# The Link Between Depression and Physical Symptoms

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Physical symptoms are common in depression, and, in fact, vague aches and pain are often the presenting symptoms of depression. These symptoms include chronic joint pain, limb pain, back pain, gastrointestinal problems, tiredness, sleep disturbances, psychomotor activity changes, and appetite changes. A high percentage of patients with depression who seek treatment in a primary care setting report only physical symptoms, which can make depression very difficult to diagnose. Physical pain and depression have a deeper biological connection than simple cause and effect; the neurotransmitters that influence both pain and mood are serotonin and norepinephrine. Dysregulation of these transmitters is linked to both depression and pain. Antidepressants that inhibit the reuptake of both serotonin and norepinephrine may be used as first-line treatments in depressed patients who present with physical symptoms. Many physicians consider patients to be in remission when their acute emotional symptoms have abated, but residual symptoms—including physical symptoms—are very common and increase the likelihood of relapse. All symptoms must be measured in order to achieve full remission. There are a number of short yet accurate measurement tools (rating scales) available that effectively measure the remission of physical symptoms as well as emotional symptoms.

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## PHYSICAL SYMPTOMS IN DEPRESSION

Physical symptoms are common in major depression and may lead to chronic pain and complicate treatment. Symptoms associated with depression include joint pain, limb pain, back pain, gastrointestinal problems, fatigue, psychomotor activity changes, and appetite changes. In the primary care setting, a high percentage of patients with depression present exclusively with physical symptoms. Simon et al.[1] analyzed a World Health Organization study of somatic symptoms in the presentation of depression. Of the 1146 patients in 14 countries included in the survey who met the criteria for depression, 69% reported only somatic symptoms as the reason for their visit. Unfortunately, depression can often go undiagnosed in these patients, as the physical symptoms associated with depression may be interpreted as symptoms of a somatic illness.

Patients who present with a high number of physical symptoms may be more likely to have a mood disorder than patients who present with only a few physical symptoms. Kroenke et al.[2] studied 1000 adult primary care clinic patients and found that the number of physical symptoms present was highly predictive of mood disorders and functional impairment. In patients who reported 0 or 1 physical symptom, 2% were found to have a mood disorder, but among patients who reported 9 or more physical symptoms, 60% were found to have a mood disorder (Figure 1). Overall, the presence of any physical symptom approximately doubled the likelihood that the patient had a mood disorder.

In general, the worse the painful physical symptoms, the more severe the depression. Physical symptoms have been found to increase the duration of depressed mood. In a study of chronic pain as a predictor of depressive morbidity in the general population, Ohayon and Schatzberg[3] found that of the study participants who reported at least 1 key symptom of depression, those with a chronic painful physical condition reported a longer duration of depressed mood (19.0 months) than those without chronic pain (13.3 months).

Physical symptoms are also generally accompanied by a significant level of dysfunction in depressed patients. Elevated rates of suicidal thoughts are found in patients with chronic pain. Ohayon and Schatzberg[3] reported that, among patients who reported at least 1 key symptom of depression, 33% of those who reported suicidal thoughts (N = 687) also reported a painful condition. A review of the literature by Fishbain[4] found that suicidal ideation, suicide attempts, and suicide completions are commonly found in patients with chronic pain. Fishbain noted that several of the reviewed studies indicated that chronic pain may be a suicide risk factor.

