Recent Advances in the Treatment of Depression in the Presence of Physical Symptoms

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights from the teleconference "Recent Advances in the Treatment of Depression in the Presence of Physical Symptoms," which was held July 27, 2005. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc. and was supported by an educational grant from Eli Lilly and Company.*

The planning teleconference was chaired by ***Madhukar H. Trivedi****, M.D., Department of Psychiatry, University of Texas, Southwestern Medical Center at Dallas. The faculty were* ***Wayne J. Katon****, M.D., Department of Psychiatry, University of Washington, Seattle;* ***Ella Daly****, M.B., M.R.C.Psych., Department of Psychiatry, University of Texas, Southwestern Medical Center at Dallas;* ***Anita H. Clayton****, M.D., David C. Wilson Professor and Vice Chair, Medical Director, University of Virginia Center for Psychiatric Clinical Research, Charlottesville; and* ***Ellen Frank****, Ph.D., Department of Psychiatry, Western Psychiatric Institute and Clinic, Pittsburgh, Pa.*

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Madhukar H. Trivedi, M.D., opened by explaining that while most evidence for antidepressant efficacy comes from trials of patients with pure major depressive disorder (MDD), the topics presented address issues of physical symptoms and medical comorbidity in terms of diagnosis and treatment, which is likely to be helpful to clinical care.

General Medical Comorbidities Associated With Depression

Wayne J. Katon, M.D., began his discussion of comorbidities associated with major depression by describing several aspects of depression and chronic medical illness. Medically ill patients have an increased prevalence of major depression, which is associated with the amplification of physical symptoms, such as pain. The comorbidity of depression and medical illness increases impairments in functioning and is associated with poor self-care and adherence to treatment regimens such as medications, diet, and exercise. Depression comorbidity in patients with medical illnesses is also associated with higher rates of adverse health behaviors such as smoking and sedentary lifestyle. Because of the association with adverse health behaviors and decreased adherence to treatment regimens, Dr. Katon noted that recent evidence suggests that the comorbidity increases mortality in patients with diabetes[1] and heart disease.

Prevalence of Depression Comorbidities

Dr. Katon related the results of 2 studies[2,3] that illustrate the high rates of prevalence of depression and medical comorbidities. Prevalence rates for depression were found to be at 3.5% in the general community and 6% in primary care offices.[2] Medical inpatients had much higher rates, at 12%.[2] Dr. Katon also reviewed evidence that showed high prevalence rates of depression in patients with diabetes (11%–15%) and coronary artery disease (15%–23%), following a stroke (9%–31%), and in patients with neurological illnesses such as Parkinson's disease (20%–30%) and multiple sclerosis (16%–30%).[3]

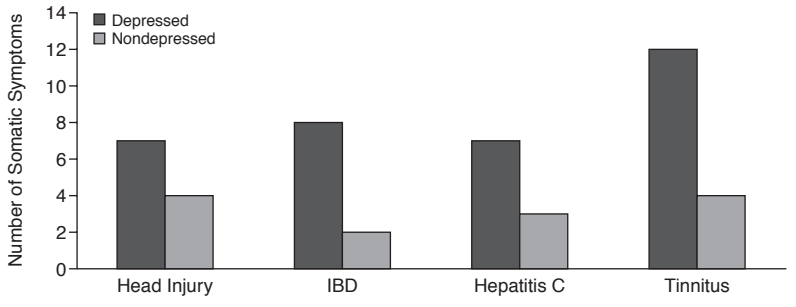
Adverse Economic Impact of Depression in Patients With Chronic Medical Illness

Dr. Katon explained that patients who screened positive for depression spent about 50% to 70% more for their total health service costs, compared with patients who screened negative for depression over a 1-year period.[4] As the severity of depression in people with chronic medical illness increases, the cost of ambulatory service also increases.[5] Psychiatric comorbidities—the most common of which is major depression—are associated with an increased length of hospital stay (compared to medical inpatients without psychiatric comorbidity), increased use of medical services, increased medical costs, increased emergency room costs, and increased rehospitalization rates for at least 4 years after discharge.[6]

Maladaptive Effects

Dr. Katon described several maladaptive effects of affective illness on chronic medical illness, such as the am-

Figure 1. Depression Comorbidity Amplifies Number of Somatic Symptoms[a]



[a]Reprinted with permission from Katon et al.[7]
Abbreviation: IBD = inflammatory bowel disease.

plification of somatic symptoms, especially pain, as well as the associated additive functional disability. Affective illness is also associated with increased adverse health behaviors such as not following diets, smoking, and leading a sedentary lifestyle as well as decreased self-care, such as not filling prescription medicines in a timely manner.

