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Exercise for Mood and Anxiety Disorders

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CME ARTICLE

**Academic Highlights: Translating Evidence on
Depression and Physical Symptoms Into
Effective Clinical Practice**



In this month's Commentary, which also appears in the May 2007 issue of The Journal of Clinical Psychiatry (2007;68:669–676), 5 experts on exercise and psychiatric disorders discuss the rationale and evidence for using exercise to treat mood and anxiety disorders. This Commentary covers a topic that is particularly relevant to primary care physicians, who are increasingly called upon to meet the mental as well as physical health care needs of patients.

—Larry Culpepper, M.D., M.P.H.

PHYSICIANS DISCUSS PRACTICAL STRATEGIES FOR CLINICIANS INSPIRED TO IMPLEMENT EXERCISE AS A PRESCRIBED TREATMENT FOR PATIENTS WITH MOOD AND ANXIETY DISORDERS.

Exercise is not only beneficial for overall health and well-being, but is proving to be highly effective in the treatment of depression, anxiety, and other psychiatric disorders. Past methodological problems with the examination of exercise efficacy in treating depression, such as not distinguishing between depressed mood and depressive disorders, have helped temper the enthusiasm for exercise interventions in clinical practice and have left open a number of crucial questions. Is exercise more beneficial for some patient subgroups and less so for other patients? Should exercise be prescribed as an augmentation strategy or as monotherapy? As most depressed patients are sedentary and disinclined to exercise, how might a clinician initiate and maintain patient adherence to an exercise intervention? Unanswered questions such as these have left exercise on the fringe of traditional treatments for depression and its benefits largely overlooked. This Commentary provides an overview of the benefits offered by exercise interventions as well as specific strategies for implementing exercise prescriptions in psychiatric practices.

On August 22, 2006, Michael W. Otto, Ph.D., an expert in cognitive-behavioral treatment of anxiety and mood disorders, assembled a group of experts in order to share and debate specific knowledge and strategies concerning the prescription of exercise as treatment for affective disorders. Their discussion appears here.

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Exercise for Mood and Anxiety Disorders

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Jasper A. J. Smits, Ph.D.;
and Madhukar H. Trivedi, M.D.

Dr. Otto: There have been a number of population-based studies on the association between exercise and mental health. What is generally found in these large-scale studies?

Dr. Church: These population-based studies vary in size, population, and the way they assess physical activity and fitness. In general, the data¹ indicate that people who participate in regular physical activity are less likely to either have depression or develop depression in the future.

Dr. Otto: It could be that individuals with disorders do not feel like exercising. Do you have a sense that causation is driven in both directions or in one direction in particular?

Dr. Church: When it comes to epidemiologic studies of depression and exercise, one can rarely claim causation. Depressed patients may be disinclined to exercise,² a fact that makes causation even more difficult to determine. In depressed individuals, an internal bias concerning exercise often exists, which is precisely why it is important to have clinical trials with rigorous methodology.

Dr. Trivedi: An interesting clinical aspect of exercise and depression studies is that some of the studies^{3–5} that have examined population-based data have not evaluated depression as a diagnosis or as a disorder. Most of the studies^{6,7} have evaluated symptoms of depression that include not only major depression, but mood disorders other than major depression. The data from these studies^{4–7} suggest that patients who are physically active have psychological well-being in addition to physical well-being. Whether or not the results of these large-scale population studies are related to depressive disorders remains unclear. Few prospective studies have been conducted to answer this question.

Dr. Otto: This lack of clarity in the epidemiologic studies introduces the idea that exercise may promote general well-being, but once well-being is lost, individuals may find maintaining exercise difficult.

THE ANTIDEPRESSANT EFFECTS OF EXERCISE AS APPLIED TO PARTICULAR PATIENT SUBTYPES

Dr. Trivedi: The relationship between exercise and depression is pivotal. This relationship must be considered when using exercise for the treatment of depression or other mood or anxiety disorders.

Dr. Otto: As compared to epidemiologic studies, clinical trials examining the relationship between exercise and depression move clinical

cians and researchers closer to understanding the efficacy of exercise as a bona fide treatment of depression.

Dr. Trivedi: Blumenthal et al.⁸ examined pharmacotherapy in combination with exercise, but only in the elderly. In this study, patients (N = 156) who exercised did so in a group setting, which raises a possible methodological issue in that some of the effect that was seen could have been the result of socialization. An important line of future research in this area is the development of well-controlled clinical trials to compare the efficacy of exercise to well-established treatments for depression.

Dr. Otto: Dr. Smits and Dr. Craft have each been involved in separate meta-analyses¹⁻⁹ of the literature on the relationship between exercise and depression. How effective is exercise as a treatment for depression and to which patient subtypes has exercise been applied?

Dr. Smits: My colleagues and I recently completed a meta-analysis¹ that examined 11 studies with patients diagnosed with major depression and who were prescribed exercise or a nonactive comparator. Most of the patients included in the meta-analysis had moderate depression. The data from the meta-analysis show promise for the effectiveness of exercise for the treatment of depression, in 2 to 4 exercise sessions per week for 12 weeks. The individuals in the studies made significant improvements, for an effect size of 1.42 (95% CI = 0.92 to 1.93) versus control. The studies included in the meta-analysis had average attrition rates of 19.9%, rates that are comparable to attrition rates found in antidepressant trials, cognitive-behavioral therapy trials, and interpersonal therapy trials.⁸

Dr. Craft: In 1998, I conducted a meta-analysis with Daniel M. Landers⁹ and found that the majority of studies supported the efficacy of exercise as an antidepressant. Our examination of different potential moderator variables, including subject characteristics such as age, gender, and severity of depression and exercise characteristics such as intensity, duration, and frequency of exercise, showed that very few variables other than the length of the exercise program impact the relationship between exercise and depression. Exercise is effective for many different patient subtypes across genders and ages, regardless of the severity of depression.