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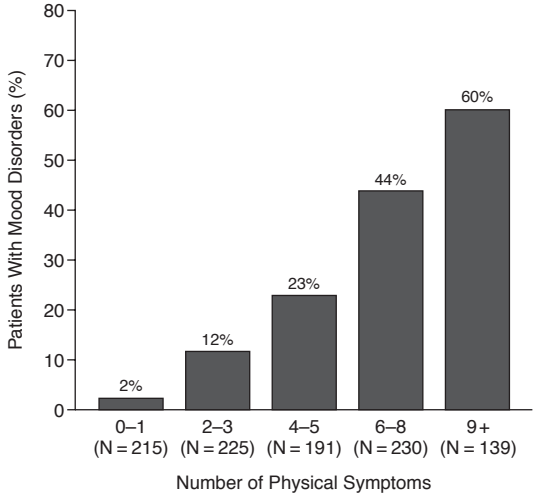
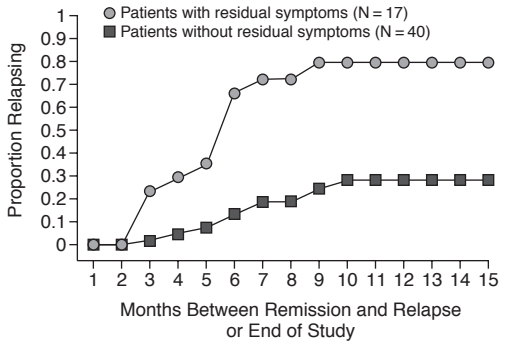
**Figure 1. Physical Symptoms as a Predictor of Mood Disorders[a]**




[a]Reprinted with permission from Kroenke et al.[2]

**Figure 2. The Relation of Residual Symptoms to Relapse in Depression[a,b]**




[a]Reprinted with permission from Paykel et al.[7]
[b]Log rank statistic = 17–43, df = 1, p < .001.

The link between pain and depression appears to be a shared neurologic pathway.[5] Response to painful physical stimuli is moderated in the brain by serotonin and norepinephrine, which also affect mood. Patients with neurotransmitter dysregulation may have an imbalance of serotonin and norepinephrine, which may explain the connection between painful physical symptoms and depression. When a patient with depression complains that he or she is feeling physical pain, there may be a chemical reason.

Therefore, antidepressants that inhibit the reuptake of both norepinephrine and serotonin have the best chance to reduce physical symptoms in patients with depression because they target the pathways that mediate both pain and depression in the brain and in the spinal cord.[6] Antidepressant medications that act as dual serotonin-norepinephrine reuptake inhibitors, such as venlafaxine and duloxetine, may aid in correcting the imbalance of serotonin and norepinephrine neurotransmission in the brain.

## INCORPORATING PHYSICAL SYMPTOMS INTO TREATMENT GOALS

As with any general medical disorder, full remission should be the long-range objective in the treatment of mood disorders. Many physicians consider a patient to be in remission from depression when his or her acute emotional symptoms have abated, but residual symptoms, including physical symptoms, increase the likelihood of relapse. Physicians should move beyond simple treatment of acute symptoms to a model in which patients are treated until full remission is achieved; a virtually asymptomatic state rather than simple response should be the ultimate goal of therapy. Many patients treated with antidepressants fail to achieve full remission, and the costs, both social and economic, of relapse or residual symptoms are high.

Numerous studies have shown[7–9] that patients with major depression who have residual symptoms after treatment have higher relapse rates and they relapse earlier than do those without residual symptoms. In fact, relapse rates are 3 times higher in individuals who have residual symptoms after they have achieved significant improvement than in individuals with no residual symptoms.[8] One may infer, then, that the likelihood of relapse is significantly reduced in patients who attain asymptomatic remission.

Paykel et al.[7] studied residual symptoms after partial remission in 64 patients with unipolar depression identified at presentation at a treatment facility; they found that residual symptoms were an important predictor of relapse of depression. All but 4 of the patients had remitted by 15 months, and 19 of those who were considered to have remitted had residual symptoms. Of the 17 individuals with residual symptoms who were followed to completion, 13 (76%) relapsed within 15 months, compared with 10 (25%) of the 40 individuals who remitted without physical symptoms (Figure 2).