Amplification of somatic symptoms. According to Dr. Katon, patients with depression and chronic medical illness reported more somatic symptoms than patients without depression (Figure 1).[7] Patients with diabetes and depression present multiple diabetes symptoms and in fact, compared with diabetic patients without depression, have significantly higher odds ratios of having every one of 10 common symptoms of diabetes (feeling cold, numbness, pain in the hands and feet, polyuria, excessive hunger, abnormal thirst, shakiness, blurred vision, feeling faint, and daytime sleepiness).[8] A linear increase in the number of diabetes symptoms correlated to the increase in the number of depressive symptoms.[8] Diabetic patients' major depression also had increased functional impairment compared with patients with diabetes alone when controlling for severity of diabetes (HbA1c and complications).[9]

Dr. Katon suggested that a bidirectional relationship exists between adverse physical symptoms and depression. When patients with chronic medical illness and pain are provided effective treatment of their depression, their interference from pain dramatically decreases,[10] which in turn improves the outcome for both the medical illness and depression. Patients with coronary artery disease and depression have been found to have decreased quality of life compared with those without depression.[11,12] Patients with inflammatory bowel disease and a psychiatric disorder like depression had significantly more impaired functioning than patients with inflammatory bowel disease alone when controlling for severity of this gastrointestinal illness.[13]

Effects of depression on treatment adherence. Dr. Katon noted that patients with depression and medical illness are 3 times more likely than nondepressed patients to not adhere to their medical treatments.[14] These patients may have negative expectations about the efficacy of treatment, increased withdrawal and social isolation, and reduced cognitive function and memory (so they forget to follow their medical regimens), and thus make poor dietary choices. Patients with coronary artery disease and depression are less likely to adhere to low-dose aspirin therapy than those with coronary artery disease without depression.[15] Patients with diabetes and depression tend to neglect refilling diabetes control medicines and[16] have an increased prevalence of smoking, increased body mass index, and above-normal hemoglobin A1c compared with patients with diabetes alone.[17] They are also more likely to have cardiac risk factors.[18]

Morbidity and Mortality

Dr. Katon further explained that depression seriously impacts morbidity and mortality in patients with medical illness. He related the findings of a meta-analysis[19] of 27 studies that showed a significant association between depression and a range of diabetes complications. Coronary artery disease is 3 times as common over a 10-year period in patients with diabetes and depression than in patients with diabetes but without depression,[20] and children with type 1 diabetes and depression have an increased risk of developing retinopathy.[21] Patients with depression and type 2 diabetes had over a 2-fold increase in mortality over a 3-year period compared with those with diabetes alone after controlling for demographic and clinical factors.[1] Among patients hospitalized following a heart attack, the patients with major depression had a 3- to 4-fold risk of death over the following 6 months compared with patients without depression.[22]

Conclusion

Dr. Katon concluded his discussion by summarizing the adverse effects that depression has on medical illness. Depression is associated with a sedentary lifestyle, smoking, and obesity and a lack of adherence to medical regimens. Depression also appears to have a bidirectional relationship with medical illnesses by leading to an increase in complications of medical illness, which often leads to greater severity of depression.

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Pain and Depression

Ella Daly, M.B., M.R.C.Psych., agreed with Dr. Katon that pain and depression are closely linked and that their relationship is bidirectional. The presence of a chronic painful condition doubles the rate of MDD,[1] which in turn appears to be associated with a 4-fold increased risk of suffering from a chronic painful condition.[2]

Features of Pain and Depression

Biological pathways. Dr. Daly explained that pain and depression appear to share the same biological pathway. Ascending noradrenergic and serotonergic pathways that originate from the locus ceruleus and raphe nuclei appear to be responsible for the disturbed psychological functioning seen in MDD. Similarly, the descending noradrenergic and serotonergic pathways have been implicated in the modulation of pain.[3]

Prevalence. Recent research,[4] according to Dr. Daly, indicates that pain has prevalence rates ranging between 15% and 100%, with a mean of 63%, in people with depression. Similarly, with regards to the prevalence of depression in patients with chronic pain, the rates range between 13% and 85%, depending on the population and the clinical condition of the patient.[4]

Functioning. Dr. Daly explained that patients with MDD and a chronic condition associated with pain had increased impairments and experienced longer durations of depressive episodes. Research[5] on patients with both depression and a painful condition found that patients were impaired for 31.4 months compared with 24.3 months for those patients with MDD alone. Similarly, patients with a history of depression had an increased likelihood of having a chronic painful condition. For example, of the patients with MDD in this study, 43.4% had at least 1 chronic painful condition.[5] In addition, the presence of a chronic painful condition is associated with an increased risk of suicide.[6]

Diagnosis and treatment. Dr. Daly noted that the presence of comorbid depression and pain can present a challenge in terms of diagnosis, with patients with depression often reporting symptoms of pain such as body aches, headaches, and gastrointestinal disturbance.[7] In addition, symptoms of chronic painful conditions and MDD have been shown to overlap (Table 1),[5] further supporting the idea that depression and chronic painful conditions share common pathways. As a result, signs of depression may be overlooked because physicians concentrate on treating physical symptoms of pain, the presence of which can compromise the validity of diagnostic questionnaires and standardized rating scales.