Dr. Otto: The strength of the effect sizes in these meta-analyses^{1,9} is surprising. Why has the effectiveness of exercise not been featured in psychological and psychiatric literature until recently?

Dr. Craft: The early literature was positive for exercise as a treatment for depression, but it suffered from a variety of methodological flaws¹⁰ and may have dampened clinicians' enthusiasm toward implementing exercise programs in their practices. Recent controlled clinical trials¹¹⁻¹⁴ examining the relationship between depression and exercise have surprised many clinicians by showing how effective exercise is, but exercise has not

yet been implemented in the treatment plans of most clinicians. Implementation should be the primary goal.

HOW DO EXERCISE INTERVENTIONS COMPARE TO OTHER TREATMENTS FOR DEPRESSION?

Dr. Otto: A common question posed clinicians is how well exercise works in the treatment of depression relative to psychosocial treatments and pharmacotherapy. What is the evidence for exercise as a treatment for depression?

The methodology of studies on exercise has improved over time: the studies have been controlled better and the populations have been larger. In other meta-analyses, the effect size seemed to taper off as larger, better-controlled trials were conducted. In contrast, studies^{8,11-13,15,16} of exercise and depression, continue to show strong efficacy findings over time.

Dr. Craft: While there have been very few studies that directly examined pharmacotherapy in combination with exercise, data subsets in these studies can be used to compare treatment with pharmacotherapy alone to treatment with pharmacotherapy in combination with exercise. Even if the subset comparisons were not present in the primary research studies, the studies so far show that exercise for depression compares favorably with traditional treatments for depression.^{9,17}

Dr. Trivedi: Some of the meta-analyses^{1,9} performed on exercise and depression have included data from small studies, raising concerns about their reliability and hence their full relevance to the armamentarium for treatment.

EXERCISE AS A TREATMENT IN CLINICAL PRACTICE

Dr. Trivedi: My colleagues and I have published a study that may answer the question raised earlier: how do clinicians use exercise to treat patients in their practices? In our study,¹¹ we compared different doses of exercise to a control condition, which was a stretching exercise program. Stretching exercises worked as a control for high-impact exercises, because, although stretching increases flexibility, it does not elevate the heart rate or require the same amount of caloric energy as high-impact cardiovascular exercises. High-dose exercise was more effective in treating depression compared with stretching, but low-dose exercise did not produce the desired benefits.

We found no noticeable difference in results between physical activity spread over 3 days and physical activity spread over 5 days. (Table 1). Some patients have asked if they could receive their entire dose of exercise all in 1 day, but 1 day of exercise may not be possible or desirable for most patients. Spreading the exercise dose over 3 to 5 days puts less stress on the patient's body and helps integrate the exercise routine into the patient's schedule.

Table 1. Response and Remission Rates in 12-Week Trial of Exercise as Augmentation of Pharmacologic Antidepressants^a

Exercise Level	N	% Responding	% Remitting
Low intensity aerobic exercise, 3 sessions/wk	16	38	25
Low intensity aerobic exercise, 5 sessions/wk	18	6	11
Moderate to high intensity aerobic exercise, 3 sessions/wk	17	41	41
Moderate to high intensity aerobic exercise, 5 sessions/wk	16	44	31
Placebo control, 3 sessions/wk ^b	13	23	15
Total	80	30	25

^aAdapted with permission from Dunn et al.¹¹

^bFlexibility exercise.

Exercise should also be considered as an augmentation to standard pharmacotherapy. Remission rates with selective serotonin reuptake inhibitors and other commonly used antidepressants are approximately 30%,¹⁴ which means there is a large percentage of patients with depression for whom antidepressant pharmacotherapy is not enough. For these patients, adding exercise to pharmacotherapy or vice versa, or starting both in combination are worthwhile clinical approaches.¹⁸

Dr. Otto: Dr. Trivedi, do the patients in your clinic in the exercise trial share similar characteristics with the patients treated with traditional pharmacotherapy?

Dr. Trivedi: My colleagues at the clinic and I have not directly compared the patient samples for the 2 treatments, but the patients' sociodemographic characteristics, clinical illness characteristics, and symptom profiles seem comparable. There may be some differences between the groups; for example, the patients who come in for exercise studies may have a slightly higher socioeconomic standing and may be more educated about the relationship between exercise and depression. Patients like these may enter the study with an expectation that exercise is likely to benefit them. This sample variation is not that different from sample variations that occur in other nonpharmacologic psychotherapy studies. Patients who participate in psychotherapy are generally similar to those in pharmacotherapy studies, but the psychotherapy patients may be better educated about the potential benefits of psychotherapy.

Dr. Otto: So, at your clinic, Dr. Trivedi, patients make a choice to receive psychotherapy, pharmacotherapy, or exercise before they participate in the study?