Psychiatrists and primary care physicians are beginning to recognize that even though symptom domains in the areas of motivation and physical illness are frequently part of depression, they are often ignored in the assessment of depression and, subsequently, in the treatment goals. Often, pain is not included in the treatment goals because it is interpreted as a sign of a somatic illness. When treating mood disorders such as depression that are frequently associated with painful physical symptoms, the pain component of treatment needs to be given full consideration. Symptom relief that does not include relief of pain may result in an incomplete or false remission.

Significant improvement in all symptoms, including physical symptoms as well as general functioning, is necessary not only in the acute period but also in the maintenance phase to prevent relapse and ensure full remission of mood disorders.

The degree of impairment associated with all symptoms of depression, including physical symptoms, should be considered when deciding on a treatment plan. Core symptoms typically dissipate early in the treatment of depression, but physical symptoms such as pain may linger. Treatment should not be discontinued until all symptoms have abated and the patient is in full remisssion.

## ACHIEVING REMISSION IN PATIENTS WITH PHYSICAL SYMPTOMS

Treating both the emotion and the physical symptoms associated with depression together is an important part of achieving remission. Unlike selective serotonin reuptake inhibitors such as sertraline and paroxetine, the dual-action antidepressants venlafaxine and duloxetine inhibit the reuptake of both serotonin and norepinephrine. This dual action gives them a robust efficacy in combating depression and preventing the persistence of symptoms, which increases the likelihood of achieving remission. Numerous reports have indicated that therapeutic agents that act on multiple neurotransmitters are associated with higher rates of remission than are single agents.[10–13] The selection of therapeutic agents proven to effectively promote both an elimination of a broad spectrum of symptoms and a return to full social functioning is important to the treatment of depression.

Because a majority of patients with depression initially seek treatment for the physical symptoms of depression rather than for their emotional symptoms, physicians are often aware of patients' physical symptoms when treatment commences. Primary care physicians may want to consider using dual-action antidepressants as a first line-treatment in depressed patients who present with physical symptoms.

Treating depression aggressively from the start may increase the chance of remission, as patients who fully remit in the acute stage tend to do better in the continuation phase. Duration of pharmacotherapy is also an important factor in achieving full remission. It is especially important to continue pharmacotherapy into the long term in patients who initially achieve only a partial remission.[14] Discontinuing pharmacotherapy too early may disrupt the patient's improvement and cause regression of symptoms.

## PHYSICAL SYMPTOMS AND OUTCOME MEASURES

In addition to choosing the most appropriate pharmacotherapeutic approach to treating the symptoms of depression, clinical management of depression should include the screening and monitoring of all symptom domains. All symptoms, including physical ones, must be measured in order to be treated fully. The symptoms still present in incomplete remission are important markers of vulnerability to relapse, and if all types of symptoms are not included in assessments, physicians cannot fully assess the treatment response and follow up on unresolved symptoms. Physicians and patients need to become aware of the broad spectrum of symptoms in depression in order to evaluate treatment effectiveness.

Reliable and effective assessment of Axis I disorders often includes utilization of a variety of rating scales used for both diagnostic purposes and follow-up evaluation. Recently there has been a call for including on rating scales all the symptom domains and social functioning/quality of life measures in the requirements for remission, but physicians may not be aware that there are already numerous standardized scales that measure these aspects of depression.

The most commonly used scales for measuring the symptoms of depression have been the Hamilton Rating Scale for Depression (HAM-D)[15] and the Montgomery-Asberg Depression Rating Scale (MADRS).[16] These 2 scales have traditionally been used in clinical trials for the express purpose of showing initial drug-placebo separation, but they are long and difficult to use in routine clinical practice. Neither scale includes all 9 DSM-IV criteria for major depressive disorder. Additionally, the parameters used to define remission on both the HAM-D and the MADRS are too inclusive. At a score of $\leq 7$ on the HAM-D or $\leq 10$ on the MADRS, which are often considered to indicate remission, patients may have shown improvement but are still clearly symptomatic. In addition, due to the demanding nature of these 2 rating scales, the chance they will be frequently used in primary care practices is small.

