Can Treating Depression Improve Disease Outcomes?

The separation of the mind and body, a legacy that can be traced from Greek philosophers to Descartes’ Meditations to modern western thought, is reflected in the attitudes and practices of western medicine. This partitioning of mental disorders as processes of the mind, separate and distinct from processes of the body, is increasingly subject to challenge. An article in this issue (1) tests the validity of partitioning mental and physical processes by assessing the effect of treatment for depression on diabetic care outcomes.

Depression is a profound source of human suffering worldwide. It is common among patients with chronic pain and frequently develops after the onset of other medical conditions, such as heart attacks, strokes, malignant disease, osteoporosis, heart failure, liver disease, end-stage renal disease, and rheumatologic disorders. We aren’t surprised when a person becomes depressed after developing a life-altering, chronic, disabling, or painful medical condition. Some of us are surprised by evidence that depression associated with chronic medical conditions leads to worse outcomes for the chronic illness. For example, patients with depression after myocardial infarction or stroke are more likely to die (2), and depressed, diabetic patients have worse glycemic control (3) and higher rates of diabetic complications (4). Most of us would be startled to learn of emerging evidence that depression may increase the risk for subsequent development of many health conditions, including osteoporosis (5), coronary artery disease (6), diabetes (7), and cerebral vascular disease (8). Although it is only logical to believe that treating depression might improve outcomes for these health conditions, this conjecture is still unproven.

By what mechanism does a process of the mind affect the outcome of processes of the body? The usual explanations are that depression reduces adherence to care recommendations and is associated with negative health behaviors, such as smoking and less exercise (9, 10). These explanations may apply to some situations, but in most cases, the answer is probably far more complex. Depression adversely affects many physiologic processes, including autonomic dysregulation (11), inflammation (12), insulin resistance (13), platelet aggregation, and decreased cellular immunity (14). Some studies have shown that markers of inflammation improve with treatment for depression. In addition, selective serotonin reuptake inhibitors seem to affect platelet aggregation, which suggests that treatment for depression may have other, as yet unobserved, beneficial effects.

Although depression may precede, potentially cause, and worsen the prognosis for certain medical conditions, the critical question for clinicians is whether treating depression improves disease outcomes. This question is not simply pragmatic; reversibility would give researchers a lead in unraveling mechanisms of disease. Strong evidence suggests that treating major depression markedly improves depressive symptoms, health-related functioning, and the patient’s quality of life. To date, no studies have studied whether treating depression can prevent the development of other conditions. A few studies have shown that depression treatment improves comorbid medical outcomes. Although observational studies have shown large effects, the effect seen in clinical trials has been smaller. For example, observational studies have shown a 3- to 4-fold increase in cardiac morbidity and mortality in patients with depression after myocardial infarction. In the only randomized, controlled trial of the effect of treating these depressed patients, sertraline reduced the risk by a statistically insignificant 5% (95% CI, −3.0% to 15%). However, this study’s purpose was to examine the safety of sertraline after myocardial infarction rather than cardiovascular outcomes; it was small and short (24 weeks) and had too few outcome events to exclude a clinically important effect (15). A larger randomized, controlled trial that examined the effects of depression treatment on cardiovascular outcomes is ongoing (16). Similarly, observational trials have found a large increase in mortality among depressed patients after a stroke, whereas most clinical trials of depression treatment have shown little mortality benefit (17).

Williams and colleagues (1) studied the effect of collaborative care for depression on diabetic outcomes. They screened diabetic patients from 18 clinical sites representing 8 health care organizations in 5 states for depression. They then randomly assigned depressed diabetic patients to either a usual care group or the IMPACT (Improving Mood–Promoting Access to Collaborative Treatment) intervention group. This intervention provided up to 12 months of collaborative care for depression and measured diabetic outcomes at 3, 6, and 12 months. Rates of comorbid diabetes and depression were high (59%), a finding that is consistent with rates seen in other studies of depression and diabetes. Although patients randomly assigned to the intervention group had improvement in depression severity, functional status, and exercise rates compared with the usual care group, the intervention had no effect on glycosylated hemoglobin levels or other diabetic care indicators, including adherence to medications and diet, glucose testing, and weekly foot inspections. These results are similar to those of previous trials in which treating depressed diabetic patients had only a small effect on glycemic control (18–20).

The study of Williams and colleagues was well designed and conducted and had enough patients to demonstrate that a small (0.3%) absolute reduction in glycosylated hemoglobin level to be statistically different. The
only limitation was that patients in both intervention and usual care groups were well-motivated and highly compliant with medication and most of the diabetes self-care recommendations. The average glycosylated hemoglobin level in both groups at the beginning of the trial was 7.28%. Whether the investigators would have seen a greater difference among less motivated diabetic patients with poorly controlled glucose levels and depression remains uncertain; however, the authors found no differences among patients with glycosylated hemoglobin values greater than 8.0%.

What is the source of the disparity between studies showing that depression worsens comorbid illness and the relatively modest benefits of depression treatment on comorbid illness? Although we do not have an answer, several hypotheses are being tested. First, the effects of treating depression might require longer follow-up to show benefit. Mood may respond faster to treatment than the indirect, negative consequences of depression on other outcomes. Second, some treatments for depression may have more benefit than others, and the optimal treatment regimen may not yet be known. For example, a selective serotonin reuptake inhibitor given to a patient who has had a stroke may have more benefit than other classes of antidepressant because of its antiplatelet effects. Depression medications with both norepinephrine and serotonin effects might be particularly effective in somatic syndromes because both norepinephrine and serotonin may modulate painful stimuli perception at the spinal cord level (21). Third, depression may not cause the adverse health outcomes seen in observational studies. If depression itself causes the negative comorbid health outcomes, one would expect that successful depression treatment would improve comorbid disease outcomes. Because clinical trials have not shown that depression treatment has this effect, a third, yet unknown, factor may cause both the depression and the comorbid disease outcomes. Treating depression may ameliorate some of the negative consequences of depression but have no effect on this unknown third factor. At least 1 study has suggested that the relationship between depression and diabetic glycemic control is moderated by other intermediate factors and is not a simple cause-and-effect relationship (18).

Much work remains to be done in this area. Although a correlation exists between depression and alterations in many of the body’s homeostatic systems, the mechanism of this relationship remains unknown. Researchers are only just beginning to penetrate the labyrinth of the interactive relationships between depression and comorbid illness. Future research may uncover interactive mind–body relationships that will spawn radical new approaches to the practice of medicine. Until that time, providers should continue to look for and treat depression in their patients. Although treating depression may not improve other disease outcomes, it will dramatically improve the quality of life for patients and their families.


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