Dr. Trivedi: Patient preference is becoming an important variable in the choice of antidepressant in practice. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) results that my colleagues and I published recently,¹⁹ at the second and third steps of the algorithm, patients often exhibited a strong preference as to whether to switch treatments or to augment antidepressant treatment after the first treatment failed. If patient

preference is introduced as a key variable in deciding treatment method, treatment may be more effective.

Dr. Craft: Individuals who are willing to participate in trials of exercise as a treatment for depression are at least interested in exercise, which may be different from the attitude of the average person who seeks treatment for depression. In ongoing research, I have found that minority individuals, who have not historically been included in some studies on exercise and depression, are highly interested in exercise as an option for treatment of depression. This trend seems particularly true of minority individuals who are not interested in or who wish to augment traditional pharmacologic treatments.

Research²⁰⁻²⁵ shows that despite the fact that depression rates among minority women are quite similar to the rates among their Caucasian peers, minority women are less likely to take antidepressants or receive specialty care. Therefore, it is important that we identify efficacious treatments for depressed minority women, who often do not fully embrace or have access to traditional therapies.²⁶ The majority of studies examining the use of exercise to reduce symptoms of depression have been conducted on Caucasian samples. Consequently, a primary gap in this literature centers on how well these findings generalize to depressed women of diverse racial and ethnic backgrounds. While exercise may be just as effective for minority women as Caucasian women, research is needed to verify that assumption.

In a recently completed randomized clinical trial (L.L.C.; K. M. Freund, M.D.; L. Culpepper, M.D., M.P.H.; et al., unpublished data, 2006), we enrolled 32 depressed sedentary women and randomly assigned them to either a facility-based or home-based exercise intervention. Just over 80% of the women enrolled were minority (African-American and Latina) and about half were not receiving any treatment for their depression at study entry. By 6-month follow-up, women in both groups had significantly increased ($p < .05$) time spent in physical activity. Further, both groups also experienced significant reductions ($p < .05$) in depression. Study results support the efficacy of exercise to reduce depression among minority women, and researchers should continue to investigate the use of exercise as an adjunct treatment in this subset of patients. However, this is the first study to examine the exercise-depression relationship utilizing a predominantly minority sample and results need replication.

Dr. Greer: Not only are minority individuals interested in exercise for the treatment of their depression, but they want to exercise to improve their global health as well. For example, the prevalence of diabetes, which is frequently comorbid with depression is increased in some minority groups.²⁷ With increasing efforts to raise public awareness of the health benefits of exercise, individuals of all racial and ethnic groups are beginning to desire physical activity to benefit both mental and physical

health. We have found that the interest in our exercise studies has been very high, and patients seem to be increasingly aware of the overall health benefits of exercise, in addition to their hope of relief from depressive symptoms.

Global Health Benefits of Exercise: Treating the Whole Patient

Dr. Otto: We should discuss the additional health benefits of exercise further. Aside from mental health benefits, what are some of the other health benefits associated with exercise?

Dr. Church: Exercise is extremely powerful in fighting cardiovascular disease.^{28,29} Physical activity reduces the risk of heart attack and stroke,³⁰ which is particularly important for individuals who have hypertension, diabetes, or cholesterol abnormalities. Physical activity also reduces the risk of developing certain cancers, such as colon cancer³¹ and breast cancer.³² Also, if aging people are physically active, their overall quality of health and quality of life are improved.

Traditional risk factors do not explain the benefits of exercise in treating cardiovascular disease. There are some hypotheses as to why exercise is powerful in the prevention and reoccurrence of cancer, but there are no concrete answers. The current inability to discover the exact mechanism by which exercise helps with mood disorders should not be a concern. If the history of cancer research and cardiovascular disease has given us a research paradigm, it could be decades before we understand why physical activity works for mental health.

Dr. Greer: Depression itself is an independent risk factor for cardiovascular disease. Cardiovascular disease is a common, chronic physical disease that is often comorbid with depression. Individuals who have had cardiac events and who also have depression exhibit poorer outcomes than individuals without comorbid depression.^{33,34} Increasing a depressed patient's physical activity is an outstanding opportunity to use exercise as a treatment for mental health and to possibly garner some physical health benefits as well.

Health Risks of Exercise Prescription

Dr. Otto: With all of the positive effects already discussed, possible adverse effects also need to be discussed. What particular health risks should be attended to when making the decision to prescribe an exercise program?

Dr. Church: The risks are relatively minimal if the individual understands the importance of starting slowly and building up the activity over time. The people who typically experience adverse effects are males in their 40s who try to perform the same workout they performed in high school. The goal of treatment should be physical

activity, not necessarily buying a pair of running shoes and joining a gym, although joining a gym does motivate some patients.

Before initial treatment, the clinician should identify high-risk individuals, such as patients with histories of stroke, heart attack, or diabetes. These patients should be medically cleared before beginning physical activity. For the vast majority of people, the risk of sudden cardiac events is minimal, as long as they start at a realistic pace. For example, a walking program at light to moderate intensity is safe for most people. Intensity can be increased over time, and the patient should pay attention to symptoms such as chest pain or shortness of breath. Common problems patients face when beginning exercise are bone and joint issues, such as sore knees and ankles, and more chronic problems, such as old injuries that are developing into arthritis. If a patient starts an exercise program slowly, joint stiffness, soreness, and pain can be minimized.

Dr. Otto: A key idea in using exercise as a treatment for depression is that of building up intensity over time. How can a clinician convince a patient who has not recently participated in regular physical activity to start an exercise program and adhere to it?

