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Effect of Obstructive Sleep Apnea on Response to Cognitive Behavior Therapy for Depression After an Acute Myocardial Infarction

Kenneth E. Freedland, PhD¹, Robert M. Carney, PhD¹, Junichiro Hayano, MD², Brian C. Steinmeyer, MS¹, Rebecca L. Reese, MA¹, and Annelieke M. Roest, MSc³

¹Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri, USA

²Department of Medical Education (J.H.), Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan ³Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Abstract

Objective—To determine whether obstructive sleep apnea (OSA) interferes with cognitive behavior therapy (CBT) for depression in patients with coronary heart disease.

Methods—Patients who were depressed within 28 days after an acute myocardial infarction (MI) were enrolled in the Enhancing Recovery in Coronary Heart Disease (ENRICH) trial; 289 (12%) of the 2,481 participants in ENRICH met the criteria for inclusion in this ancillary study.

Results—A validated ambulatory ECG algorithm was used to detect OSA. Of the 289 participants, 64 (22%) met the criteria for OSA. CBT was efficacious relative to usual care (UC) for depression ($p=.004$). OSA had no effect on 6-month Beck Depression Inventory (BDI) scores ($p=.11$), and there was no interaction between OSA and treatment ($p=.42$). However, the adjusted mean (s.e.) 6-month BDI scores among patients without OSA were 12.2 (0.8) vs. 9.0 (0.8) in the UC and CBT groups (Cohen's $d=.40$); among those with OSA, they were 9.5 (1.4) and 8.1 (1.5) in the UC and CBT groups ($d=.17$). There were no significant OSA by Treatment interactions in the major depression ($n=131$) or minor depression ($n=158$) subgroups, but in those with major depression, there was a larger treatment effect in those without ($d=.44$) than with ($d=.09$) OSA. In those with minor depression, the treatment effects were $d=.37$ and $d=.25$ for the non-OSA and OSA subgroups.

Conclusion—CBT is efficacious for depression after an acute myocardial infarction in patients without obstructive sleep apnea, but it may be less efficacious for post-MI patients with OSA.

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Corresponding author: Kenneth E. Freedland, PhD, Department of Psychiatry, Washington University School of Medicine, 4320 Forest Park Avenue, Suite 301, St. Louis, Missouri 63108 USA, Telephone: 314-286-1311, Fax: 314-286-1301, freedlak@bmc.wustl.edu.

Disclosure Statements

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MeSH Keywords

Cognitive Therapy; Depression; Depressive Disorder/therapy; Depressive Disorder/psychology; Electrocardiography; Ambulatory; Myocardial Infarction/psychology; Sleep Apnea; Obstructive

Introduction

Depression is a treatable disorder, but at least 30% of patients do not respond to standard therapies [1]. For example, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial tested a stepped treatment algorithm that incorporated patient preference. About 33% of 3,671 participants remitted during initial treatment with citalopram. Subsequent treatments for patients who did not remit on citalopram included up to 3 more steps involving switching to, or augmentation with, other antidepressants and/or cognitive behavior therapy (CBT). Of the 3,671 patients who were initially treated with citalopram, 1,872 remitted at the first, second, third, or fourth step, for a cumulative remission rate of 51% [2,3]. Thus, even with an aggressive, stepped treatment protocol, almost half of the patients did not remit. Furthermore, relapse rates increased along with the number of steps [4].

Early response to treatment has emerged as a relatively strong predictor of subsequent remission of depression [5–7]. Efforts to identify pretreatment patient characteristics that can accurately predict response to treatment for depression have been less successful [5]. Pretreatment predictors of poor response to treatment include a history of attempted suicide [8]; recent, severely stressful life events, particularly involving job loss or financial distress [9]; high levels of anxiety [8]; and somatic symptoms [10] in general and painful somatic symptoms in particular [11]. Candidate gene and genome-wide association studies have begun to identify single nucleotide polymorphisms that may be related to treatment responsiveness [12–15]. Other promising biomarkers have been identified as well, including ones derived from proteomic, metabolomic, and brain imaging studies [16]. Nevertheless, our ability to identify treatment-resistant cases of depression prior to treatment remains quite limited.

Treatment-resistant depression may have particularly serious implications for patients with coronary heart disease (CHD). Recent findings from several clinical trials have shown that patients who do not respond to standard treatments for depression are at high risk for mortality after acute coronary syndrome [17].

The prevalence of comorbid major depression in CHD is approximately 15 to 20%, and scores in the “depressed” range on self-report questionnaires are even more common.[18] Many patients with CHD and comorbid depression also have obstructive sleep apnea (OSA) [19]. Patients with OSA have repetitive episodes of complete (apnea) or partial (hypopnea) obstruction of the upper airway during sleep. During these episodes, there are efforts to breathe but inspiration is temporarily blocked. Many patients with obstructive OSA also have central apneic episodes in which breathing stops temporarily but without any airway blockage or respiratory effort. Both kinds of episodes can cause harmful reductions in the level of oxygen in the blood.[20] The prevalence of OSA is increasing along with the epidemic of obesity in the United States [21]. Sleep apnea is associated with a variety of adverse cardiovascular and metabolic effects [22,23]. It is also associated with depression [24], cognitive impairment [25], and structural changes in the brain [24,26]. Nevertheless, OSA is still markedly underdiagnosed and undertreated, even among cardiac patients at high risk of OSA-related mortality [19,27].

