The Significance of Treating Somatic Symptoms on Functional Outcome Improvement in Patients With Major Depressive Disorder: A Post Hoc Analysis of 2 Trials

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Background: Functional impairment is associated with major depressive disorder (MDD), and patients with MDD often present with somatic symptoms.

Objective: To examine the relationships between improved global functioning and core depressive symptoms as well as painful and nonpainful somatic symptoms in patients with MDD.

Method: This post hoc analysis of 2 identical trials compared the efficacy of duloxetine with that of paroxetine or placebo as treatment of MDD. In the trials, patients with DSM-IV–defined MDD received duloxetine 80 mg/day (N = 188), duloxetine 120 mg/day (N = 196), paroxetine 20 mg/day (N = 183), or placebo (N = 192) for 8 weeks. The Sheehan Disability Scale (SDS), Maier subscale of the 17-item Hamilton Rating Scale for Depression, 21-item Somatic Symptom Inventory, and Visual Analog Scale for overall pain were used to measure functional impairment, core symptoms of depression, and nonpainful and painful somatic symptoms, respectively. Baseline-to-endpoint mean changes in SDS total and subdomains were measured using analysis of variance with last-observation-carried-forward Pearson partial correlations, and path analysis was used to assess the significance of associations and relative contributions of improvement in global functional impairment, depression, and somatic symptoms. The trials were conducted from November 2000 to July 2002.

Results: The difference between antidepressant treatment and placebo in SDS total and subdomains was significant ($p < .001$). At baseline and in change from baseline to endpoint, associations between global functional impairment and core depressive and somatic symptoms were all significant ($p < .05$). Path analysis demonstrated improvement of functional impairment attributed to treatment effect as 37.0% (core depressive symptoms), 13.0% (nonpainful somatic symptoms), and 11.0% (painful somatic symptoms).

Conclusion: In patients with MDD, over a third of functional improvement associated with antidepressant therapy was mediated through improvement in core depressive symptoms. In addition, a significant proportion of functional improvement, although to a lesser degree, was associated with the treatment of both nonpainful and painful somatic symptoms.

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The authors accept full responsibility for the conduct of this study, had full access to all data from this study, and participated in the decision to publish the data.

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Patients with major depressive disorder (MDD) often present with a broad range of core mood symptoms, including depressed mood, anhedonia, guilt, worthlessness, and anxiety. Additionally, symptoms reflecting cognitive and/or behavioral deficits, as well as those of a somatic nature, are often present. Recent evaluations of the prevalence and character of painful somatic symptoms associated with depression suggest that such symptoms are common and that treatment of these symptoms plays an important role in achieving optimal outcomes with antidepressant treatment.[1–6] About 65% of patients with depression in clinical care settings were reported to have concomitant pain.[7] In primary care centers, 69% of the patients who met the criteria of major depression reported only somatic symptoms as their chief complaint.[8]

The definitions and prevalence of painful and nonpainful somatic conditions vary from study to study depending on a number of known factors, including geographic location and patient care setting.[9] Qualitative assessments of patients with MDD have shown that the severity of depression was higher in patients with painful somatic symptoms (PSS) compared to those without PSS.[10,11] It has also been reported that the baseline severity of PSS was associated with poor health outcomes, including more severe depression and pain-related functional limitations.[10,12]

The goal of treatment with antidepressant medications is the remission of MDD symptoms.[13] Implications of

remission are not only symptom resolution, but patient functioning.[14] Judd and coauthors[15] concluded that even the mildest residual symptoms can negatively impact depression treatment outcomes and found that patients with depression who recovered with no symptoms remained well for a median of 4.3 years (224 weeks) before recurrence of depression, compared to approximately 6 months for recovered patients who had residual symptoms. These data highlight the importance of broadly treating the symptoms of depression. In MDD, effective treatment of core mood symptoms as well as painful somatic symptoms increases the chance of remission. Fava and colleagues[3] found that in an acute-treatment study (9 weeks), the remission rate for patients with depression who had at least a 50% improvement in painful somatic symptoms (36.2%) was nearly twice that of patients with depression who had less than 50% improvement in painful somatic symptoms (17.8%; $p < .001$), regardless of treatment with duloxetine or placebo.