Dr. Greer: One recommendation is to have patients who are interested in exercise record the frequency, the duration, and the modality of each exercise session and then solve any issues that arise from integrating an exercise regimen into everyday life. A sample exercise log that includes many of the desired data to be recorded is available in our recent pilot study of exercise augmentation.²

Dr. Craft: Research shows that self-monitoring exercise behavior and addressing key psychosocial issues, such as barriers to exercise, exercise self-efficacy, and social support for exercise, as well as providing brief and supportive follow-up contact, can improve exercise adherence by up to 25% in the general population.¹³

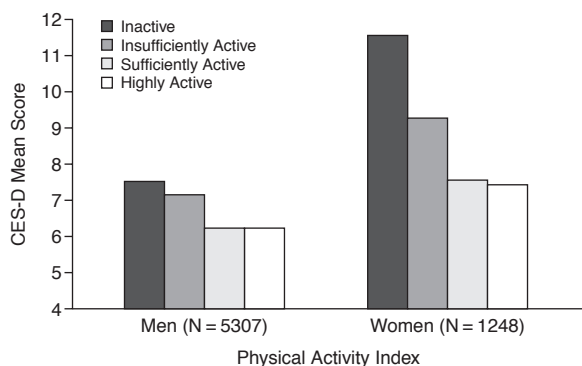
Although studies^{3,12} have found a greater reduction in depression with a greater intensity of exercise, it is important to keep in mind that exercise does not have to be lengthy or intense for an individual to benefit (Figure 1).

Dr. Church: A useful tool for self-monitoring and for incorporating physical activity into individuals' daily lives is the step counter, which is a device that clips on to the belt and shakes with every step. It supplies readouts of how many steps are taken during the day. The step counter is inexpensive, easy to use, and provides a simple way to quantify daily physical activity. They can be bought for around \$20 at most sporting goods stores.

Activity: The Proper Dose

Dr. Otto: Many clinicians may have heard in media reports that a proper dose of activity is 10,000 steps per day. Is 10,000 steps the range that we are recommending to clinicians in practice?

Figure 1. Physical Activity Reduces Depression Scores on the CES-D^a



^aReprinted with permission from Galper et al.³ Physical activity levels: inactive = < 1 mile per week of walking, jogging, and running; insufficiently active = 1 to 10 miles per week; sufficiently active = 11 to 19 miles per week; highly active = \geq 20 miles per week.

Abbreviation: CES-D = Center for Epidemiologic Studies Depression Scale.

Dr. Church: The round number “10,000 steps” sounds scientific in the media, but there is little research to support that number. People with step counters should wear the counter for a few days to find the average number of steps they take each day. A sedentary American will average between 3000 and 5000 steps.³⁵ Once people know their average, they should add 1000 to 2000 steps per week. For sedentary people, a realistic goal is approximately 8000 steps per day. For those who want to be more active, the goal may be closer to 10,000 steps per day. Finally, for people truly interested in losing weight and seeing physiologic changes, the number of steps desired may be greater than 10,000.

Dr. Craft: From a research perspective, a goal of 10,000 steps a day is unrealistic for most individuals with depression. Depressed people tend to be sedentary, be overweight, and have reduced work capacities.¹⁷ In my experience, the baseline number of steps for individuals with depression tends to be a range of 2000 to 3000 steps per day. The number popular in the media, 10,000 steps, equals about 5 miles per day. Walking 5 miles per day is an unrealistic goal for a sedentary, depressed person. Find the individual’s baseline and then gradually add steps.

Dr. Otto: What sort of dose and duration should be suggested for the average depressed patient?

Dr. Church: The general consensus for treatment is about 30 minutes of physical activity a day, at least 5 days a week.^{15,18} I recommend that physical activity be performed once every 3 days.

Dr. Otto: Exercise 3 to 5 days a week seems to be the most effective dose. How long does it take for the average patient to see benefits from exercise? When do patients tend to report feeling better?

Dr. Craft: In the study I published in 2005,¹⁵ depressive symptoms were evaluated at baseline, at week 3, and at week 9. By week 3, individuals who exercised (N = 9) had reduced their mean scores on the Beck Depression Inventory-II scale from 21.2 to 9.3, while the mean scores of the control individuals (N = 10) remained approximately the same (with significant differences between these groups).

Clinicians should emphasize to patients the short-term benefits of exercise: improvements in mood, energy level, the ability to concentrate and focus, and quality of sleep. Many individuals are focused on the distant outcomes, such as weight loss, so emphasizing short-term benefits can help patients adhere to a new exercise regimen.

While 150 minutes of physical activity per week is the ultimate goal of treatment, for depressed individuals, 3 to 5 periods of exercise a week for 30 minutes per period is overwhelming at first. When starting a depressed individual on an exercise program, a reasonable and attainable goal can be as minimal as 10, 15, or 20 minutes of physical activity at a time. A good tool in the beginning is to reinforce frequency so that physical activity becomes habitual. The clinician can then work with the patient to increase the duration of the activity, and later work on building the intensity of the activity.¹⁵

EXERCISE ALSO BENEFITS PATIENTS WITH ANXIETY DISORDERS

Dr. Otto: Is there literature that shows that physical activity can provide benefits for patients with disorders other than depression, for example, anxiety?