Dr. Daly noted that treatment for chronic pain and major depressive disorder must address both the psychological and pain symptoms.[8] In addition, she suggested that goal-directed psychotherapy might be considered in addition to pharmacotherapy.[9]

Functional Somatic Syndromes

Functional somatic syndromes, according to Dr. Daly, are conditions with predominant somatic symptoms and high comorbidity with MDD. While somatic symptoms initially appear to be associated with MDD, an ongoing debate exists about the nature of the exact relationship of depression and these syndromes.

Fibromyalgia. One controversial theory is that MDD may play a role in the pathogenesis of fibromyalgia. Dr. Daly listed several common symptoms of fibromyalgia, which include

Table 1. Overlapping Symptoms of Comorbid Depression and Chronic Painful Physical Conditions[a]

Initial insomnia
Middle insomnia
Fatigue
Loss of appetite
Difficulty concentrating
Psychomotor retardation
Psychomotor agitation

[a]Based on Ohayon.[5]

nonrestorative sleep, profound fatigue, malaise, morning stiffness, headache, psychological distress, and indications of autonomic dysfunction. However, the exact relationship between depression and fibromyalgia is not known. Research[10,11] has shown that between 14% and 71% of patients with fibromyalgia have a concurrent diagnosis of depression, and some researchers[12] suggest that fibromyalgia is part of an affective spectrum disorder. While some research[12] has found evidence of high rates of MDD and familial mood disorders in patients with fibromyalgia, other research[13,14] has found no difference in the rates of depression between patients with fibromyalgia and those with other chronic painful conditions, such as rheumatoid arthritis.

Pharmacologic treatments for fibromyalgia have been found to have uneven efficacy. Anti-inflammatory drugs for treating fibromyalgia have not proven to be particularly effective,[15] while antidepressants have been shown to have some benefit.[16] In general, tricyclic antidepressants appear to be more effective than the selective serotonin reuptake inhibitors (SSRIs) in chronic unexplained pain.[17] Serotonergic-noradrenergic reuptake inhibitors (SNRIs) have also shown promise in the treatment of fibromyalgia.[18–20] The mechanism of action of SNRIs appears to result from effects on the biological pathways that pain and depression share. Research[18] found that 37% of patients with fibromyalgia reported a 50% or greater reduction in pain intensity when treated with milnacipran compared with 14% of patients taking placebo. Other research[19] reported significant improvement in symptoms of fibromyalgia with duloxetine compared with placebo in patients with and without comorbid MDD. Lastly, venlafaxine was found to reduce reports of fibromyalgia symptoms by 50% in 55% of patients treated.[20]

Chronic fatigue syndrome. Dr. Daly described the central feature of chronic fatigue syndrome as persistent and excessive fatigue, accompanied by various somatic and psychological symptoms, including depression. Chronic fatigue syndrome is further characterized by unrefreshing sleep, problems with concentration, sore throat, tender lymph nodes, muscular pain or tenderness, joint pain, headache, and post-exertional malaise for at least 6 months.[21] In addition, comorbid depression and chronic fatigue syndrome are associated with high rates of other psychiatric disorders.[22] Depression may also predate fatigue symptoms.[23] The rates of MDD in patients with chronic fatigue syndrome have ranged from 48% to 67%.[24,25] Others however, report rates of only 12.5%.[26]

Chronic fatigue syndrome and depression often co-occur and share common symptoms, including fatigue, malaise, poor sleep, and pain. The etiology of chronic fatigue syndrome, which has both biological and psychological features, remains controversial. Both abnormal serological and immunological function have been implicated, as well as the association with a flu-like viral infection.

Dr. Daly next stated that tricyclic antidepressants have been evaluated for the treatment of comorbid MDD and chronic fatigue syndrome in the past with variable success. Amitriptyline,[27] clomipramine,[28] and nortriptyline[29] have been shown to be effective, although serotonergic tricyclics appear to have a greater effect on pain.[30] To date, research shows that the SSRIs, such as fluoxetine, may improve chronic fatigue syndrome symptoms.[31–33] In addition, the noradrenergic reuptake inhibitor, bupropion, has shown some initial efficacy, but these results have not been supported by placebo-controlled trials.[34]

Diabetic neuropathy. Diabetic neuropathy is a common complication of diabetes and is associated with significant morbidity. Dr. Daly explained that the prevalence of diabetic neuropathy appears to be 30% in hospitalized and 20% in community-dwelling diabetics, and the annual incidence appears to be in the range of 2%.[35] Sensorimotor neuropathy, or distal symmetrical polyneuropathy, is the most common complication of diabetes seen at the clinical level. Diabetic neuropathy may affect sensory, motor, or autonomic nerves, and the primary risk factor appears to be high blood sugar or hyperglycemia.