We recently reported that untreated OSA predicts a poor response to sertraline in patients with stable CHD and comorbid major depressive disorder (MDD) [28]. This was a secondary analysis of a randomized, double blind, placebo-controlled trial of omega-3 free fatty acid augmentation of sertraline, the primary results of which were reported elsewhere [29]. A previously validated algorithm [30] for detecting OSA was applied to 105 of the trial participants' baseline electrocardiographic (ECG) data; 30 (29%) were classified as having moderate to severe OSA, with an algorithm-derived AHI ≥ 15 . The mean (standard deviation) scores on the Beck Depression Inventory (BDI-II) [31] after treatment with sertraline were 19.0 (11.0) among patients with OSA and 13.0 (9.2) in those without OSA ($p=0.01$). This difference remained significant after adjustment for the baseline severity of depression, treatment group (omega-3 vs. placebo), body mass index (BMI), and inflammatory markers.

These findings suggest that untreated OSA can interfere with antidepressant therapy, but their generalizability to other forms of treatment for depression is unknown. Because OSA is often associated with daytime sleepiness, fatigue, and poor concentration, especially if left untreated [32], it might be especially problematic for nonpharmacological interventions such as CBT that depend upon the patient's attentive engagement in therapy.

The present study investigated this question in a secondary analysis of data from the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial. In ENRICHD, patients with a recent history of acute myocardial infarction (MI) were randomly assigned to CBT or to usual care (UC) for depression. Data on OSA were obtained from a subset of ENRICHD participants. We used these data to test the hypothesis that OSA moderates the effect of CBT on depression in patients with a recent MI, and specifically that patients with OSA do not respond as well to CBT for depression as do patients without OSA.

Methods

Eligibility criteria

The methods, treatment protocol, and primary findings of the ENRICHD trial have been reported elsewhere [33–35]. Briefly, consenting patients were assessed for depression and low perceived social support within 28 days after an acute MI. Those who met the trial's eligibility criteria were randomly assigned to 6 months of CBT or to UC for depression. In some cases, the cognitive-behavioral intervention was augmented with an antidepressant. Antidepressant therapy was offered only to patients who were severely depressed at enrollment or who had an inadequate response to the first 5 weeks of CBT. The primary analyses showed that although the intervention had significant effects on depression and social support, it had no impact on reinfarction-free survival [33]. To be included in this ancillary study, participants had to meet the ENRICHD criteria for a major or minor depressive episode at baseline, have a Beck Depression Inventory (BDI)[36] score of 10 or greater, and to have provided usable baseline ECG data for an ENRICHD Holter monitoring substudy [37]. The ENRICHD trial and the ancillary ECG study were approved by the institutional review board at each participating site and were carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Procedures

OSA was identified from cyclic variation of heart rate (CVHR) patterns detected in 24-hour Holter ECG recordings that were obtained within 28 days (median, 13 days) after the index MI. The ECGs were scanned on an SXP Laser scanner (Marquette Electronics). The labeled beat files were exported to a computer workstation on which CVHR was detected by an autocorrelated wave detection with adaptive threshold (ACAT) algorithm. The ACAT

algorithm is a time-domain method for detecting CVHR from interbeat interval data. Details of this method have been reported elsewhere [38]. Briefly, the algorithm detects transient tachycardia as CVHR when it meets the following criteria: 1) width from 10 to 120 seconds, 2) depth-to-width ratio >0.7 ms/s, 3) depth $>40\%$ of the 90% CI of local interbeat interval variations, 4) cycle length (interdip interval) from 25 to 120 seconds, 5) similar waveforms for 5 consecutive dips (morphological correlation coefficients >0.4) and 6) three equivalent consecutive cycle lengths with a tolerance of 22% against the mean cycle length. In a validation study of 862 patients referred to a sleep medicine center for a diagnostic evaluation, the CVHR index correlated very highly ($r=0.84$) with the apnea-hypopnea index (AHI) derived from polysomnography. The CVHR index cutoff of ≥ 15 per hour approximates an AHI of ≥ 15 , the standard polysomnographic cutoff for identifying patients with moderate-to-severe OSA [39]. At this cutpoint, the CVHR index has 83% sensitivity, 88% specificity, and 91% accuracy vis-à-vis the AHI cutoff [38].