The presence of significant functional impairment in patients with depression is well documented. Such impairment affects patients' ability to maintain healthy interpersonal relationships and causes diminished work capacity.[10–12] Additionally, the coexistence of depression and pain often leads to decreased productivity and results in lower rates of help seeking.[9]

The diagnosis and treatment of depression with associated pain or painful somatic symptoms may often be overlooked for various reasons including patients' and/or physicians' lack of awareness/understanding of the comorbid relationship,[16,17] and because the severity of pain/painful somatic conditions concomitant with depression may affect functioning. It is a clinical challenge for physicians to understand the comorbid relationship of depression and pain in the counseling and treatment of patients.[18] Thus, it is important to recognize and quantify this relationship as part of antidepressant treatment.

Here, we report on the relationships between global functioning and core symptoms of MDD, nonpainful somatic symptoms, and PSS in patients with MDD prior to and during treatment with one of 2 antidepressants or placebo in 2 phase 3 safety and efficacy studies. Further, relationships between functional status changes, depressive symptomatology, and nonpainful somatic symptoms and PSS during acute antidepressant treatment are presented to quantitatively assess the relative contribution that improvements in each of these symptoms make to overall functional improvement in patients with MDD.

METHOD

The findings presented here are post hoc analyses based on data pooled from 2 identical, randomized, double-blind, active-comparator, clinical trials designed to compare the safety and efficacy of 8 weeks of duloxetine versus paroxetine or placebo as treatment of MDD.[19,20] These 2 studies were specifically chosen for this assessment because they contained well-validated and accepted measures of functional impairment, pain, and somatic symptomatology. Patients were randomly assigned to receive duloxetine 80 mg/day (N = 188), duloxetine 120 mg/day (N = 196), paroxetine 20 mg/day (N = 183), or placebo (N = 192). The trials were conducted from November 2000 to July 2002.

Patients ≥ 18 years of age with MDD as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), and confirmed using the Mini International Neuropsychiatric Interview (MINI),[21] were potentially eligible. Inclusion criteria included a Clinical Global Impressions-Severity of Illness scale (CGI-S) score ≥ 4 and a 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) total score ≥ 15 at screening and baseline study visits. Patients screened for these studies were not selected based on the presence or severity of pain or somatic symptoms. Participating centers' institutional review boards approved these studies prior to the enrollment of any patients. All participating patients provided written informed consent consistent with all regulatory requirements prior to receiving any study treatment or undergoing any study procedure.

The Maier subscale of the $HAM\text{-}D_{17}$ (representing the sum of $HAM\text{-}D_{17}$ items 1 = depressed mood, 2 = feelings of guilt, 7 = work and activities, 8 = retardation, 9 = agitation, and 10 = psychic anxiety) was used as a measure of core symptoms of MDD.[22] The Visual Analog Scale (VAS) for overall pain was used to measure PSS.[23] Patients were asked to indicate the severity of their pain by placing marks on a 100-mm line, where 0 mm represented no pain and 100 mm represented pain as severe as the patient could imagine. A patient's score was determined by measuring his/her mark to the nearest millimeter.

The 5 pain-related items of the 26-item Somatic Symptom Inventory (SSI) were removed to create the SSI-21 average (mean) score as a measure of general nonpainful somatic symptoms, which include the following: 1 = nausea or vomiting; 4 = feeling faint or dizzy; 5 = trouble with your vision; 6 = your muscles twitching or jumping; 7 = feeling fatigued, weak, or tired all over; 8 = a fullness in your head or nose; 10 = constipation; 11 = trouble catching your breath; 12 = hot or cold spells; 13 = a ringing or buzzing in your ears; 15 = difficulty keeping your balance while walking; 16 = indigestion, upset stomach, or acid stomach; 17 = the feeling that you are not in as good physical health as most of your friends; 18 = numbness, tingling, or burning in parts of your body; 20 = a lump in your throat; 21 = feeling weak in parts of your body; 22 = not feeling well most of the time in the past few years; 23 = heavy feelings in your arms and legs; 24 = your heart pounding, turning over, or missing a beat; 25 = your hands and feet not feeling warm enough;