Diabetes is associated with a 2-fold increased rate of depression compared with the general population, with approximately 30% of patients with diabetes having depressive symptoms.[36] In addition, the presence of depression is associated with negative consequences with regards to outcomes for diabetes in terms of adherence to diet, exercise, glycemic control, and increased rates of complications.[37]

Pharmacologic treatments for MDD and comorbid pain caused by diabetic neuropathy include tricyclic antidepressants, such as amitriptyline,[38] desipramine,[39] and imipramine.[40] However, the tricyclics have significant adverse effects including sedation, dry mouth, blurred vision, hypotension, urinary retention, and increased blood sugar rates. Conflicting evidence for the efficacy of SSRIs has been found. Both paroxetine[41] and citalopram[42] were found to be effective, but fluoxetine was not any more effective than placebo.[43] However, in general it is recommended that SSRIs are not used as monotherapy for diabetic neuropathic pain.[44] Other antidepressants such as bupropion-SR[45,46] appear to be effective in terms of pain relief compared to placebo. More recently the SNRIs—including venlafaxine[47,48] and duloxetine[49–51]—have shown evidence of clinical benefits through their action on both the serotonergic and noradrenergic pathways.

Conclusion

Dr. Daly concluded by stating that, for patients who have co-occurring chronic pain and depression, physicians should address both physical and psychological symptoms.

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Strategies and Tactics of Treatment for Complicated Depression: An Algorithmic Approach

Madhukar H. Trivedi, M.D., began his discussion by stating that remission should be a treatment objective. To achieve this objective, he suggested several strategies to treat resistant depression, including augmentation and the use of the serotonin-norepinephrine or serotonin-norepinephrine-dopamine reuptake blockade agents as broad-spectrum agents.

Remission as a Treatment Goal

Dr. Trivedi described the goals that physicians should have in mind when treating patients. In addition to achieving remission of depressive symptoms (the standard goal of treatment), physicians should work toward the restoration of full functioning capacity. This goal includes returning to work, resuming hobbies and personal interests, and restoring personal relationships.[1] Recent research[2] in patients with MDD found that MDD is still largely untreated. Of the patients studied (N = 9090), only 51.6% received treatment, meaning that 48.4% received no treatment. Ultimately, only 21.7% of the patients were adequately treated over a 12-month period.

Drug Selection

Dr. Trivedi related his view that physicians, when selecting a first-line treatment, need to make their selection based on the broad spectrum of depressive symptoms. Because depression is a systemic illness that involves both serotonin and norepinephrine neurotransmitter systems, disturbances in these pathways are thought to be associated with both the emotional and physical symptoms of depression.[3] Challenge studies from Yale[4] provide some evidence that SSRI responders will be more likely to achieve remission if they receive an agent that affects both serotonin and norepinephrine pathways. Recent research[5] on desipramine and fluoxetine found that patients responded to both treatments individually but did not achieve remission. However, when desipramine and fluoxetine were used in combination, high rates of patient remission were found. Meta-analyses that compared SSRIs with tricyclic antidepressants (TCAs) suggested comparable efficacy within the SSRI class,[6] comparable efficacy with TCAs,[7,8] and better tolerability with SSRIs compared with TCAs.[7,9] However, TCAs have been found to be more effective than SSRIs in certain subgroups such as inpatients and inpatient studies of patients with more severe illness. TCAs with an advantage over SSRIs appear to be limited to the dual-reuptake TCAs such as amitriptyline and clomipramine.[11] The SNRIs venlafaxine and duloxetine have shown higher remission rates compared with SSRIs,[5,10–12] effectiveness in a broad spectrum of patients,[13,14] and resolution of a wide array of the emotional and physical symptoms of depression.[15] Further research[14] of treatment-resistant patients who failed to respond to one antidepressant and were then randomized to either paroxetine or venlafaxine showed a much higher rate of remission with venlafaxine than the SSRI.

Recommendations of TMAP and STAR*D

Sequences or combinations of treatments are essential if first treatment is unsuccessful, and the decisions that are made to modify treatment should be based on symptom improvement as well as side effect burden. After initial treatment is administered, physicians need to decide which symptoms should be monitored, how these symptoms should be monitored, and how to monitor the progress of patients towards remission. The Texas Medication Algorithm Project (TMAP) and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study from NIMH both address monitoring questions.

Dr. Trivedi related the recommendations of the TMAP study,[16,17] which include steps for patients who partially respond and for those who do not respond to first treatment. Physicians can maximize the dose and duration of initial pharmacologic treatment, switch to another agent, augment one pharmacologic agent with another agent to enhance antidepressant effect, combine 2 or more antidepressants, use atypical antipsychotics, or use electroconvulsive therapy (Table 2).[17]

TMAP emphasized its clinical effectiveness by asking whether or not the algorithm produces better symptom results than treatment-as-usual based on clinician- and self-rating measures. The algorithm used measures of symptoms and side effect burden and made recommendations to aggressively ensure that the treatment goal of remission is met. Patients showed a significantly higher benefit, especially on self-test scores.[18] Similarly, the STAR*D study,[19–21] a NIMH study involving over 4000 patients, made concrete recommendations in its Clinical Procedures Manual that included exact dosages.[22] Both algorithms ensure a thorough measurement of symptoms, side effects, and medication dosage in addition to an evaluation of the patient's overall clinical picture, which ensures that patients are moved to full remission.