Dr. Smits: The qualitative review¹ that my colleagues and I performed found that not much work has been done on the use of exercise as a treatment for other mental disorders. We found a few randomized, controlled trials on alcohol abuse,³⁶ eating disorders,³⁷⁻³⁹ and anxiety disorders.⁴⁰ The literature shows some promise for exercise as a treatment for anxiety disorders and for panic disorder⁴⁰ in particular.

The exercise model for panic disorder is different from the exercise model for depression. Physical activity may serve as exposure treatment for panic disorder. Exercise may create physical sensations that produce fear in people with panic disorder. The activity may provide necessary exposure to these sensations so that patients with panic disorder can begin to recover.⁴¹ Preliminary work⁴⁰ on the relationship between exercise and panic disorder showed that exercise outperformed placebo in the reduction of panic disorder symptoms, and approached the level of benefit offered by clomipramine.

Dr. Otto: The side effects from exercise such as sweating, light-headedness, and rapid heartbeat are useful tools for treating panic disorder. Clearly, clinicians should not fear comorbid disorders when treating patients with exercise.

THE WELL-BEING EFFECT ACROSS MULTIPLE SYMPTOM DOMAINS

Dr. Otto: Exercise has been discussed as having far-reaching effects, including improving resiliency to stress and treating panic disorder. Are the same effects seen in clinical applications or, since exercise trials for depression are more prominent than exercise trials for other mood disorders, are researchers in those trials commenting on broad-based changes? Has an effect on well-being been observed across multiple symptom domains, either in trials or in clinical practice?

Dr. Greer: Our work in this area suggests that in addition to reductions in depressive symptom severity, exercise augmentation produces psychosocial benefits and improved quality of life. Participants who received 12 weeks of exercise augmentation showed a mean increase of 14 points on the Quality of Life Enjoyment and Satisfaction Questionnaire (short form, general activities).²

Dr. Craft: In my current clinical trial work, patients tend to readily report reduction in depression and those patients who have an anxiety component to their depression often say that their feelings of anxiety diminish as well when they exercise regularly. In patients who exercise, an overall sense of well-being is enhanced.

Dr. Otto: Why does exercise lead to these improvements? Dr. Smits has already mentioned that the mechanism of action for exercise in the treatment of panic disorder may be different from the mechanism of action in depression. What does the literature show about the mechanism of action in depression?

Dr. Greer: Animal studies⁴²⁻⁴⁴ have observed increases in neuromodulators, like serotonin and norepinephrine, when the animals exercised. The increased production of neuromodulators caused by exercise is consistent with the target of antidepressant pharmacotherapy. Exercise is likely to play an important role in mood elevation.

Dr. Otto: In effect, exercise produces the same neurochemical changes that are often targeted by pharmacotherapy.

Dr. Trivedi: In addition to the neurochemical changes, inherent in exercise is the attainment of self-efficacy. Patients play a large part in the successful achievement of the correct dose of treatment.¹² Self-efficacy, the belief that one has the ability to produce a desired effect, may enhance the antidepressant effect and may even be the cause of the neurochemical changes.

Dr. Otto: Activity assignments alone are effective for the treatment of depression. Simply initiating physical activity in a goal-driven way may relieve depression. Could a simple increase in activity level relate to self-efficacy?

Dr. Trivedi: In studies,^{45,46} self-efficacy has been shown to have some antidepressant effect. A randomized trial could confirm whether self-efficacy is an additional benefit of exercise or not.

Dr. Smits: Changing patients' action tendencies, getting people to take action that is inconsistent with how they feel, is a common theme of psychotherapy for depression and anxiety disorders and may improve patients' moods.

Dr. Otto: The proposed mechanisms of action for antidepressant agents have changed over the years as researchers learned more about the brain. A treatment may be known to be effective for many years without us knowing the mechanism of action.

Dr. Church: Lack of a mechanism of action is part of the reason physical activity has not gained acceptance in the mental health arena.

CLINICAL TOOLS FOR EXERCISE MAINTENANCE

Dr. Trivedi: The effectiveness of exercise as a treatment for depression is gaining recognition. Interest in exercise, especially as an augmentation to pharmacotherapy, is increasing. Exercise needs to become an accepted treatment option.

Once the patient has accepted physical activity as a treatment option, the challenge for the physician is to help each patient find the right dose of exercise and maintain it. This question of dose and maintenance has not been well studied. In our studies,^{2,3,11,12} my colleagues and I have focused on trying to make sure that the patients followed through with the prescribed dose of exercise. The clinical challenge will be to find strategies that ensure patients continue to exercise after the first several weeks, when their motivation declines.

Dr. Church: Maintenance of physical activity is a challenge, but ongoing research may soon give clinicians scientifically proven tools to encourage maintenance of activity. Clinicians should emphasize the incorporation of regular physical activity, not just vigorous activity, into daily life.

Dr. Craft: In clinical work, I have found that once patients begin to feel better as a result of exercise, they are eager to continue their exercise if the clinician can help them attribute their improved mood to the exercise regimen. Improved mood as a result of increased physical activity may be obvious to the researcher or clinician, but the connection is not always obvious to the patient.

Dr. Smits: Reinforcing the connection between mood change and exercise is particularly relevant for patients with panic disorder. The prescription for exercise for panic disorder requires patients to engage in intense exercise in order to elevate their heart rates so that they can become accustomed to sensations that will help them overcome their fear of panic.