26 = the sense that your hearing is not as good as it used to be. The 5 pain items removed were 2 = soreness in your muscles, 3 = pains or cramps in your abdomen, 9 = pains in your lower back, 14 = pains in your heart or chest, and 19 = headaches. The average of the 21 items was calculated across the items for each patient at each visit. The Sheehan Disability Scale (SDS) was used as a measure of global functioning.[24] The SDS is a validated tool for measuring patient functioning and assesses the level of disruption caused by symptoms across 3 distinct domains: work/school, social life/leisure activities, and family life/home responsibilities. Response categories for each of the 3 items range from 0 to 10, with higher values indicating greater disruption in the respective area of life. The SDS global functioning score is the sum of the scores from the 3 items and can range from 0 to 30. In a validation study of the SDS using primary care patients, SDS global functioning scores ≥ 5 were associated with role impairment due to psychiatric illness.[25]

Statistics

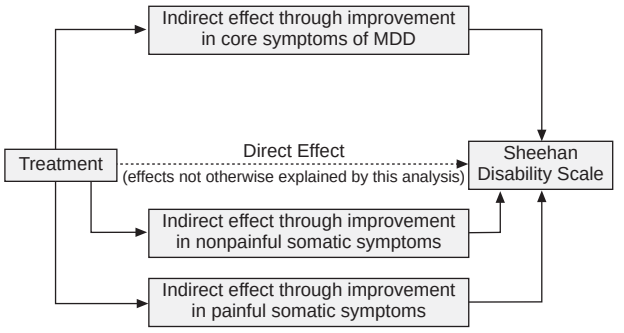
Baseline characteristics were summarized for the 2 antidepressant and placebo treatment groups. Continuous variables were compared across treatment group using an analysis of variance (ANOVA) model with terms for investigator and therapy. Categorical variables were compared using Fisher exact test. All statistical comparisons were tested at the $\alpha = .05$ significance level.

Mean change in the SDS total score, SDS individual item scores, VAS overall pain score, SSI-21 average score, and HAM-D_{17} Maier subscale score from baseline to endpoint were compared between the pooled active treatment arms and placebo using ANOVA with a last-observation-carried-forward (LOCF) approach. The model included terms for study, baseline score, and therapy.

The associations between the functional impairment, MDD symptomatology, and nonpainful and PSS at baseline, and for changes from baseline to endpoint, were quantified using Pearson correlation coefficients for all randomized patients. Pairwise partial correlations were derived. Change from baseline was determined using each patient's LOCF during the 8-week treatment period.

Path analyses were conducted to assess the benefits in functional outcome associated with the treatment of both nonpainful and PSS beyond that due to treatment of core MDD symptoms.[26,27] Since there were no statistically significant differences between duloxetine and paroxetine in improvements in VAS overall pain scores or SSI-26 average item scores in the 2 studies, these 2 treatment groups were combined into a single group in order to better estimate the contribution of treatment effects in MDD and somatic symptoms. Path analysis was also used to estimate the percentage of the overall treatment effect on improving global functioning due to improvement in core symptoms of MDD as assessed by the Maier subscale of the HAM-D_{17}, as well as effects that occurred as a result of improvement in both nonpainful somatic symptoms (assessed by the SSI-21) and PSS (assessed by the VAS). This is accomplished using a set of multivariate regression models, one modeling the mean change in VAS overall pain score with predictors for treatment group, baseline SSI-21 average score, baseline VAS overall pain score, and change in HAM-D_{17} Maier subscale score, and 3 others modeling the mean change in SSI-21 average score, VAS overall pain score, and HAM-D_{17} Maier subscale score with a predictor for treatment group. Path analysis provides a mechanism for partitioning the overall treatment effect on functioning into quantitative components that represent the relative contribution of improvement in functioning as associated with treatment of painful somatic symptoms, nonpainful somatic symptoms, and core symptoms of MDD as well as a direct effect. The direct effect is composed of the pure treatment effect, that effect solely mediated by therapy on the outcome of interest, as well as any (unknown) indirect effects. Figure 1 shows the general description of a path diagram.[28] Further analyses were conducted on the subset of patients who had moderate to severe pain, defined as a baseline VAS overall pain score ≥ 30.