Both approaches ensure that ready-to-use and easy-to-implement instruments are available and can be used in clinical practice, thus facilitating clinical symptom measures that are used in research to be easily translated into practice, which is very similar to the approaches used in chronic medical diseases like diabetes, arthritis, and hypertension.

Conclusion

Dr. Trivedi concluded by explaining that the treatment of depression should aim for the early, vigorous, and complete treatment of all symptoms to remission. Physicians have traditionally only evaluated emotional symptoms of

Table 2. Progression of Decisions of the Texas Medication Algorithm Project[a]

Critical Decision Point (CDP)	Clinical Status[b]	Plan
Week 0	Symptomatic	Initiate medication; adjust dose to the lower end of therapeutic dose range or serum level
Week 4	Full response	Continue current dose
	Partial response	Continue current dose Consider increasing dose
	Minimal or no response	Increase dose Go to the next stage
Week 6	Full response	Go to continuation phase if full response sustained for at least 4 weeks; otherwise, continue current dose
	Partial response	Maximize dose Augment with another agent
	Minimal or no response	Augment with another agent Go to the next stage
Week 8	Full response	Go to continuation phase if full response sustained for at least 4 weeks; otherwise, continue current dose
	Partial response	Augment with another agent Go to the next stage
	Minimal or no response	Discontinue and go to the next stage
Week 10	Full response	Go to continuation phase if full response sustained for at least 4 weeks; otherwise, continue current dose
	Partial response	Adjust dose (antidepressant and/or augmentation dose) Go to the next stage
	Nonresponse or minimal response	Go to the next stage
Week 12	Full response	Go to continuation phase if full response sustained for at least 4 weeks; otherwise, continue current dose
	Partial response	Go to the next stage

[a]Based on Trivedi and Kleiber.[17]
[b]Response scores based on Quick Inventory of Depressive Symptoms-Self Report scores: full response ≤ 5; partial response = 6 to 8; minimal or no response ≥ 9.

depression, but they should also evaluate physical symptoms such as lethargy. Achieving remission in clinical practice often requires affecting multiple neurotransmitter systems and using sequential treatment approaches. Measurement of symptoms and function should be routine because physicians will be unlikely to thoroughly evaluate patients without careful measurements. Using critical decision points as outlined in either the TMAP or the STAR*D trials provides an avenue for achieving adequacy of treatment outcomes and ensuring remission. It also allows practicing physicians to ensure that they do not move to the next stage until a thorough treatment trial has been conducted for the previous treatment. A systematic approach is likely to increase improved outcomes.

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Treatment of Comorbid Depression and Anxiety

Anita H. Clayton, M.D., opened her discussion by explaining that comorbid depression and anxiety disorders are common, but patients are sometimes not forthcoming with complaints about depression or anxiety symptoms when they visit physicians. Research[1] has shown that anxiety disorders and physical disorders are closely related. Patients with a physical disorder and comorbid anxiety disorder had an increased likelihood of disability compared with patients with physical disorders but no concomitant anxiety.

Prevalence

Dr. Clayton explained that comorbid depression and anxiety is a common problem that is not always recognized by patients or health care providers. A study[2] of over 75,858 patients assessed with the Zung Self-Rating Depression Scale found that 21% had clinically significant depression. However, only 1.2% of them cited depression as the reason for a primary care visit. Greater severity of depression was seen in those patients who thought they had poor health, in older women, in women with lower education levels, and in single individuals. Other research[3] found that 58% of those with MDD have a secondary anxiety disorder and that 68% of those with a primary anxiety disorder have secondary MDD. Kessler and colleagues[4] concluded that, despite many people having both major depression and generalized anxiety disorder (GAD), the group with MDD may also include a significant number of individuals with comorbid anxiety who do not meet diagnostic criteria for GAD.[5]

Symptomatology

Dr. Clayton noted that the onset of anxiety disorders, particularly generalized anxiety disorder (GAD), social phobia, and posttraumatic stress disorder (PTSD), precedes the onset of MDD approximately two thirds of the time.[6] Onset of major depression comes about 1.5 years after the onset of GAD, compared with over 10 years after the onset of other anxiety disorders.[3] Nearly all patients with GAD will develop a depressive illness at some point.