Holter diary data and diurnal heart rate patterns were used to establish each participant's sleep period. The average number of CVHRs per hour during the sleep period was calculated by a technician who was blinded to patient characteristics and CVHR analysis results. Participants who averaged >15 CVHRs per hour were classified as having OSA. The ENRICHHD medical history data collection forms did not include any questions about OSA, so it is not possible to determine whether any of the patients had been evaluated at a sleep medicine center, diagnosed with OSA, or treated with continuous positive airway pressure (CPAP). However, if other research on cardiac patients [19] generalizes to the ENRICHHD sample, it is likely that very few of the participants had ever been clinically evaluated or treated for OSA. In middle-aged adults, about 93% of moderate to severe cases of OSAHS in women and 82% in men escape clinical diagnosis [27].

The Beck Depression Inventory [36] is a 21-item measure of the severity of self-reported depression symptoms. Each symptom is rated on a 0 – 3 scale, and the total scores range from 0 to 63. A score of 10 or higher is the standard cutoff for clinically significant depression. The BDI was administered at baseline and repeated 6 months later to assess depression outcomes. The Depression Interview and Structured Hamilton (DISH) [40] was used to classify participants as meeting the study's criteria for a major or minor depressive episode at baseline.

Statistical analysis

Forty-seven (16%) of the participants had missing 6-month BDI scores. These scores, which were plausibly missing at random, were imputed in order to perform intention-to-treat (ITT) analyses and to derive unbiased estimates of treatment effects. The imputer's model included all of the variables used in the primary ENRICHHD analyses. The primary ITT analyses were performed on 20 imputed datasets generated by SAS Proc MI. Secondary analyses that were limited to participants with complete data (i.e., "completers" analyses) were also performed.

The primary hypothesis was that OSA adversely moderates the effect of CBT on depression. This was tested in a sequential analysis of covariance (ANCOVA) model, with the 6-month BDI score as the outcome. In the first step, the main effect of treatment assignment (CBT vs. UC) was tested, adjusted only for the baseline BDI score. The purpose of this initial step was to confirm that the intervention had a significant effect on depression in the ancillary study subset, as it had in the entire ENRICHHD sample. The main effect of OSA category (absent vs. present) was added in the second step, and the OSA by Treatment interaction was added in the third step. A significant interaction would indicate that the intervention had different effects on depression in patients with than without OSA.

Our earlier study of untreated OSA as a moderator of the effect of sertraline was limited to patients with major depression. Some of the participants in the present study also had major depression at enrollment, but others had minor depression. In order to facilitate comparison of the two studies, as well as to determine whether OSA moderates the effects of treatment in both major and minor depression, we stratified the sample by depression diagnosis and then repeated the sequential ANCOVA procedure described above.

We artificially dichotomized CVHR at the standard cutoff score of >15 in order to differentiate between patients with or without OSA. However, artificial categorization of continuous predictor variables can distort statistical models, even if the categories are formed around a clinically valid cutpoint [41–43]. In a sensitivity analysis, we repeated the preceding models after replacing the artificially dichotomized CVHR with continuous CVHR scores.

SAS version 9.2 was used for all statistical analyses. SAS Proc GLM was used to perform the ANOVAs and ANCOVAs. Standard diagnostic tests found no violations of the assumptions of the ANCOVA model. The criterion for statistical significance was .05 per comparison.

Results

Sample

Of the 2,481 patients who participated in the ENRICH trial, 1,834 met the criteria for major or minor depression at enrollment. Three hundred forty-two of the depressed patients participated in the Holter monitoring substudy, and 289 (131 with major depression, 158 with minor depression) of them provided ECG data that were suitable for CVHR analysis. A flowchart of the derivation of the sample is presented in Figure 1.

Sixty-four (22%) of the patients had a CVHR index >15 , i.e., they screened positive for OSA. Patients with an AHI >30 are generally considered to have severe OSA.[44] Forty-one of the participants had a CVHR between 15 and 30, consistent with moderate OSA, and 23 participants had a CVHR >30 , consistent with severe OSA. Of the 136 patients who were randomized to CBT, 29 (21%) met the CVHR criterion for OSA, and of the 153 patients who were randomized to UC, 35 (23%) met the CVHR criterion. Study psychiatrists prescribed antidepressants to 16 (12%) of the participants in the intervention arm; 12 of these patients were given sertraline and 4 received other antidepressants.

The demographic and baseline medical characteristics of the patients with and without OSA are compared in Table 1. The patients with OSA were predominantly male and older than those without OSA. They were more likely to be taking a beta blocker and to have a prior history of coronary bypass surgery, and they also tended to have other indications of more severe heart disease including a low left ventricular ejection fraction and a prior history of MI.

Primary intention-to-treat analysis

As shown in Table 2, the effect of treatment remained significant after adjusting only for baseline BDI scores, thereby confirming the efficacy of the intervention in the analysis subset. The main effect of OSA on depression at 6 months was tested in the second step, and it was not significant. The OSA by Treatment interaction term was added in the third step, and it was also nonsignificant. Thus, the primary analysis did not support the hypothesis that OSA moderates the effect of CBT on depression. However, as shown in Table 3, the treatment effect was larger in patients without OSA (Cohen's $d=.40$) than in those with OSA ($d=.17$).