If patients do not have a sense of how exercise is going to work to treat their disorder, or if patients fail to see improvement after the first few sessions, then it will be exceedingly difficult to maintain the program. Giving

Table 2. Sample Exercise Dose Calculations^a

	Prescribed Energy Expenditures (kcal)		
	Per Week (kg × 16 kcal/kg/wk)	Per Session	
Sex (weight, lb/kg)		3 d/wk	5 d/wk
Male (180/81.8)	1309	437	262
Female (140/63.6)	1018	340	204
Exercise	Estimated Duration (min)		
		3 d/wk	5 d/wk
Walking 4 mph		75	45
Jogging 5 mph		63	38

^aAdapted with permission from Trivedi et al.¹⁸

patients a model of exercise as treatment before beginning therapy and reminding patients to maintain their exercise program once they have started are important in treating patients with panic disorder effectively.

Dr. Otto: Clinicians already have a variety of skills relevant for enhancing adherence to exercise. Psychosocial therapists and cognitive-behavioral therapists have developed strategies introducing and maintaining behavior change. Likewise, psychopharmacologists have strategies to introduce patients to medication treatment: developing the routine of taking a pill daily and maintaining the use of the medication for long-term treatment. Clinicians can apply related strategies for promoting adherence to this new intervention, exercise.

Dr. Craft: Many of the strategies used with cognitive-behavioral therapy could easily be applied to exercise: self-monitoring, goal-setting, homework activities, and supportive follow-up. All of these strategies will help maintain the new behavior.

Dr. Otto: What advice would you give a clinician who wants to add exercise as an adjunctive treatment for depression? What is a good way to start a patient with a prescription for exercise?

Dr. Trivedi: My colleagues and I¹⁸ recently discussed some tools that clinicians can use to implement exercise as a treatment augmentation. The most important part of beginning exercise treatment is to motivate patients. Motivation ensures adherence to the treatment, just as a patient treated with pharmacologic agents is motivated to take his or her medication on the prescribed basis. Patients may need to be educated about the fact that exercise effectiveness truly depends on dose, and if a patient does not receive the right dose of exercise, the patient will not attain the desired benefits.

In our article,¹⁸ we provided a sample dose calculation by weight, which allows patients to recognize how many hours per week they need to spend walking, jogging, or participating in other physical activities (Table 2). Applicable and practical pointers for clinicians are included in the article.

Dr. Otto: Patients have some leeway in working up to the exercise dose. What matters is not that the patient

achieves the goal right away, but that the individual reaches the optimum dose over time.

NEW RESEARCH FOR EXERCISE AND CLINICAL PRACTICE

Dr. Otto: What do you see in the near future for exercise research and practice?

Dr. Church: Using neuroimaging, researchers are comparing the neurologic changes associated with pharmacotherapy in people who are depressed with the neurologic changes in people who have used exercise as an antidepressant. The results can be viewed using neuroimaging.

Dr. Trivedi: In practice, although exercise may be helpful as a single agent, most clinicians are likely to use exercise as an augmentation agent for partial responders or as an adjunct for patients who have very specific residual symptoms. Partial responders are the ideal patient sample to which physicians and clinicians will prescribe goal-directed exercise interventions. Once goal-directed exercise interventions are a practice that clinicians can readily implement, as Dr. Church suggested, goal-directed exercise may become commonly used in clinical care.

Drug name: clomipramine (Anafranil and others).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, clomipramine is not approved by the U.S. Food and Drug Administration for the treatment of panic disorder.

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For the CME Posttest for this article, see pages 325–326.



Translating Evidence on Depression and Physical Symptoms Into Effective Clinical Practice

This ACADEMIC HIGHLIGHTS section of The Primary Care Companion to The Journal of Clinical Psychiatry presents the highlights of the planning teleconference "Translating Evidence on Depression and Physical Symptoms Into Effective Clinical Practice," which was held November 27, 2006. 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 **David A. Fishbain, M.D.**, from the Departments of Psychiatry and Behavioral Sciences, Neurological Surgery, and Anesthesiology, University of Miami School of Medicine, Miami, Fla. The faculty were **Ronald M. Glick, M.D.**, Departments of Psychiatry, Physical Medicine and Rehabilitation, and Family Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pa.; **Louis Kuritzky, M.D.**, Department of Community Health and Family Medicine, University of Florida, Gainesville; and **Bill H. McCarberg, M.D.**, Founder, Chronic Pain Management Program, Kaiser Permanente, San Diego, Calif.

In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME article were asked to complete a statement regarding all relevant financial relationships between themselves or their spouse/partner and any commercial interest (i.e., a proprietary entity producing health care goods or services consumed by, or used on, patients) occurring at least 12 months prior to joining this activity. The CME Institute has resolved any conflicts of interest that were identified. The disclosures are as follows:

Dr. Fishbain is a consultant for, has received honoraria from, and is a member of the speakers/advisory board for Eli Lilly. **Dr. Kuritzky** is a member of the speakers/advisory boards for GlaxoSmithKline, Bayer, Pfizer, Eli Lilly, and IMS Global Insights. **Dr. McCarberg** is a member of the speakers/advisory boards for Purdue, Pfizer, Mylan, Merck, Eli Lilly, Ligand, PriCara, Forest, Endo, Abbott, Alparma, and Cephalon. **Dr. Glick** has no personal affiliations or financial relationships with any proprietary entity producing health care goods or services consumed by, or used on, patients to disclose relative to the presentation.

The opinions expressed herein are those of the faculty and do not necessarily reflect the views of the CME provider and publisher or the commercial supporter.

