, Taylor EB, Dickstein S, Harding K. Primary early-onset dysthymia: comparison with primary nonbipolar nonchronic major depression on demographic, clinical, familial, personality, and socioenvironmental characteristics and short-term outcome. J Abnorm Psychol 1988 November;97(4):387-98.

20.Surtees PG, Wainwright NW. Fragile states of mind: neuroticism, vulnerability and the long-term outcome of depression. Br J Psychiatry 1996; 169: 338-347

21.Duggan CF, Lee AS, Murray RM. Does personality predict long-term outcome in depression? Br J Psychiatry 1990 July;157:19-24.

22.Rhebergen D, Beekman AT, Graaf R et al. The three-year naturalistic course of major depressive disorder, dysthymic disorder and double depression. J Affect Disord 2009 June;115(3):450-9.

23.Scott J, Eccleston D, Boys R. Can we predict the persistence of depression? Br J Psychiatry 1992 November;161:633-7.

24.Nolen-Hoeksema S, Davis CG. "Thanks for sharing that": ruminators and their social support networks. J Pers Soc Psychol. 1999; 77(4):801-14

25.Roberts JE, Gilboa E, Gotlib IH. Ruminative Response Style and Vulnerability to Episodes of Dysphoria: Gender, Neuroticism, and Episode Duration. Cognitive Therapy and Research 1998; 22, 401-423

26.Nolan SA, Roberts JE, Gotlib IH. Neuroticism and Ruminative Response Style as Predictors of Change in Depressive Symptomatology. Cognitive Therapy and Research, 1998; 22, 445-455

27.Clarke D. Neuroticism: moderator or mediator in the relation between locus of control and depression? Personality and Individual Differences 2004; 37, 245-258

28.Horner KL. Locus of control, neuroticism, and stressors: Combined influences on reported physical illness. Personality and Individual Differences 1996; 21, 195-204

29.Klein DN, Santiago NJ, Vivian D et al. Cognitive-behavioral analysis system of psychotherapy as a maintenance treatment for chronic depression. *J Consult Clin Psychol* 2004 August;72(4):681-8.

30.earmonth D, Rai S: Taking Computerized CBT beyond primary care. Br J Clin Psychol 2008;47:111-8.

31.Kaltenthaler E, Parry G, Beverley C, Ferriter M: Computerised cognitive behavioral therapy for depression: systematic review. Sr J Psychiatry 2008; 193: 181-184

32.Spek, V, Cuijpers P, Nyklicek I, Riper H, Keyzer J, Pop V: Internet based cognitive behavioral therapy for symptoms of depression and anxiety: a meta-analysis Psycho I Med.; 2007; 37: 319-28.

33.Perini S, Titov N, Andrews G: Clinician-assisted Internet-based treatment is effective for depression: randomized controlled trial. Aust N Z J Psychiatry 2009;43: 571-578.

34.Andersson G, Cuijpers P: Internet based and other computerized psychological treatments for adult depression: a meta-analysis. Cog Behav Ther 2009;38: 196-205

35.Titov N, Andrews G, Davies M, Mcintyre K, Robinson E, Solley K: Internet Treatment for Depression: A Randomized Controlled Trial Comparing Clinician vs Technician Assistance. PI oS ONE 2010;5: e10939

36.Judd LL, Paulus MJ, Schettler PJ: Does Incomplete Recovery From First Lifetime Major Depressive Episode Herald a Chronic Course of Illness? Am J Psychiatry 2000;157:1501-1504.

37.Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A: Residual symptoms after partial remission: An important outcome in depression. Psychol Med 1995; 25: 1171-1180.

38.Penninx BWJH, Beekman ATF, Smit JH, et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. Int J Methods Psychiatr Res 2008; 17: 121-140

39.American Psychiatric Association. Diagnostic and statistical manual of mental disorders 2001. Washington.

40.Nemeroff CB, Heim CM, Thase ME, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. Proc Natl Acad Sci U S A 2003;100: 14293-14296

41.Riso LP, Newman CF. Cognitive therapy for chronic depression. J Clin Psychol. 2003; 59: 817-831

42.Watkins E, Scott J, Wingrove J, et al. Rumination-focused cognitive behavioral therapy for residual depression: a case series. Behav Res Ther 2007; 45: 2144-54

43.Thase ME, Friedman ES, Howland RH. Management of treatment-resistant depression: psychotherapeutic perspectives. J Clin Psychiatry 2001;62 Suppl 18:18-24 National Institute for Health and Clinical Excellence (NICE). Depression guidelines, 2006. (http://guidance.nice.org.uk/CG23)

44.Jarrett RB, Kraft D, Doyle D, Foster BM, Eaves GG, Silver PC: Preventing Recurrent Depression Using Cognitive Therapy With and Without a Continuation Phase. A Randomized Clinical Trial. Arch Gen Psychiatry 2001;58:381-388.

45.Vos T, Haby MM, Barendregt JJ, Kruijshaar M, Corry J, Andrews G: The Burden of Major Depression Avoidable by Longer-term Treatment Strategies. Arch Gen Psychiatry 2004;61:1097-1103.

46.Fava GA, Ruini C, Belaise C: The concept of recovery in major depression. Psychological Medicine, 2007, 37, 307–317.