Secondary analyses

The ITT model was applied in a secondary analysis to the subset of patients who met the criteria for major depression at baseline. In the first step, CBT had a significant effect on depression at 6 months after adjusting for the baseline BDI score. The main effect of OSA on depression was not significant in the second step, and the OSA by Treatment interaction was not significant in the third step. However, the intervention had a larger effect among patients without OSA (Cohen's $d=.44$) than with OSA ($d=.09$); see Figure 2a.

The model was then repeated in the subset of patients with minor depression. The main effect of treatment was significant in the first step. The main effect of OSA was significant in the second step, but not in the expected direction, i.e., patients with OSA had lower depression scores at 6 months than did those without OSA. There was no significant OSA by Treatment interaction in the third step. The difference in effect sizes was smaller among patients with minor depression than it was among those with major depression. In the minor depression subset, the effect size was $d=.37$ in patients without OSA and $d=.25$ in those with OSA; see Figure 2b.

As a sensitivity analysis, all of the previous models were rerun after substituting the continuous CVHR score for the artificially dichotomized CVHR indicator. The findings were consistent with those of the main analyses. All of the analyses were also rerun on the completers subset. The only difference between the completers and the intention-to-treat results was that the main effect of treatment was nonsignificant in the group with minor depression who completed the six month evaluation, with first-step least-squares adjusted mean (s.e.) 6-month BDI scores of 11.1 (0.7) in the UC arm and 10.1 (0.8) in the CBT arm ($t_{132}=1.68$, $p=.07$). We also re-ran the analyses excluding the 16 participants who reported taking antidepressant medications. The resulting effect sizes were nearly identical to those reported in Table 3.

Discussion

Our previous study [28] showed that sertraline was less efficacious for major depression in patients with stable coronary disease who screened positive for untreated OSA than in those who screened negative on ECG. One of the possible reasons for this is that sertraline can have adverse affects on sleep architecture and quality [45,46].

In the present study, we investigated whether the adverse effects of OSA on depression treatment outcomes generalize to cognitive behavior therapy. The primary statistical analyses did not support the hypothesis that OSA moderates the effect of CBT on depression in post-MI patients. This contrasts with our recent report in which the efficacy of sertraline for major depression in patients with coronary heart disease differed significantly between patients with vs. without OSA. However, inspection of the effect sizes in Table 3 suggests that OSA may attenuate the impact of CBT on depression, even though the analysis did not support the treatment moderation hypothesis. OSA diminished the effect of treatment in patients with minor depression, and it nearly abolished it in those with major depression. Daytime sleepiness, fatigue, and other symptoms of OSA might make it difficult for patients to cooperate fully with a cognitive-behavioral intervention. Thus, OSA may interfere both with antidepressant therapy and cognitive behavior therapy, but it may do so through different mechanisms.

This study has several limitations. First, it was based on a secondary analysis of data from a subset of the participants in a clinical trial. It was not a prospective RCT conducted specifically to test the hypothesis that OSA moderates the efficacy of CBT. Second, ENRICHD did not include a clinical evaluation for sleep disorders, and OSA was identified

by a validated ECG algorithm rather than by gold-standard polysomnography. Although the algorithm has been shown by its developers to have high sensitivity and specificity vis-à-vis polysomnography [38], its accuracy has not been evaluated in post-MI patients. Consequently, some of the patients who were classified as having OSA might not have met the full diagnostic criteria for obstructive sleep apnea-hypopnea syndrome (OSAHS) [39] if they had been clinically evaluated at a sleep medicine center. Conversely, some of the patients who screened negative for OSA might have met the criteria for OSAHS if they had been clinically evaluated. The lack of medical history data about OSA also leaves uncertainty as to whether any patients were being treated for OSA, although it is unlikely that many (if any) were on CPAP. Furthermore, it is possible that some of the participants in this study would have been less depressed or more responsive to CBT if they had been on CPAP therapy. Some studies suggest that CPAP may have little effect on depression or other negative mood states [47,48], but at least one study has shown that depressive symptoms may improve substantially on CPAP [49]. Third, some of the symptoms of depression (e.g., sleep disturbance and fatigue) are also symptoms of OSAHS [50]. Consequently, it is possible that OSAHS rather than depression may be responsible for some of the persistent symptoms that were identified on the BDI. Fourth, the sample was limited to patients with a recent acute myocardial infarction. It is possible that OSA could have different effects on CBT for depression in other patient populations. Finally, the confidence intervals around the effect size estimates are relatively large.

