Introduction

Emerging Evidence in the Treatment of Depression and Chronic Pain in Primary Care: All Antidepressants Are *Not* Created Equal

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Depression is one of the leading causes of global disease burden and is expected to be the second leading cause within 2 decades.[1] There is a vast body of evidence to demonstrate the potential effects of untreated or inadequately treated depression, including an increased likelihood of negative outcomes in comorbid medical conditions[2–5] and increased health care costs,[6,7] as well as outcomes specific to depression, such as significant psychosocial impairment,[6,8–10] an increased risk of relapse or recurrence, a longer time to recovery, and a shorter time between episodes.[11–14] In addition, depression is frequently associated with troublesome physical symptoms, such as sleep disturbances, fatigue, and appetite changes, which have been increasingly recognized as part of the constellation of symptoms of major depression. In fact, these symptoms are frequently the reason why patients seek treatment.[15,16] Thus, the most effective treatments for depression should alleviate both emotional and physical symptoms of depression.

Current treatment guidelines suggest that remission of symptoms (i.e., virtual elimination of symptoms) is the optimal treatment goal of major depression.[17,18] Clinical trials of antidepressants have typically evaluated efficacy in terms of response to treatment (e.g., 50% decrease in baseline symptoms), which led to the belief that, in general, antidepressants are comparably effective. Further, studies of antidepressant treatment have generally evaluated efficacy by measuring improvements in the emotional symptoms of depression. Impact on physical symptoms has only recently begun to receive specific attention.

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Supported by funding from Wyeth Pharmaceuticals, Philadelphia, Pa.

Dr. McPherson reports no financial affiliation or other relationship relevant to the subject matter of this article.

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Results of recent analyses of clinical trial data suggest that meaningful differences in efficacy exist among antidepressants of different classes. Specifically, analyses of pooled original patient data suggest that the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine offers a significant advantage over selective serotonin reuptake inhibitors (SSRIs) in terms of bringing patients to remission (defined as a Hamilton Rating Scale for Depression score ≤ 7).[19,20]

Additional analyses have demonstrated that the efficacy advantages of the dual-acting venlafaxine extend to physical symptoms of depression as well,[21] a constellation of symptoms associated with poor outcome if not treated adequately.[22] Compared with SSRIs, venlafaxine was significantly more effective in reduction of somatization symptoms (i.e., heaviness in limbs, back, or head; backaches, headaches, muscle aches; and loss of energy, fatigability) related to depression and was associated with a greater likelihood of complete somatic symptom resolution.[21] Evidence of the efficacy of the SNRI duloxetine in ameliorating the physical symptoms of depression is consistent with these findings.[23,24]

The efficacy of dual-mechanism antidepressants in alleviating painful physical symptoms is further supported by evidence of their analgesic efficacy in chronic pain states. Dual-acting tricyclic antidepressants (e.g., amitriptyline) have been used successfully in the treatment of pain states, such as chronic neuropathic pain,[25] headaches,[26] and fibromyalgia.[27] In addition, preclinical and clinical investigations of venlafaxine have demonstrated its analgesic properties[28,29] and its potential utility in treating various types of neuropathic pain, including migraine,[30] painful polyneuropathy,[31] neuropathic pain following breast cancer treatment,[32] fibromyalgia,[33] and chronic neuropathic pain.[34]

Primary care physicians face numerous challenges in managing patients with depression and/or painful physical symptoms. From undifferentiated patients who present with vague symptomatic complaints, to the realities of clinical practice time constraints, the obstacles to accurate diagnosis and assessments of treatment effectiveness are

considerable. It is important for primary care physicians to be aware of these challenges and of how to overcome them to provide optimal patient care. The articles in this supplement review the connections between depression and physical symptoms, the use of antidepressants in the primary care setting, and the clinical implications of differences in antidepressant mechanisms of action.

Dr. Lieberman begins the discussion with a review of the history of antidepressant development and the use of these agents in the primary care setting. This article describes how the first pharmaceuticals used for treating depression were developed, how they were associated with a significant potential for dangerous side effects, and, as a result, subspecialists were most commonly prescribing these antidepressants. The discussion continues by outlining how newer antidepressants were developed that possessed significant tolerability and safety advantages over existing agents and antidepressant prescribing by primary care physicians became more common. The current status of antidepressant use in the primary care setting is reviewed, including the potential utility of these agents for painful physical symptoms.

Dr. Sussman reviews the role of neurotransmitters in the manifestation of symptoms of depression and pain, potential neurobiological links between these symptoms, and the mechanisms by which antidepressants exert their effects on relevant neurotransmitter systems. The review considers how the mechanism of action of various classes of antidepressants may be related to the efficacy of these agents in treating the emotional and physical symptoms of depression and chronic pain states and discusses their tolerability in patients who experience these symptoms. The effects of antidepressants with different mechanisms of action on health outcomes measures (e.g., impairment in work and daily activities) are also reviewed, including comparisons of cost-effectiveness data.

Dr. Kroenke discusses the strong association of symptoms of depression and pain and the implications for primary care providers. Specific considerations include the relationship of physical symptoms to clinical presentation of the patient and the consequences of inadequate treatment of physical symptoms. A stepwise approach to the treatment of patients with physical symptoms is reviewed, which may assist the primary care clinician in recognizing and managing these symptoms.

Dr. Shelton concludes by discussing the antidepressant properties of drugs and methods by which antidepressants may be classified. The discussion includes a review of interactions between antidepressant drugs and neurotransmitter receptors as well as data on differences in binding potencies. The physiologic implications of these properties and interactions are considered in terms of how they may be useful in guiding treatment decisions.

Recent reports of epidemiologic data have cast a negative light on the adequacy of treatment of depression in the primary care setting, as suggested by the results of the National Comorbidity Survey Replication.[35] Kessler and colleagues[35] reported that the 12-month prevalence of depression encompassed 13 to 14 million adults and that these patients reported significant impairment in work and activities, yet only approximately 1 in 5 received adequate treatment. Limitations of the assessments of treatment adequacy may have affected the results (e.g., if visits to primary care physicians were not coded as "depression" visits, they may not have been identified, suggesting less than adequate treatment). The findings are, in fact, indicative of meaningful progress in terms of recognition and treatment of depression over the last decade. Nevertheless, it is clear that there remains room for further improvement and a change in the approach to treatment.

Drug names: amitriptyline (Endep, Elavil, and others), venlafaxine (Effexor and others).

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