The overlap of symptoms of comorbid MDD and anxiety can be subdivided into more specific diagnostic categories than are outlined in the DSM-IV.[7] First, patients who meet criteria for both a depressive and anxiety disorder are identified as having comorbid major depression and anxiety. Second, patients who meet syndromal criteria for depression and have anxiety symptoms but do not meet the full criteria for an anxiety disorder would be identified as having anxious depression. Third, patients who have symptoms of both depression and anxiety but do not meet criteria for either disorder can be identified as having mixed anxiety and depression. Because of this overlap, physicians should differentiate among types of anxiety symptoms when diagnosing patients. The 2 types of anxiety are (1) psychic anxiety, which is characterized by worry, nervousness, tension, fear, and irritability, and (2) somatic anxiety, which is characterized by physical symptoms such as aches, pains, sympathetic arousal, and gastrointestinal complaints. Functional impairment may also be associated with somatic anxiety.

Risk Factors and Consequences

Dr. Clayton noted that risk factors for developing depression are related to risk factors for developing anxiety disorders. In addition to the increased risk of developing depression among patients with anxiety disorders, a family history of or genetic risk for depression or anxiety disorder puts patients at greater risk for developing either disorder.[8] Functional impairment because of anxiety puts patients at greater risk for developing MDD. In terms of consequences, risks[9] associated with either or both disorders include increased morbidity, a greater risk of suicide, treatment resistance in which substantial residual symptoms can remain, poor work and social function, greater likelihood of comorbid alcohol or substance abuse compared with patients without the comorbidity, and patient perception of poorer health.[10]

Patient Outcome

Dr. Clayton explained that treating patients to full remission is helpful in prevention of future relapse, which in turn reduces disease burden and functional impairment. Research[11] in patients with major depression who had persistent residual symptoms despite treatment found that Hamilton Rating Scale for Depression (HAM-D) scores of greater than 7 were strong predictors of subsequent early relapse. Of the study's subjects, 76% of the patients with scores of 8 or higher relapsed, compared with only 25% of the patients with a score of 7 or less. Recent research[12] into the long-term outcomes of patients with anxiety and depressive disorders showed discouraging results. The 12-year follow-up of 210 people with depression, anxiety disorders, or both showed that those with severe anxious depression had the worst outcome. In addition, the presence of personality disorders—comorbid avoidant personality disorder, in particular—contributes to poor outcome.

Other comorbid conditions negatively impact outcomes in patients with depression.[13] Stress-response disorders like depression, anxiety disorders, and eating disorders may worsen in women with hormonal changes associated with reproductive life-events, such as the premenstrual period, pregnancy, postpartum period, or menopausal transition. In addition, comorbid chronic episodic disorders, such as fibromyalgia, irritable bowel syndrome, and sexual dysfunction, occur at a greater frequency both in patients with depression and in those with anxiety disorders. Other comorbid medical conditions, such as thyroid disease, migraine, obesity, and cardiovascular disease, are also more likely and must

Table 3. Treatment Options for Patients With Comorbid Depression and Anxiety

Healthy lifestyle:
Exercise
Nutritional supplements (eg. vitamin B)
Reduce caffeine and alcohol
Pharmacotherapy
Light therapy
Psychotherapy
Electroconvulsive therapy (ECT)
Combination therapy

be considered in treatment planning as they may contribute to treatment resistance and to functional physical impairment.

Treatment

Dr. Clayton suggested that treatment options (Table 3) for depression with anxiety should begin with a healthy lifestyle, which includes exercising, taking nutritional supplements (e.g., vitamin B), and reducing caffeine and alcohol intake. In addition to promoting a healthy lifestyle for patients, physicians can also incorporate pharmacotherapy, phototherapy, psychotherapy (cognitive behavioral therapy), and electroconvulsive therapy. And because comorbid depression and anxiety can be more difficult to treat than either condition alone, treatments should be used in combination when appropriate.

Pharmacotherapy

Dr. Clayton noted that the mainstay of pharmacotherapy options for MDD and for many anxiety disorders is antidepressant medications. When remission is not achieved with a single agent, then augmentation strategies should be considered.[14] Augmentation with a second antidepressant with a different mechanism of action may best combat comorbid depression and anxiety. Additional augmentation agents include antianxiety agents (e.g., 5-HT 1A agonists, γ-aminobutyric acid agonists), atypical antipsychotic medications, and exogenous hormones (e.g., hormone replacement therapy). However, there is a greater likelihood of moderate-to-severe adverse effects if anxiety is present with depression[15] than with depression alone. No increase is seen in the number of side effects, but different types of complaints are reported secondary to pharmacotherapy in patients with depression plus anxiety.

Because of the risk of adverse effects, Dr. Clayton recommended starting antidepressants at the lowest possible dose and then increasing by the smallest possible increment after side effects abate. The dosage needs to be increased until a fully therapeutic regimen has been found, which should target the most severe component of the condition. For example, if the patient has a more severe depression with milder anxiety, the depressive symptoms need to be targeted and dosage should be adjusted accordingly to achieve full remission. Baseline levels of anxiety are not predictive of response to specific types of antidepressants (e.g., a serotonin reuptake inhibitor as compared with a noradrenergic and dopamine reuptake inhibitor, or an SSRI versus a tricyclic antidepressant) in patients with major depression.[16] Treatment to remission is important in order to prevent relapse, and duration of therapy may need to be longer in the presence of anxiety, which is a chronic condition, versus major depression, which tends to be episodic and recurrent.