Given the limitations of this study, it is important to interpret the results with caution. The findings suggest that CBT may be less efficacious for depression in cardiac patients with obstructive sleep apnea than for those without OSA. However, randomized controlled trials of antidepressants and CBT are needed to conclusively determine whether either form of treatment is efficacious for depression in patients with clinically diagnosed OSAHS. The need for such trials is increasing along with the prevalence of OSAHS. This study also highlights the need for more systematic efforts to identify and treat OSAHS in cardiac patients, both to reduce the risks of medical morbidity and mortality and to facilitate the treatment of depression.

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Abbreviations

ACAT	Autocorrelated wave detection with adaptive threshold
AHI	Apnea-hypopnea index
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BDI	Beck Depression Inventory
CBT	Cognitive behavior therapy
CHD	Coronary heart disease

CVHR	Cyclic variation of heart rate
DISH	Depression Interview and Structured Hamilton
ECG	Electrocardiogram
ENRICHD	Enhancing Recovery in Coronary Heart Disease
ESSI	ENRICHD Social Support Instrument
ITT	Intention-to-treat
MI	Myocardial infarction
OSA	Obstructive sleep apnea
OSAHS	Obstructive sleep apnea-hypopnea syndrome
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
UC	Usual care

References

1. Stimpson N, Agrawal N, Lewis G. Randomised controlled trials investigating pharmacological and psychological interventions for treatment-refractory depression. Systematic review. *Br J Psychiatry*. 2002; 181:284–294. [PubMed: 12356654]
2. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006; 163:1905–1917. [PubMed: 17074942]
3. Thase ME, Friedman ES, Biggs MM, Wisniewski SR, Trivedi MH, Luther JF, Fava M, Nierenberg AA, McGrath PJ, Warden D, Niederehe G, Hollon SD, Rush AJ. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. *Am J Psychiatry*. 2007; 164:739–752. [PubMed: 17475733]
4. Warden D, Rush AJ, Trivedi MH, Fava M, Wisniewski SR. The STAR*D Project results: a comprehensive review of findings. *Curr Psychiatry Rep*. 2007; 9:449–459. [PubMed: 18221624]
5. Kuk AY, Li J, Rush AJ. Recursive subsetting to identify patients in the STAR*D: a method to enhance the accuracy of early prediction of treatment outcome and to inform personalized care. *J Clin Psychiatry*. 2010; 71:1502–1508. [PubMed: 21114950]
6. van CD, Zobel I, Dykierck P, Deimel CM, Kech S, Lieb K, Berger M, Schramm E. Time course of response to antidepressants: predictive value of early improvement and effect of additional psychotherapy. *J Affect Disord*. 2009; 114:243–253. [PubMed: 18849079]
7. Henkel V, Seemuller F, Obermeier M, Adli M, Bauer M, Mundt C, Brieger P, Laux G, Bender W, Heuser I, Zeiler J, Gaebel W, Mayr A, Moller HJ, Riedel M. Does early improvement triggered by antidepressants predict response/remission? Analysis of data from a naturalistic study on a large sample of inpatients with major depression. *J Affect Disord*. 2009; 115:439–449. [PubMed: 19027961]
8. Kim JM, Kim SW, Stewart R, Kim SY, Yoon JS, Jung SW, Lee MS, Yim HW, Jun TY. Predictors of 12-week remission in a nationwide cohort of people with depressive disorders: the CRESCEND study. *Hum Psychopharmacol*. 2011
9. Amital D, Fostick L, Silberman A, Beckman M, Spivak B. Serious life events among resistant and non-resistant MDD patients. *J Affect Disord*. 2008; 110:260–264. [PubMed: 18262654]
10. Silverstein B, Patel P. Poor response to antidepressant medication of patients with depression accompanied by somatic symptomatology in the STAR*D Study. *Psychiatry Res*. 2011; 187:121–124. [PubMed: 21216475]
11. Leuchter AF, Husain MM, Cook IA, Trivedi MH, Wisniewski SR, Gilmer WS, Luther JF, Fava M, Rush AJ. Painful physical symptoms and treatment outcome in major depressive disorder: a