Physical symptoms that seem to have no physical cause may obscure a mood disorder. In a series of presentations chaired by David A. Fishbain, M.D., experts reviewed evidence and offered opinions regarding diagnosis and treatment for overlapping pain and depression in primary care patients.

Pain and Depression in Primary Care

Although a patient may be more concerned with physical symptoms than emotional ones, Bill H. McCarberg, M.D., stated that clinicians must remember that painful physical symptoms often have an emotional aspect.

Presentation and Diagnosis

In primary care, patients often have physical symptoms that health care providers are unable to explain. Kroenke and Mangelsdorff¹ reviewed 1000 patient records from an internal medicine clinic and found an organic etiology for patients' symptoms in only 16% of cases despite diagnostic testing in more than two thirds of the cases (Table 1). Ten percent of the symptoms were considered to have a psychological cause related to depression, stress, anxiety, or grief. A review² of European studies showed an association between depression and painful physical symptoms in 46 of the 70 studies reviewed, whether in the general population, in patients presenting to a primary care physician, or in patients presenting to pain clinics or psychiatric clinics.

Kroenke and Price³ found that in patients with any of 14 physical symptoms common in primary care, the lifetime risk of common psychiatric disorders was at least twice as high as in those without the symptom. Further, Dr. McCarberg advised that the greater the number of unexplained physical symptoms a patient has, the less likely it is that the primary problem is an

anatomical abnormality. Katon et al.⁴ found that when the number of medically unexplained somatic symptoms rose above 5 in women or 3 in men, the rates of lifetime major depressive disorder (MDD) or panic disorder increased significantly.

Physical symptoms are often the chief complaint of patients with depression, particularly in a primary care setting. Simon et al.⁵ showed that 69% of patients with depression reported only somatic symptoms. Dr. McCarberg commented that when patients focus on physical symptoms, psychiatric disorders are more difficult for physicians to recognize than when patients report psychological symptoms. One study showed a drop in physician recognition of depression from 77% when psychological symptoms were described by patients to 22% when only physical symptoms were mentioned.⁶

Relationship Between Pain and Depression

Neurochemical pathways provide a link between depressive symptoms and physical symptoms. Many of the ascending serotonin and norepinephrine pathways in the brain mediate mood, suicidal ideation, changes in appetite, sleep, and pleasure; descending serotonergic and noradrenergic pathways modulate pain, such as headache and vague joint, back, or abdominal pain.^{7,8} If norepinephrine-serotonin pathways malfunction, many emotional areas of the brain as well as physical areas of the body may be affected, and patients

Table 1. Three-Year Incidence and Probable Etiology of 14 Common Symptoms in 1000 Internal Medicine Outpatients^a

Symptoms	Symptoms, No.	Probable Etiology, %		
		Organic	Psychological	Unknown
Chest pain	96	11	6	83
Fatigue	82	13	21	66
Dizziness	55	18	2	80
Headache	52	10	15	75
Edema	45	36	0	64
Back pain	41	10	0	90
Dyspnea	37	24	3	73
Insomnia	34	3	50	47
Abdominal pain	30	10	0	90
Numbness	26	19	4	77
Impotence	24	21	4	75
Weight loss	18	5	28	67
Cough	15	40	0	60
Constipation	12	0	0	100
Total	567	16	10	74

^aReprinted with permission from Kroenke and Mangelsdorff.¹

may experience physical complaints as well as depression.⁸

Significant associations have been found between pain conditions and mood and anxiety disorders. McWilliams et al.⁹ found that people with arthritis, migraine, and low back pain were at greater risk (odds ratio [OR]= 1.48 to 3.86) of having MDD, panic disorder, and generalized anxiety disorder, than people without a pain condition. Dr. McCarberg remarked that conversely, people with emotional symptoms are at increased risk for physical health problems. For example, at a 13-year follow-up¹⁰ of people free

of heart trouble at baseline, those with a history of a major depressive episode were at a 4 times greater risk for myocardial infarction than those who did not experience a depressive episode (the risk was independent of major coronary risk factors).

Conclusion

Dr. McCarberg concluded that depression not only affects the brain but also has an effect on the body; therefore, treating the whole patient, not just the pain and not just the emotional symptoms, is important for achieving a successful outcome.

The Effect of Painful Physical Symptoms on Depression Remission

Response and Remission

Response and *remission* are not interchangeable terms, explained David A. Fishbain, M.D. *Response* refers to the level of change in symptoms since baseline, *nonresponse* is a less than 25% decrease in baseline rating scale scores, *partial response* is a 25% to 50% decrease in baseline scores, and *response* is a greater than 50% decrease in baseline scores.¹¹ *Remission* is the complete resolution of depressive symptoms and is defined as a

score of less than 8 on the 17-item Hamilton Rating Scale for Depression (HAM-D) or a score of less than 11 on the Montgomery-Asberg Depression Rating Scale. Remission is the optimal outcome of treatment but is difficult to achieve. For example, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,¹² only 28% of patients achieved remission by 12 to 14 weeks.