Well-tolerated newer antidepressants with dual action may improve response in patients with comorbid MDD and anxiety without the need to add a second agent.[17] Antidepressant therapy plus psychotherapy (e.g., cognitive behavioral analysis system of psychotherapy) was found superior to either intervention alone in treating anxiety symptoms in chronically depressed patients.[18]

Conclusion

Dr. Clayton summarized that in the treatment of comorbid depression and anxiety, physicians should consider dual-acting agents. Treatments should be started at the lowest possible dose, with the dosage increasing only after acute adverse events have resolved or abated, which may increase the time to titrate the dose to a fully therapeutic dose. The final dose may need to be higher in patients with comorbid anxiety and depression than for MDD alone. Patients should be educated about the diagnosis, treatment plan, the goal of treatment, the projected length of treatment, and the timing and type of possible short-and long-term adverse effects associated with treatment. Nonpharmacologic interventions such as psychotherapy, healthy lifestyle, and phototherapy should be introduced early. Short-term benzodiazepine administration for acute anxiety and for augmentation in patients who partially respond to treatment should be considered. Depressive and anxiety symptoms should be monitored until symptoms are relieved and the patient achieves functional remission. If remission is not achieved, physicians should revisit the diagnosis in order to redefine the target symptoms and to potentially change therapy.

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The Role of Psychotherapy in the Treatment of Complicated Depression

Ellen Frank, Ph.D., outlined her presentation as addressing validated psychotherapies for depression, including evidence for psychotherapeutic efficacy in patients whose depression is complicated by medical illness, which medical patients with depression are candidates for psychotherapy, and how psychotherapies are best modified to meet the needs of these patients.

Empirically Validated Psychotherapies

Dr. Frank explained that only 3 empirically validated forms of psychotherapy exist for acute depressive episodes: cognitive therapy developed by Beck et al.,[1] interpersonal psychotherapy developed by Klerman et al.,[2] and problem-solving therapy developed by Catalan et al.[3]

Cognitive therapy. Dr. Frank stated that more than a dozen controlled trials since 1977 have demonstrated the efficacy of cognitive therapy[4] in outpatients with major depression. In cognitive therapy, the clinician examines the daily activities of patients who are encouraged to regularize their routines and engage in activities that provide pleasure or mastery.[1] The clinician also examines the maladaptive (i.e., negative) thought patterns and reactions of patients. Patients are then taught methods for counteracting negative thinking.

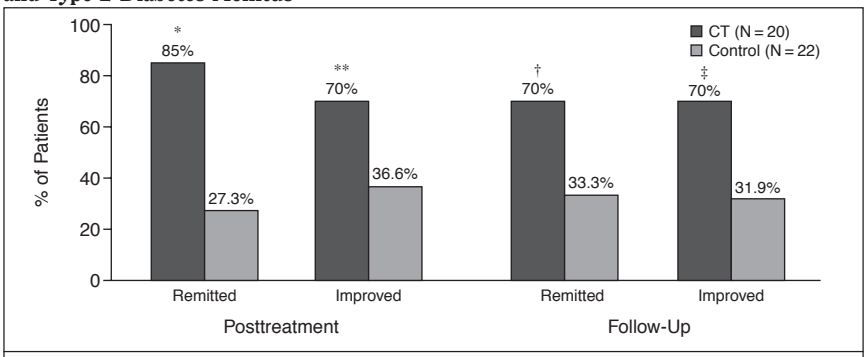
Recent interest in the extent to which cognitive therapy might be applicable to medical patients with depression has produced research that suggests that cognitive therapy is highly effective. Koike et al.[5] examined depressed patients with one or more comorbid medical conditions who were either given a quality improvement (QI) program that included a cognitive therapy approach or given usual care. Patients who participated in the QI program were found to have significantly better outcomes at 6 months and 1 year compared with patients given usual treatment. Similarly, another study[6] found a significant difference between patients who received usual care compared with patients who received either QI therapy or medications in addition to their usual care. Patients in either additional treatment program had better outcomes than patients in usual care. Research[7] in patients with type II diabetes found that a higher percentage of patients who received cognitive therapy either remitted or improved at posttreatment and at follow-up compared with patients in control conditions (Figure 2).