- STAR*D (Sequenced Treatment Alternatives to Relieve Depression) report. *Psychol Med.* 2010; 40:239–251. [PubMed: 19493369]
12. Garriock HA, Kraft JB, Shyn SI, Peters EJ, Yokoyama JS, Jenkins GD, Reinalda MS, Slager SL, McGrath PJ, Hamilton SP. A genomewide association study of citalopram response in major depressive disorder. *Biol Psychiatry.* 2010; 67:133–138. [PubMed: 19846067]
 13. Uher R, Huezio-Diaz P, Perroud N, Smith R, Rietschel M, Mors O, Hauser J, Maier W, Kozel D, Henigsberg N, Barreto M, Placentino A, Dernovsek MZ, Schulze TG, Kalember P, Zobel A, Czerski PM, Larsen ER, Souery D, Giovannini C, Gray JM, Lewis CM, Farmer A, Aitchison KJ, McGuffin P, Craig I. Genetic predictors of response to antidepressants in the GENDEP project. *Pharmacogenomics J.* 2009; 9:225–233. [PubMed: 19365399]
 14. Laje G, Perlis RH, Rush AJ, McMahon FJ. Pharmacogenetics studies in STAR*D: strengths, limitations, and results. *Psychiatr Serv.* 2009; 60:1446–1457. [PubMed: 19880459]
 15. Porcelli S, Drago A, Fabbri C, Gibiino S, Calati R, Serretti A. Pharmacogenetics of antidepressant response. *J Psychiatry Neurosci.* 2011; 36:87–113. [PubMed: 21172166]
 16. Leuchter AF, Cook IA, Hamilton SP, Narr KL, Toga A, Hunter AM, Faull K, Whitelegge J, Andrews AM, Loo J, Way B, Nelson SF, Horvath S, Lebowitz BD. Biomarkers to predict antidepressant response. *Curr Psychiatry Rep.* 2010; 12:553–562. [PubMed: 20963521]
 17. Carney RM, Freedland KE. Treatment-resistant depression and mortality after acute coronary syndrome. *Am J Psychiatry.* 2009; 166:410–417. [PubMed: 19289455]
 18. Jiang, W.; Xiong, GL. Epidemiology of the comorbidity between depression and heart disease. In: Glassman, AH.; Maj, M.; Sartorius, N., editors. *Depression and heart disease.* Chichester, West Sussex: John Wiley & Sons; 2011. p. 1–37.
 19. Carney RM, Howells WB, Freedland KE, Duntley SP, Stein PK, Rich MW, Miller GE. Depression and obstructive sleep apnea in patients with coronary heart disease. *Psychosom Med.* 2006; 68:443–448. [PubMed: 16738077]
 20. American Academy of Sleep Medicine. The international classification of sleep disorders: diagnostic and coding manual. 2. Westchester, Ill: American Academy of Sleep Medicine; 2005.
 21. Yaggi HK, Strohl KP. Adult obstructive sleep apnea/hypopnea syndrome: definitions, risk factors, and pathogenesis. *Clin Chest Med.* 2010; 31:179–186. [PubMed: 20488280]
 22. Lui MM, Ip MS. Disorders of glucose metabolism in sleep-disordered breathing. *Clin Chest Med.* 2010; 31:271–285. [PubMed: 20488286]
 23. Selim B, Won C, Yaggi HK. Cardiovascular consequences of sleep apnea. *Clin Chest Med.* 2010; 31:203–220. [PubMed: 20488282]
 24. Cross RL, Kumar R, Macey PM, Doering LV, Alger JR, Yan-Go FL, Harper RM. Neural alterations and depressive symptoms in obstructive sleep apnea patients. *Sleep.* 2008; 31:1103–1109. [PubMed: 18714782]
 25. Twigg GL, Papaioannou I, Jackson M, Ghiassi R, Shaikh Z, Jaye J, Graham KS, Simonds AK, Morrell MJ. Obstructive sleep apnea syndrome is associated with deficits in verbal but not visual memory. *Am J Respir Crit Care Med.* 2010; 182:98–103. [PubMed: 20299536]
 26. Morrell MJ, Jackson ML, Twigg GL, Ghiassi R, McRobbie DW, Quest RA, Pardoe H, Pell GS, Abbott DF, Rochford PD, Jackson GD, Pierce RJ, O'Donoghue FJ, Corfield DR. Changes in brain morphology in patients with obstructive sleep apnoea. *Thorax.* 2010; 65:908–914. [PubMed: 20861295]
 27. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep.* 1997; 20:705–706. [PubMed: 9406321]
 28. Roest AM, Carney RM, Stein PK, Freedland KE, Meyer H, Steinmeyer BC, de Jong P, Rubin EH. Obstructive sleep apnea hypopnea and poor response to antidepressant medication in patients with coronary heart disease. *J Clin Psychiatry.* 2011 Published online ahead of print.
 29. Carney RM, Freedland KE, Rubin EH, Rich MW, Steinmeyer BC, Harris WS. Omega-3 augmentation of sertraline in treatment of depression in patients with coronary heart disease: a randomized controlled trial. *JAMA.* 2009; 302:1651–1657. [PubMed: 19843899]