There are several other rating scales to choose from, however. One that has been used for a number of years at the University of Texas Southwestern Medical School is the Inventory of Depressive Symptomatology (IDS).[17] The IDS began as a 30-item rating scale, but has now been reduced to a 16-item scale, the Quick Inventory of Depressive Symptomatology (QIDS),[18] that includes all 9 DSM-IV depression criteria. The advantage of the IDS and the QIDS is that they have both a clinician-rated version (IDS-C and QIDS-$C_{16}$) and a self-rated version (IDS-SR and QIDS-$SR_{16}$). The QIDS-$SR_{16}$ takes about 5 to 7 minutes for patients to complete, and they can take it repeatedly to measure their progress during treatment (Appendix 1). Patients reportedly find it user-friendly. The psychometrics have been established enough to say that a score of 5 on the QIDS-$SR_{16}$ can be defined as remission.[18]

Rush et al.[18] have published data showing that, in nonpsychotic major depressive disorder, the self-rated

**Table 1. Patient-Rated Depression Rating Scales**

| |
|---|
| Inventory of Depressive Symptomatology[17] |
| Beck Depression Inventory[19] |
| Zung Self-Rating Depression Scale[20] |
| Patient Health Questionnaire for depression[21] |

versions of scales produce a significant correlation with the results of the clinician-rated versions and can be substituted easily. They are extremely useful and effective for both diagnosis and measuring improvement. There are a number of other self-rated scales available, including the Beck Depression Inventory,[19] the Zung Self-Rating Depression Scale,[20] and the Patient Health Questionnaire for depression (PHQ-9)[21] (Table 1). Although the PHQ-9 has been traditionally used as a screening instrument, it is increasingly viewed as a brief and accurate tool to measure symptoms during the course of treatment.

## CONCLUSION

Although the diagnostic criteria emphasize emotional and vegetative symptoms, major depression is also associated with painful physical symptoms such as headache, backache, stomach ache, joint ache, and muscle ache. Because depression and pain share a common neurochemical pathway in that they are both influenced by serotonin and norepinephrine, depression and associated painful physical symptoms must be treated together in order to achieve remission. In fact, research[22] has shown that physical symptom improvement was correlated with the improvement of other depression symptoms, which suggests that the patient's ability to achieve depression remission may be directly related to the reduction of painful physical symptoms. Patients may experience significant response to treatment; however, if residual symptoms persist, patients might not fully remit and might be at greater risk for subsequent relapse. A treatment regimen that does not address physical symptoms and only focuses on core emotional symptoms could result in an incomplete remission and a poor treatment prognosis for the patient. It is necessary to choose efficacious therapeutic agents that promote the elimination of both the core symptoms and associated physical symptoms of depression to ensure remission and a return to full social functioning and to prevent relapse. There are many standardized rating scales that effectively measure the remission of physical symptoms as well as emotional symptoms.

*Drug names:* paroxetine (Paxil and others), sertraline (Zoloft), and venlafaxine (Effexor).

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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Appendix 1 appears on page 16.

## Appendix 1. Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR$_{16}$)

Name _____ Today's Date _____

Please circle the one response to each item that best describes you for the past seven days.

**1. Falling Asleep:**
- 0 I never take longer than 30 minutes to fall asleep.
- 1 I take at least 30 minutes to fall asleep, less than half the time.
- 2 I take at least 30 minutes to fall asleep, more than half the time.
- 3 I take more than 60 minutes to fall asleep, more than half the time.

**2. Sleep During the Night:**
- 0 I do not wake up at night.
- 1 I have a restless, light sleep with a few brief awakenings each night.
- 2 I wake up at least once a night, but I go back to sleep easily.
- 3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

**3. Waking Up Too Early:**
- 0 Most of the time, I awaken no more than 30 minutes before I need to get up.
- 1 More than half the time, I awaken more than 30 minutes before I need to get up.
- 2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.
- 3 I awaken at least one hour before I need to, and can't go back to sleep.