Figure 1. Schematic Diagram of the Path Analysis Showing the Benefit in Functional Outcome by Treatment of Nonpainful Somatic Symptoms and Painful Somatic Symptoms in Addition to Core Major Depressive Disorder (MDD) Symptoms



RESULTS

A total of 759 patients were randomly assigned to duloxetine 80 mg/day (N = 188), duloxetine 120 mg/day (N = 196), paroxetine 20 mg/day (N = 183), or placebo (N = 192). Demographic and baseline disease characteristics for the patient sample are presented in Table 1. A total of 192 patients from placebo group and 567 patients from combined treatment group were included in the pooled data. No significant differences were observed in baseline characteristics between the antidepressant treatment and placebo groups.

Table 1. Baseline Demographics and Characteristics of All Randomized Patients

Characteristic	Placebo (N = 192)	Antidepressant (N = 567)[a]
Age, mean (SD), y	44.2 (11.1)	44.4 (11.1)
Female, N (%)	134 (69.8)	407 (71.7)
Ethnic origin, N (%) white	192 (100.0)	567 (100.0)
HAM-D_{17} total, mean (SD)	20.2 (3.7)	20.7 (3.7)
HAM-D_{17} Maier subscale, mean (SD)	10.0 (2.2)	10.3 (2.2)
SSI-21 item average, mean (SD)	2.2 (0.7)	2.2 (0.7)
VAS, overall, mean (SD)	33.3 (25.7)	35.6 (26.4)
Clinically significant pain ≥ 30 mm, N (%)	92 (47.9)	292 (52.1)[b]
SDS, total, mean (SD)	19.5 (6.4)	19.7 (6.1)

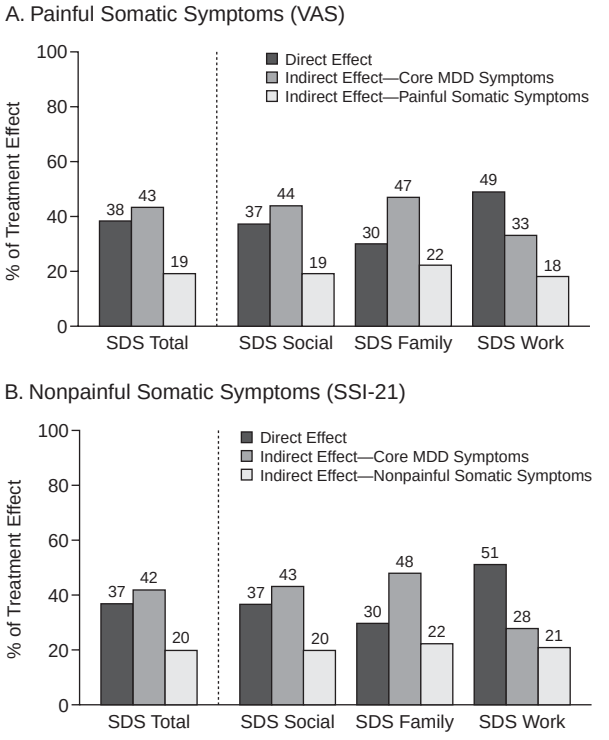
[a]Includes patients randomly assigned to duloxetine 80 mg (N = 188), duloxetine 120 mg (N = 196), and paroxetine 20 mg (N = 183).
[b]N = 561.
Abbreviations: HAM-D_{17} = 17-Item Hamilton Rating Scale for Depression, SDS = Sheehan Disability Scale, SSI-21 = 21-item Somatic Symptom Inventory, VAS = Visual Analog Scale.

