Commentary

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Somatic Symptoms, Depression, and Antidepressant Treatment

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The article by Detke and colleagues[1] in this issue of the *Journal* presents very interesting data on the effect of a novel dual-action antidepressant, duloxetine, on painful physical symptoms from a placebo-controlled study of patients suffering from major depressive disorder (MDD). MDD is a psychiatric disorder involving a range of psychological, physical, somatic, and behavioral symptoms. The DSM classification of MDD has traditionally had a greater focus on some of the psychological symptoms of depression, such as depressed mood, lack of interest, excessive guilt, suicidal thoughts, feelings of worthlessness, and indecisiveness. Although some of the physical/somatic MDD symptoms, primarily fatigue and both sleep and appetite disturbances, are included in the DSM-IV classification of this disorder,[2] it is apparent that somatic and physical symptoms are underrepresented in the current nosology, despite the fact that they represent the chief complaint for a substantial proportion of patients suffering from MDD. Indeed, as many as 76% of patients suffering from depression were found to report somatic symptoms, including various types of pain, such as headaches, stomach pain, vague, poorly localized pain, and back pain.[3,4] In addition, physical symptoms such as back pain, musculoskeletal complaints, and chest pain have been shown to predict greater depression severity.[5]

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NOSOLOGICAL ISSUES

The nosology of some of the subtypes of MDD, however, has placed a much greater emphasis on the debilitating aspects of MDD-associated somatic and physical symptoms. For example, in the case of the DSM-IV classification of MDD with atypical features or atypical depression, physical or somatic symptoms comprise 3 of the 4 required associated features (extreme fatigue/leaden paralysis, hyperphagia, and hypersomnia). The leaden paralysis of atypical depression is an interesting physical symptom that captures the common description by depressed patients of severe fatigue/heaviness in arms and legs (as if the limbs were filled with lead). On the other hand, in addition to fatigue and sleep and appetite disturbances (included in the DSM-IV definition of MDD), MDD is associated with many other troublesome somatic and physical symptoms. These symptoms range from muscle tension to headaches, backaches, and a general symptomatology of pain. In some instances, these common somatic symptoms of pain have been attributed to other medical conditions or to conditions whose relationship with depression is poorly understood, such as fibromyalgia.

One could argue that the current, DSM-IV-based conceptualization of MDD, emphasizing psychological symptoms as key features of the disorder, has led to a bias toward the underestimation of the rate of MDD in populations that primarily complain of somatic symptoms. A study by Posse and Hallstrom[6] identified cases of masked depression in primary health care, by employing a 2-stage design. In the first stage, involving a study of 442 patients, the prevalence of recognized depression was 1.8%. In the second stage, of 62 patients screened negative at stage 1 and investigated further because of high somatization scores, 39 (63%) were found to have a mood

disorder (MDD or dysthymia) according to DSM-III-R. Stage 2 almost tripled the estimate of MDD prevalence in this population, providing support to the view that somatic symptoms may be the presenting and key features of MDD in a significant proportion of patients.[6] Interestingly, the diagnostic category with the highest rate of depressed patients was "musculoskeletal diseases."[6] The issue of underrecognition of MDD secondary to the greater emphasis on psychological than somatic symptoms is even more crucial in minority populations, as these populations have, historically, had limited access to medical resources in general.[7]

ASSESSMENT OF SOMATIC SYMPTOMS

Many clinicians have been led to believe by the current nosology that it is more important to track psychological symptoms and only some, but certainly not many, of the concurrent somatic symptoms. For that reason, few clinicians systematically assess somatic symptoms among depressed patients, and, even in the presence of significant somatic symptomatology at the outset, they do not target and/or track such symptoms during the course of the treatment. The use in clinical practice of sensitive scales assessing somatic symptoms remains rather uncommon, and, similarly, the conventional scales used to measure depression in clinical trials rarely include significant numbers of somatic symptoms. For example, the Montgomery-Asberg Depression Rating Scale (MADRS)[8] is a 10-item clinician-rated scale that includes only 3 somatic symptoms (decreased appetite, insomnia, and fatigue). The Hamilton Rating Scale for Depression (HAM-D)[9] is typically administered in its 17-item version, which does include a greater number of somatic symptoms (insomnia, decreased appetite/weight loss, fatigue, somatic/anxiety symptoms) than the MADRS. However, while psychological symptoms (depressed mood, feelings of guilt, suicidal thoughts, reduced interest/productivity, psychic anxiety, reduced libido, hypochondriasis, insight) and psychological/behavioral symptoms (retardation and agitation) may account for up to 38 points of the possible total score of 56, somatic symptoms may account for up to only 18 points (32% of the maximum total score). In addition, the HAM-D still places a much greater emphasis on sleep and appetite disturbances, which can account for up to 10 of the total 18 points related to somatic symptoms, and mixes fatigue with aches and backaches in one of the remaining items, thereby poorly tracking pain symptoms. These problems are not unique to the HAM-D and the MADRS. In fact, most scales that focus on depression tend to concentrate primarily on the psychological symptoms, as pointed out by Zung.[10] In summary, it appears that most of the scales used to assess depression in clinical studies have failed to bring the somatic aspect of depression to a level of attention and assessment equal to that of the psychological symptoms. The study by Detke and colleagues in this issue,[1] by utilizing visual analogue scales to track changes in painful physical symptoms during their study, was able to show a greater effect of duloxetine on these domains compared with placebo.