30. Stein PK, Duntley SP, Domitrovich PP, Nishith P, Carney RM. A simple method to identify sleep apnea using Holter recordings. *J Cardiovasc Electrophysiol*. 2003; 14:467–473. [PubMed: 12776861]
31. Beck, AT.; Steer, RA.; Brown, GK. Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation; 1996.
32. Patil SP, Schneider H, Schwartz AR, Smith PL. Adult obstructive sleep apnea: pathophysiology and diagnosis. *Chest*. 2007; 132:325–337. [PubMed: 17625094]
33. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, Czajkowski SM, DeBusk R, Hosking J, Jaffe A, Kaufmann PG, Mitchell P, Norman J, Powell LH, Raczynski JM, Schneiderman N. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICH) Randomized Trial. *JAMA*. 2003; 289:3106–3116. [PubMed: 12813116]
34. ENRICH Investigators. Enhancing Recovery in Coronary Heart Disease (ENRICH) study intervention: rationale and design. *Psychosom Med*. 2001; 63:747–755. [PubMed: 11573023]
35. ENRICH Investigators. Enhancing recovery in coronary heart disease patients (ENRICH): study design and methods. *Am Heart J*. 2000; 139:1–9. [PubMed: 10618555]
36. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961; 4:561–571. [PubMed: 13688369]
37. Carney RM, Blumenthal JA, Freedland KE, Stein PK, Howells WB, Berkman LF, Watkins LL, Czajkowski SM, Hayano J, Domitrovich PP, Jaffe AS. Low heart rate variability and the effect of depression on post-myocardial infarction mortality. *Arch Intern Med*. 2005; 165:1486–1491. [PubMed: 16009863]
38. Hayano J, Watanabe E, Saito Y, Sasaki F, Fujimoto K, Nomiyama T, Kawai K, Kodama I, Sakakibara H. Screening for obstructive sleep apnea by cyclic variation of heart rate. *Circ Arrhythm Electrophysiol*. 2011; 4:64–72. [PubMed: 21075771]
39. American Academy of Sleep Medicine. AASM manual for scoring of sleep and associated events: rules, terminology, and technical specifications. Westchester, IL: American Academy of Sleep Medicine; 2007.
40. Freedland KE, Skala JA, Carney RM, Raczynski JM, Taylor CB, Mendes de Leon CF, Ironson G, Youngblood ME, Krishnan KR, Veith RC. The Depression Interview and Structured Hamilton (DISH): rationale, development, characteristics, and clinical validity. *Psychosom Med*. 2002; 64:897–905. [PubMed: 12461195]
41. Flemons WW, Littner MR. Measuring agreement between diagnostic devices. *Chest*. 2003; 124:1535–1542. [PubMed: 14555591]
42. Altman DG, Royston P. The cost of dichotomising continuous variables. *BMJ*. 2006; 332:1080. [PubMed: 16675816]
43. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat Med*. 2006; 25:127–141. [PubMed: 16217841]
44. Berry, RB. Fundamentals of sleep medicine. Philadelphia: Elsevier/Saunders; 2012. Obstructive sleep apnea syndromes: definitions, epidemiology, diagnosis, and variants; p. 237–61.
45. Thase ME. Treatment issues related to sleep and depression. *J Clin Psychiatry*. 2000; 61 (Suppl 11):46–50. [PubMed: 10926055]
46. Smith SS, Dingwall K, Jorgenson G, Douglas J. Associations between the use of common medications and sleep architecture in patients with untreated obstructive sleep apnea. *J Clin Sleep Med*. 2006; 2:156–162. [PubMed: 17557489]
47. Yu BH, Ancoli-Israel S, Dimsdale JE. Effect of CPAP treatment on mood states in patients with sleep apnea. *J Psychiatr Res*. 1999; 33:427–432. [PubMed: 10504011]
48. Haensel A, Norman D, Natarajan L, Bardwell WA, Ancoli-Israel S, Dimsdale JE. Effect of a 2 week CPAP treatment on mood states in patients with obstructive sleep apnea: a double-blind trial. *Sleep Breath*. 2007; 11:239–244. [PubMed: 17503102]
49. Habukawa M, Uchimura N, Kakuma T, Yamamoto K, Ogi K, Hiejima H, Tomimatsu K, Matsuyama S. Effect of CPAP treatment on residual depressive symptoms in patients with major depression and coexisting sleep apnea: Contribution of daytime sleepiness to residual depressive symptoms. *Sleep Med*. 2010; 11:552–557. [PubMed: 20488748]

50. Harris M, Glozier N, Ratnavadivel R, Grunstein RR. Obstructive sleep apnea and depression. *Sleep Med Rev.* 2009; 13:437–444. [PubMed: 19596599]

Figure 1.
Enrollment, randomization, and follow-up diagram.

Figure 2A

Figure 2B

Figure 2.

Figure 2a. Unadjusted baseline and 6-month BDI scores within OSA group $\times$ treatment arm in patients with major depression (n=131).

Figure 2b. Unadjusted baseline and 6-month BDI scores within OSA group $\times$ treatment arm in patients with minor depression (n=158).