Table 2. Change From Baseline to Endpoint in Measures of Functioning, Core MDD Symptoms, and Painful and Nonpainful Somatic Symptoms, Mean (SE)

Measure	Placebo (N = 184)	Antidepressant (N = 538)	p Value
SDS			
Total score	–6.09 (0.56)	–8.94 (0.32)	< .001
Social life/leisure	–2.09 (0.20)	–3.05 (0.12)	< .001
Family life/home	–2.08 (0.19)	–2.89 (0.11)	< .001
Work/school	–1.77 (0.21)	–2.79 (0.12)	< .001
VAS overall pain score	–7.48 (1.57)	–12.14 (0.92)	.011
SSI-21 average score	–0.26 (0.04)	–0.39 (0.02)	.004
HAM-D_{17} Maier subscale score	–4.74 (0.23)	–5.98 (0.13)	< .001

Abbreviations: HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, MDD = major depressive disorder, SDS = Sheehan Disability Scale, SSI-21 = 21-item Somatic Symptom Inventory, VAS = Visual Analog Scale.

Figure 2. Benefit in Functional Outcome via Treatment of Core MDD Symptoms and (A) Painful Somatic Symptoms and (B) Nonpainful Somatic Symptoms: Path Analysis



Abbreviations: MDD = major depressive disorder, SDS = Sheehan Disability Scale, SSI-21 = 21-item Somatic Symptom Inventory, VAS = Visual Analog Scale.

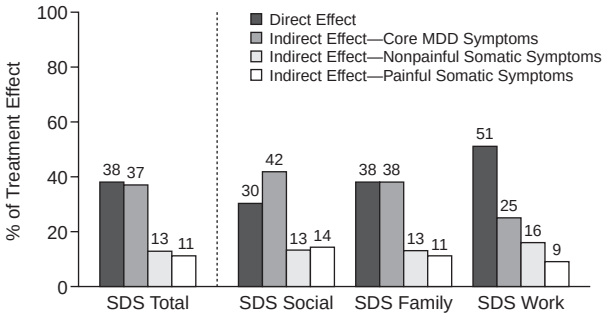
The least squares mean changes ± standard error from baseline for the SDS total score and its individual items are presented in Table 2. There were significantly greater reductions in the SDS total score and its individual items in the antidepressant treatment group versus the placebo group ($p < .001$).

At baseline, the correlation between global functioning (SDS) and core depressive symptoms (HAM-D_{17} Maier subscale) was 0.16, and the partial correlation controlling for nonpainful somatic symptoms and PSS (SSI-21 and VAS, respectively) was 0.13. The correlation between global functioning and PSS was 0.35, and the partial correlation controlling for core depressive symptoms was 0.34. The correlation between global functioning and nonpainful somatic symptoms was 0.49, and the partial correlation controlling for core depressive symptoms was 0.48. All baseline correlations were statistically significant ($p < .05$).

The correlation for change from baseline to endpoint between global functioning and core depressive symptoms was 0.56, and the partial correlation controlling for nonpainful and PSS was 0.40. The correlation between global functioning and painful somatic symptoms was 0.55, and the partial correlation controlling for core depressive symptoms was 0.45. The correlation between global functioning and nonpainful somatic symptoms was 0.56, and the partial correlation controlling for core depressive symptoms was 0.46. All the associations in changes from baseline to endpoint were significant ($p < .05$).

Results of the path analyses on the SDS total score and its individual items with the HAM-D_{17} Maier subscale score and VAS overall pain or SSI-21 average score as indirect factors are presented in Figures 2A and 2B. Similarly, in patients with clinically significant pain, the total SDS scores were as follows: direct effect, 48%; indirect effect–core MDD symptoms, 32%; indirect effect–nonpainful somatic symptoms, 9%; and indirect effect–PSS, 11%. Findings of the path analysis on the SDS total score and its individual items containing both nonpainful somatic symptoms (SSI-21) and PSS (VAS) along with core depressive symptoms (HAM-D_{17} Maier subscale) as indirect factors are presented in Figure 3.

Figure 3. Benefit in Functional Outcome via Treatment of Core MDD Symptoms, Painful Somatic Symptoms (VAS), and Nonpainful Somatic Symptoms (SSI-21): Path Analysis



Abbreviations: MDD = major depressive disorder, SDS = Sheehan Disability Scale, SSI-21 = 21-item Somatic Symptom Inventory, VAS = Visual Analog Scale.