Which instruments can clinicians use to assess and track somatic symptoms of depression? Unfortunately, the literature does not help us much, as most of the best-studied somatic symptom instruments, such as the Illness Attitude Scale[11] and the Somatization Sensation Inventory,[12] are focused more on somatization and hypochondriacal concerns and tend to be relatively more predictive of the presence of anxiety disorders than of depression. Many such scales tend to include more "trait" than "state" measures for somatic symptoms, thereby reducing their sensitivity to detect changes following treatment. Probably, the instruments that help clinicians and clinical researchers the most in tracking somatic symptoms are those that are "state measures" and broad-based, such as the Symptom Questionnaire[13] and the 90-item Hopkins Symptom Checklist (SCL-90).[14] In particular, the Symptom Questionnaire, which is a yes/no questionnaire containing 4 "state" scales of depression, anxiety, anger-hostility, and somatic symptoms, has been widely used in clinical studies and has shown excellent sensitivity to detect change in somatic symptoms following treatment.[13,15] A multicenter study among depressed patients who had not responded to selective serotonin reuptake inhibitors (SSRIs) showed a statistically significant reduction in the Symptom Questionnaire somatic symptoms scale scores following treatment with mirtazapine, an antidepressant affecting both norepinephrine and serotonin neurotransmission,[16] and a recent study from our group[17] showed that, among 148 outpatients with MDD, there was a significant ($p < .0001$) reduction in the Symptom Questionnaire somatic symptoms scale scores, from a mean of 9.4 to a mean of 6.2, following treatment with the antidepressant fluoxetine.

MDD REMISSION AND SOMATIC SYMPTOMS

This traditional view of focusing on psychological symptoms as key features of MDD has also clearly affected and biased our definition of response and remission. Many of the definitions used in the literature[18,19] suggest that a HAM-D score ≤ 7 is consistent with remitted MDD. Yet, someone with a 7 or less on the HAM-D may still be suffering from somatic symptoms that are not tracked adequately by the scale itself. How do we really know whether patients are truly in remission if in fact somatic symptoms that we do not ask about or track still persist? Our recent study[17] showed that responders (50% or greater reduction in HAM-D score) who have not achieved remission have significantly more somatic symptoms than remitters following 8 weeks of treatment with fluoxetine. These data suggest that we should be thinking critically

about our current definitions of remission and begin a process of redefinition of MDD and improvement/response. It is essential that such redefinition pay greater attention to the physical and somatic symptoms that are quite disabling and greatly affect the quality of life for our patients.

UNANSWERED QUESTIONS

There is yet another interesting aspect of the relationship between somatic symptoms and depression. Do the physical/somatic symptoms improve in a way that parallels improvement of psychological symptoms? Is there a tight correlation between these 2 dimensions? Is there a differential effect? Are there some antidepressants that lead to a simultaneous improvement in both and some that primarily help psychological symptoms? In fact, there is a large and long clinical experience of using tricyclic antidepressants (TCAs) in the treatment of chronic pain, with TCAs appearing to have greater analgesic efficacy than selective SSRIs.[20–23] Moreover, anecdotal case reports suggest that serotonin-norepinephrine reuptake inhibitors (SNRIs) also possess analgesic properties,[20,22] consistent with data indicating that both serotonin and norepinephrine exert analgesic effects via descending pain pathways.[24–26] The lack of a systematic assessment of all the symptoms of MDD, including those physical and somatic symptoms that are not part of the DSM-IV definition of the disorder, does not allow us to determine whether differential responsiveness exists across antidepressant drugs in terms of such broader definition of improvement. We clearly need studies assessing such potential differences and examining whether the correlation between somatic and psychological symptoms is strong or weak. On the other hand, the study by Detke and colleagues[1] in this issue does suggest that a dual-action antidepressant such as duloxetine, affecting both serotonin and norepinephrine neurotransmission, may be particularly efficacious in treating both depression and painful physical symptoms among MDD patients.

Finally, another important aspect of the relationship between somatic symptoms and depression involves the potential effect of the somatic symptoms themselves on depression. If we treat somatic symptoms and get patients to be pain-free or to attain significant reduction in aches and pains, will the physical and somatic symptom improvement bring about a more rapid and perhaps more robust improvement in depression? Future studies need to elucidate the relationship between treatment of somatic symptoms and remission to see whether treatments that are particularly effective with respect to somatic symptoms lead to greater rates of remission of MDD.

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