Table 1

Baseline Characteristics by Sleep Apnea Classification

Characteristic	Obstructive Sleep Apnea		p
	Present (n=64)	Absent (n=225)	
Age (years)	61.5 (10.9)	55.2 (12.0)	.0002
Gender (female)	19 (29.7%)	119 (52.9%)	.001
Caucasian	50 (78.1%)	157 (69.8%)	.19
Education > 12 years	46 (75.4%)	152 (70.0%)	.41
Body mass index (kg/m ²)	28.9 (6.2)	29.6 (6.1)	.42
Cigarette smoker			.36
Never	20 (31.3%)	50 (22.6%)	
Former	21 (32.8%)	78 (35.3%)	
Current	23 (35.9%)	93 (42.1%)	
Hypertension	13 (20.6%)	51 (23.2%)	.67
Diabetes	27 (42.2%)	70 (31.7%)	.12
Cerebrovascular disease	7 (11.1%)	23 (10.7%)	.94
Left ventricular ejection fraction < 40%	17 (29.3%)	39 (19.1%)	.09
Killip class III–IV	4 (6.7%)	8 (3.8%)	.34
Creatinine (mg/dl)	1.19 (.71)	1.12 (.89)	.56
Previous myocardial infarction	19 (30.2%)	41 (19.0%)	.06
Previous coronary bypass surgery	10 (15.9%)	16 (7.4%)	.04
Coronary bypass surgery after index MI	4 (6.3%)	34 (15.2%)	.07
Coronary angioplasty after index MI	36 (57.1%)	134 (60.1%)	.67
ENRICHD treatment group			.75
Usual Care	35 (54.7%)	118 (52.4%)	
Intervention	29 (45.3%)	107 (47.6%)	
Depression diagnosis			.99
Minor depression	35 (54.7%)	123 (54.7%)	
Major depression	29 (45.3%)	102 (45.3%)	
Beck Depression Inventory (BDI)			
Baseline	17.5 (7.8)	17.2 (7.3)	.83
6 month	8.0 (7.7)	10.4 (9.0)	.08
ENRICHD Social Support Instrument (ESSI)			
Baseline	26.8 (5.9)	25.5 (6.5)	.14
6 month	28.8 (4.6)	26.9 (5.9)	.04
Medications at baseline			
Aspirin	56 (88.9%)	191 (89.3%)	.94
Ace inhibitor	35 (55.6%)	96 (44.0%)	.11
Beta blocker	56 (88.9%)	170 (78.0%)	.05
Calcium channel blocker	8 (12.9%)	39 (17.9%)	.35
Antidepressant	9 (14.5%)	24 (11.0%)	.45
Cyclic Variation of Heart Rate Index (CVHRI)	29.2 (14.6)	6.1 (4.0)	<.0001

Continuously-distributed variables are displayed as mean (standard deviation); categorical variables are listed as number (percentage of subjects with the characteristic). Chi-square tests and analyses of variance were used to determine significance.

Table 2

Effects of Obstructive Sleep Apnea on Depression Treatment Outcomes

Model	Model R ²	Baseline BDI		Treatment (T)		OSA (O)		O × T Interaction	
		t	p	t	p	t	p	t	p
<u>All patients (n=289)</u>									
Step 1	.18	7.20	<.0001	2.88	.004				
Step 2	.19	7.24	<.0001	2.92	.004	1.60	.11		
Step 3	.19	7.26	<.0001	1.97	.05	1.53	.13	0.80	.42
<u>Minor Depression (n=158)</u>									
Step 1	.08	3.00	.003	2.16	.03				
Step 2	.12	2.90	.004	2.13	.03	2.54	.01		
Step 3	.12	2.90	.004	1.61	.11	2.50	.01	0.34	.74
<u>Major Depression (n=131)</u>									
Step 1	.17	4.55	<.0001	2.03	.04				
Step 2	.17	4.53	<.0001	2.02	.04	0.10	.92		
Step 3	.18	4.54	<.0001	1.22	.22	0.04	.97	0.80	.42

Table 3

Beck Depression Inventory Scores 6 Months Post-Randomization

Sample	Group ^J		Effect Size	
	Usual Care	Treatment	Cohen's <i>d</i>	95% C.I.
Overall (n=289)	11.5 (0.7)	8.8 (0.7)	0.34	(0.12, 0.58)
Obstructive sleep apnea				
Absent (n=225)	12.2 (0.8)	9.0 (0.8)	0.40	(0.14, 0.67)
Present (n=64)	9.5 (1.4)	8.1 (1.5)	0.17	(-0.32, 0.66)
Depression diagnosis				
Minor depression (n=158)	9.4 (0.8)	6.9 (0.8)	0.35	(0.04, 0.67)
Major depression (n=131)	14.3 (1.6)	11.1 (1.1)	0.36	(0.02, 0.71)
Obstructive sleep apnea within depression subgroups				
Minor depression				
Obstructive sleep apnea absent (n=123)	10.2 (0.9)	7.6 (1.0)	0.37	(0.01, 0.73)
Obstructive sleep apnea present (n=35)	6.4 (1.6)	4.7 (1.7)	0.25	(-0.41, 0.92)
Major depression				
Obstructive sleep apnea absent (n=102)	14.8 (1.4)	10.8 (1.2)	0.44	(0.05, 0.84)
Obstructive sleep apnea present (n=29)	13.1 (2.3)	12.3 (2.6)	0.09	(-0.64, 0.82)

^J Cell values represent the least-squares mean (standard error) 6-month BDI score, adjusted for baseline Beck Depression Inventory score.