DISCUSSION

Impairment of social and occupational functioning is a core effect of MDD according to the DSM-IV. The current analysis demonstrates that antidepressant therapy improves global functioning in patients with MDD, as demonstrated by the significantly greater improvement with active treatment (duloxetine or paroxetine) versus placebo in the SDS total score and its individual domains: work/school, social life/leisure activities, and family life/home responsibilities.

Furthermore, patients with MDD may present with a broad range of symptoms including those related to mood alteration, cognitive deficit(s), and somatization, all of which may contribute to global functional impairment. This post hoc analysis assessed quantitative contributions of core mood symptoms and nonpainful and painful somatic symptoms in improving functional impairment in a cohort of patients with MDD.

At baseline, global functioning was mildly correlated with core depressive symptoms (0.16), moderately correlated with PSS (0.35), and highly correlated with nonpainful symptoms (0.49). Partial correlation coefficients were very similar in magnitude, reflecting strong independence among core depressive symptoms and nonpainful and painful somatic symptoms at baseline. Although baseline correlations are limited in their interpretability, these results suggest that somatic symptoms are more strongly associated with functional impairment in depressed patients compared with core depressive symptoms.

Improvement in global functioning was highly correlated with improvement in core depressive symptoms (0.56) and nonpainful (0.56) and painful (0.55) somatic symptoms. Partial correlations were smaller, ranging from 0.40 to 0.46, but still comparably high, suggesting that improvements in all 3 domains are independent factors that are strongly associated with improvement in functional impairment in patients with MDD.

Quantitative assessments of the relative contributions that nonpainful and painful somatic symptoms make to functional improvement further support the above notion. The current path analysis data demonstrate that, while nearly 40% of the improvement seen in functioning was driven primarily through improvement in core depressive symptomatology, 19% to 20% was attributed to nonpainful somatic symptoms and PSS when assessed separately. Findings were similar across the individual work/school, social life/leisure activities, and family life/home responsibilities domains of the SDS. When assessed in conjunction, improvement in nonpainful somatic symptoms accounted for 13% of the improvement in functioning, while improvement in PSS accounted for 11% of the improvement in functioning, suggesting that improvements in somatic symptoms contribute similarly to functional improvement. Additionally, the similarity of findings in the subset of patients with clinically significant pain at baseline to those mentioned above supports that the above findings are relevant to the overall cohort of patients studied in these trials and are not confined to depressed populations with coexisting somatic symptoms.

This report reinforces the need to effectively treat both mood and somatic symptoms associated with depression in order to achieve optimal functional improvement. Recent findings that painful somatic symptoms are important predictors not only of improvement in quality of life, but also of successful antidepressant treatment[11] including remission[3] further demonstrate the importance of treating painful somatic symptoms in patients with MDD.

There are several limitations of this study that should be considered when reviewing this work. The 8-week treatment period used in these studies is most likely too short to assess maximum improvement in depressive symptoms and functional impairment. As such, it is unknown if the relationships between functional improvement, core depressive symptoms, and nonpainful and painful somatic symptoms hold constant during the longer treatment periods usually associated with antidepressant therapy. Additionally, these trials utilized specific scales to measure functional impairment, core depressive symptoms, and somatic symptoms. Other scales that measure such factors, either more or less broadly, may provide different results. Finally, the analytic approaches presented herein assume that changes in core depressive symptomatology and nonpainful and painful somatic symptoms have a unidirectional cause-and-effect relationship with changes in functional impairment. Although this is a reasonable assumption given the extensive research on the treatment of depression, it cannot be ruled out that the cause-and-effect relationship may be bidimensional and that changes in functional impairment may affect changes in core depressive or somatic symptoms.

In summary, the greatest proportion of functional improvement associated with antidepressant therapy in MDD patients was mediated through improvement in core depressive symptoms. In addition, a significant proportion of functional improvement, although to a lesser degree, was associated with the treatment of both nonpainful and painful somatic symptoms. These findings support other published work demonstrating the importance of treating somatic symptoms to achieve optimal outcomes in patients with MDD.