Interpersonal psychotherapy. Dr. Frank next described interpersonal psychotherapy (IPT) as a treatment that addresses the relationship between depression and problems in interpersonal and role functioning.[2] IPT is also used to ameliorate unresolved grief, role transitions, role disputes, and interpersonal deficits. Like cognitive therapy, controlled trials suggest that IPT has benefit as an acute, continuation, and maintenance treatment for patients with major depression.[8,9]

Research[10] on IPT for patients infected with HIV and with depression asserted that the state of depression is never normal, not even in someone with a life-threatening illness, although a sense of anticipatory sadness about death is appropriate for patients. In order for IPT to work for patients with HIV, modifications were made to the basic treatment paradigm. The psychoeducational component alleged that depression is treatable, and the interpersonal component maintained that interpersonal relationships and roles are more valuable and should be made as positive as possible precisely because time is limited. The individuals who received IPT versus supportive psychotherapy did not differ in levels of depression at the outset of the study, but at week 15, patients who received IPT were significantly more improved than patients who received the supportive therapy option.

Problem-solving therapy. Dr. Frank noted that problem-solving therapy (PST) was developed with the idea that a very brief, focused treatment might be appropriate to the primary care or other medical setting.[3] PST involves a 4-session intervention over 6 weeks that focuses on a detailed assessment of the patient's clinical state, an explanation of the symptoms of depression and reassurance about them, problem-solving in 5 stages focused on a single

Figure 2. Cognitive Therapy Efficacy for Patients With Depression and Type 2 Diabetes Mellitus[a]



[a]Reprinted with permission from Lustman et al.[7]
*p < .001.
**p = .01.
†p = .03.
‡p = .04

problem identified by the patient, and then a rehearsal of problem-solving techniques for any future problems that might emerge.

PST was first studied[11] in primary care patients with MDD and was contrasted with amitriptyline or placebo. At week 6 and at week 12, patients assigned to problem-solving treatments were significantly less depressed than those patients assigned to placebo and essentially not different from the patients who received amitriptyline. However, in a protocol funded by The Hartford and MacArthur Foundation that looked at older patients with minor depression and dysthymia in primary care, the findings were inconclusive.[12] Randomly assigned patients received either paroxetine, PST, or placebo. Only the patients with dysthymia were found to have any significant improvement with any of the treatments, and only in those who received paroxetine. While a specific benefit for problem-solving treatments was not found, the study looked at only patients with minor depression and dysthymia and not major depression. Finally, a similar kind of intervention was used in a study of a collaborative care management strategy among late-life patients with major depression in the primary care setting.[13] Patients were found to benefit from an intervention treatment similar to problem-solving treatments.

Candidates for Psychotherapy

Dr. Frank next explained that the best candidates for psychotherapy include patients already on complex medication regimens who might benefit from not adding another type of pharmacotherapy, patients for whom antidepressant medication is contraindicated, and patients who express a preference for psychotherapy. Other factors can also influence treatment. However, primary care patients who were starting antidepressant therapy appeared to benefit from telephone psychotherapy and telephone care management.[14] The proximity of psychotherapy treatment to primary care facilities appears to be an important factor. One study[15] found that the further from the primary medical care center the patients had to travel to receive psychiatric or substance abuse care, the less likely they were to engage in treatment.

Modifying Psychotherapies

Dr. Frank noted that depression psychotherapy intended for patients without a general or specific medical condition can be modified for patients with a medical condition. Physicians should consider the essential elements of the therapy and how each element applies to patients with the specific medical condition. Physicians should also consider which additional elements might be needed to treat the patient's medical condition plus depression. The elements should be consistent with the theoretical basis, strategies, and tactics of the original treatment. For some patients, a cognitive approach might be more effective, while an interpersonal or a problem-solving approach might be more effective for other patients.

For patients with cardiovascular disease and depression, Dr. Frank suggested interpersonal psychotherapy be modified by focusing on the component that refers to managing the illness and involves psychoeducation. The purpose of psychoeducation is to aid the patient in understanding heart disease, pulmonary problems, and major depression as well as the management of these conditions. In addition, patients may need a context in which they can grieve for the "lost healthy self" in order to aid them in accepting the disabled role.

When using therapy for patients with medical conditions and depression, physicians should consider how the medical illness might interfere or fit with the theoretical rationale for the therapy. The illness may affect the therapist's measurement of treatment outcome, and so the same expectations for wellness should not necessarily be anticipated as with medically healthy patients. In addition, the illness may affect the patient's ability to participate in the key ingredients of the therapy. For example, therapy that focuses on social interaction may be hampered if the illness limits a patient's ability to socially interact.

Conclusion

Dr. Frank concluded by stating that empirically validated psychotherapies have demonstrated efficacy in the management of the patients with medical illness and depression. The best candidates for these forms of treatment are patients already on complex medical regimens, for whom medication is contraindicated, and who express a preference for psychotherapy. Modifications for specific populations will need to take into account the specific needs and issues associated with the disease process.

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Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), imipramine (Tofranil and others), nortriptyline (Pamelor and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft), venlafaxine (Effexor).

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

For the CME Posttest for this ACADEMIC HIGHLIGHTS, see pages 332–334.