**4. Sleeping Too Much:**
- 0 I sleep no longer than 7–8 hours/night, without napping during the day.
- 1 I sleep no longer than 10 hours in a 24-hour period including naps.
- 2 I sleep no longer than 12 hours in a 24-hour period including naps.
- 3 I sleep longer than 12 hours in a 24-hour period including naps.

**Enter the highest score on any 1 of the 4 sleep items (1–4 above) _____**

**5. Feeling Sad:**
- 0 I do not feel sad.
- 1 I feel sad less than half the time.
- 2 I feel sad more than half the time.
- 3 I feel sad nearly all of the time.

**6. Decreased Appetite:**
- 0 There is no change in my usual appetite.
- 1 I eat somewhat less often or lesser amounts of food than usual.
- 2 I eat much less than usual and only with personal effort.
- 3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

**7. Increased Appetite:**
- 0 There is no change from my usual appetite.
- 1 I feel a need to eat more frequently than usual.
- 2 I regularly eat more often and/or greater amounts of food than usual.
- 3 I feel driven to overeat both at mealtime and between meals.

**8. Decreased Weight (Within the Last Two Weeks):**
- 0 I have not had a change in my weight.
- 1 I feel as if I've had a slight weight loss.
- 2 I have lost 2 pounds or more.
- 3 I have lost 5 pounds or more.

**9. Increased Weight (Within the Last Two Weeks):**
- 0 I have not had a change in my weight.
- 1 I feel as if I've had a slight weight gain.
- 2 I have gained 2 pounds or more.
- 3 I have gained 5 pounds or more.

**Enter the highest score on any 1 of the 4 appetite/weight change items (6–9 above) _____**

**10. Concentration/Decision Making:**
- 0 There is no change in my usual capacity to concentrate or make decisions.
- 1 I occasionally feel indecisive or find that my attention wanders.
- 2 Most of the time, I struggle to focus my attention or to make decisions.
- 3 I cannot concentrate well enough to read or cannot make even minor decisions.

**11. View of Myself:**
- 0 I see myself as equally worthwhile and deserving as other people.
- 1 I am more self-blaming than usual.
- 2 I largely believe that I cause problems for others.
- 3 I think almost constantly about major and minor defects in myself.

**12. Thoughts of Death or Suicide:**
- 0 I do not think of suicide or death.
- 1 I feel that life is empty or wonder if it's worth living.
- 2 I think of suicide or death several times a week for several minutes.
- 3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

**13. General Interest:**
- 0 There is no change from usual in how interested I am in other people or activities.
- 1 I notice that I am less interested in people or activities.
- 2 I find I have interest in only one or two of my formerly pursued activities.
- 3 I have virtually no interest in formerly pursued activities.

**14. Energy Level:**
- 0 There is no change in my usual level of energy.
- 1 I get tired more easily than usual.
- 2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking or going to work).
- 3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

**15. Feeling Slowed Down:**
- 0 I think, speak, and move at my usual rate of speed.
- 1 I find that my thinking is slowed down or my voice sounds dull or flat.
- 2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.
- 3 I am often unable to respond to questions without extreme effort.

**16. Feeling Restless:**
- 0 I do not feel restless.
- 1 I'm often fidgety, wringing my hands, or need to shift how I am sitting.
- 2 I have impulses to move about and am quite restless.
- 3 At times, I am unable to stay seated and need to pace around.

**Enter the highest score on either of the 2 psychomotor items (15 or 16 above) _____**

**Total Score: _____ (Range 0–27)**

**QIDS-SR$_{16}$ Scoring Criteria**

| | |
|---|---|
| 0–5 Normal | 16–20 Moderate to Severe |
| 6–10 Mild | 21+ Severe |
| 11–15 Moderate | |