Drug names: duloxetine (Cymbalta), paroxetine (Paxil, Pexeva, and others).

REFERENCES

1. Karp JF, Buysse DJ, Houck PR, et al. Relationship of variability in residual symptoms with recurrence of major depressive disorder during maintenance treatment. Am J Psychiatry 2004;161:1877–1884
2. Ohayon MM. Specific characteristics of the pain/depression association in the general population. J Clin Psychiatry 2004;65(suppl 12):5–9
3. Fava M, Mallinckrodt CH, Detke MJ, et al. The effect of duloxetine on painful physical symptoms in depressed patients: do improvements in these symptoms result in higher remission rates? J Clin Psychiatry 2004 Apr;65(4):521–530
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000:356
5. Kroenke K, Spitzer RL, Williams JB, et al. Physical symptoms in primary care: predictors of psychiatric disorders and functional impairment. Arch Fam Med 1994;3:774–779
6. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289:3095–3105
7. Bair MJ, Robinson RL, Katon W, et al. Depression and pain comorbidity: a literature review. Arch Intern Med 2003;163:2433–2445
8. Simon GE, VonKorff M, Piccinelli M, et al. An international study of the relation between somatic symptoms and depression. N Engl J Med 1999;341:1329–1335
9. Demyttenaere K, Bonnewyn A, Bruffaerts R, et al. Comorbid painful physical symptoms and depression: prevalence, workloss, and help seeking. J Affect Disord 2006;92:185–193
10. Von Korff M, Simon G. The relationship between pain and depression. Br J Psychiatry Suppl 1996 Jun;(30):101–108
11. Bair MJ, Robinson RL, Eckert GJ, et al. Impact of pain on depression treatment response in primary care. Psychosom Med 2004;66:17–22
12. Von Korff M, Ormel J, Katon W, et al. Disability and depression among high utilizers of health care: a longitudinal analysis. Arch Gen Psychiatry 1992;49:91–100
13. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder [Revision]. Am J Psychiatry 2000;157(suppl 4):1–45
14. Miller IW, Keitner GI, Schatzberg AF, et al. The treatment of chronic depression, pt 3: psychosocial functioning before and after treatment with sertraline or imipramine. J Clin Psychiatry 1998 Nov;59(11):608–619
15. Judd LL, Akiskal HS, Maser JD, et al. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. J Affect Disord 1998;50:97–108
16. Tylee A, Gandhi P. The importance of somatic symptoms in depression in primary care. Prim Care Companion J Clin Psychiatry 2005;7(4): 167–176
17. Wise TN, Arnold LM, Maletic V. Management of painful physical symptoms associated with depression and mood disorders. CNS Spectr 2005;10(suppl 12):1–13
18. Wise TN, Fishbain DA, Holder-Perkins V. Painful physical symptoms in depression: a clinical challenge. Pain Med 2007 Sep;8(suppl 2):S75–S82
19. Detke MJ, Wiltse CG, Mallinckrodt CH, et al. Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Neuropsychopharmacol 2004;14: 457–470
20. Perahia DG, Wang F, Mallinckrodt CH, et al. Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Psychiatry 2006;21:367–378
21. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(suppl 20):22–33
22. Maier W, Philipp M. Improving the assessment of severity of depressive states: a reduction of the Hamilton Depression Scale. Pharmacopsychiatry 1985;18:114–115
23. DeLoach LJ, Higgins MS, Caplan AB, et al. The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. Anesth Analg 1998;86:102–106
24. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol 1996 Jun;11(suppl 3):89–95
25. Leon AC, Olfson M, Portera L, et al. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. Int J Psychiatry Med 1997;27:93–105
26. Retherford RD, Choe MK. Statistical Models for Causal Analysis. New York, NY: John Wiley & Sons; 1993
27. Johnson RA, Wichern DW. Applied Multivariate Statistical Analysis. 3rd ed. Englewood Cliff, NJ: Simon & Schuster; 1992
28. Alwin DF, Hauser RM. The decomposition of effects in path analysis. Am Sociol Rev 1975;40:37–47