Dr. Fishbain stated that patients who achieve remission have a better

prognosis for their depression, function better, have a lower risk of relapse, and use fewer medical services compared with patients who merely respond to antidepressant treatment.¹³ For patients who have demonstrated nonresponse, partial response, or response, treatment options for achieving remission include switching to an antidepressant in the same or another class as the first agent, augmenting with an antidepressant from a different class, or augmenting with an agent other than an antidepressant (Table 2).¹⁴

Prevalence and Consequences of Physical Symptoms and Depression

Pain is common in depression. Dr. Fishbain cited a large community survey¹⁵ in Europe that found painful physical symptoms in 50% of respondents with depression. Further, another study¹⁶ reported that primary care outpatients with 1 physical symptom had a 2% prevalence of mood disorders, whereas among outpatients with 9 or more physical symptoms, mood disorder prevalence was 60%.

Patients with physical symptoms associated with depression were more likely than depressed patients who did not have physical symptoms to^{3,15-18}:

- be severely depressed
- have nonremitting depression
- be at risk for depression relapse
- have complex symptoms
- be difficult to treat
- have other psychiatric comorbidities
- have poor treatment outcomes
- lose work productivity
- require polypharmacy

Pain in patients with MDD is associated with increased health care costs¹⁹ and increased severity of fatigue, insomnia, psychomotor retardation, weight gain, and impaired concentration.²⁰

Dr. Fishbain further suggested that a bilateral relationship may exist between pain and depression. For ex-

Table 2. Treatment Options Adapted From STAR*D to Bring Patients With Depression Into Remission^a

Switch from one antidepressant to another antidepressant within the same class
Switch to an antidepressant from a different class of antidepressants
Augment antidepressant therapy with an antidepressant from a different class
Augment an antidepressant with another agent, such as lithium or triiodothyronine (T ₃)
^a Adapted from Rush et al. ¹⁴
Abbreviation: STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

ample, among neurology outpatients, the odds of having pain increased in patients with depression, and the odds of having depression increased in patients with pain.²¹ A community survey²² in Canada found that only 5.9% of respondents without back pain had major depression but in comparison, 19.8% of respondents with chronic back pain had major depression. As pain severity increased, the rate of major depression increased in a linear fashion. Greater severity of painful physical symptoms has also been associated with increased severity of depression.²³

Response to antidepressants and remission of depression are affected by physical symptoms. One study²⁴ showed that a greater number of somatic symptoms present at baseline predicted delayed response to fluoxetine, and another study²⁵ found that more severe body pain at baseline predicted nonresponse to paroxetine among patients with late-life depression. Denninger et al.¹⁸ reported that the degree of improvement in physical symptoms correlated with achievement of remission. Karp et al.²⁶ found that time to remission with imipramine was significantly longer in subjects with more pain at baseline.

Further, risk of relapse is greater in patients who have residual symptoms, including somatic symptoms, after depression treatment. Paykel et al.¹⁷ reported that 76% of subjects with residual symptoms relapsed, whereas 25% of those without residual symptoms relapsed. Dr. Fishbain emphasized the importance of treating physical symptoms as well as psychological ones to prevent relapse after depression treatment.

Efficacy of Antidepressants for Pain and Achieving Remission

Managing somatic symptoms and pain are important considerations when selecting medications to treat comorbid depression. A meta-analysis by Fishbain and colleagues²⁷ of studies of patients diagnosed with psychogenic pain or somatoform pain disorder showed that antidepressants significantly decreased pain intensity ($z = 5.71$, $p < .0001$) compared with placebo.

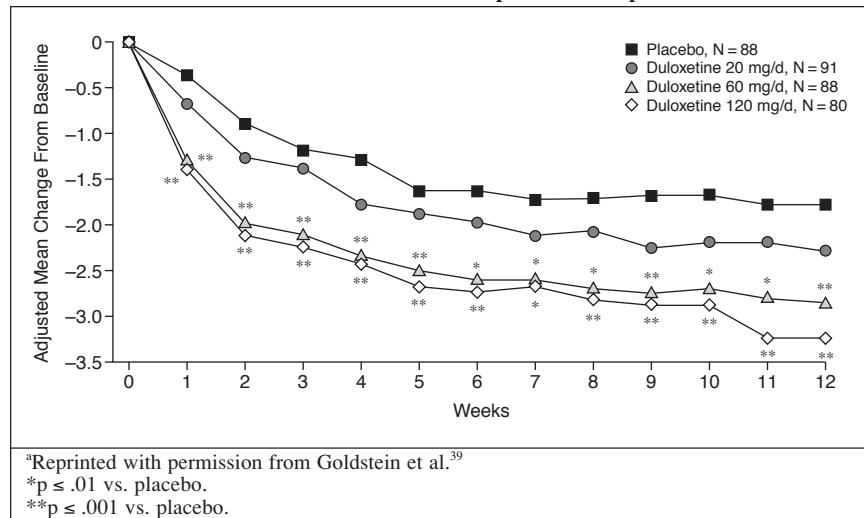
Further, dual-action antidepressants that block both serotonergic and noradrenergic reuptake have been found to be more effective than other antidepressants for the treatment of pain. In a review of animal and human studies by Fishbain et al.,²⁸ pain relief was demonstrated in 100% of trials of serotonergic-noradrenergic antidepressants, compared with 89% of studies using noradrenergic antidepressants, and 14% of studies using serotonergic antidepressants. Similarly, a meta-analysis by O'Malley et al.²⁹ found that tricyclic antidepressants (TCAs), which are all dual-action antidepressants but are serotonergic and noradrenergic in varying proportions, appeared to have a greater likelihood of analgesic effect than selective serotonin reuptake inhibitors (SSRIs) for headache, fibromyalgia, functional gastrointestinal syndromes, and idiopathic pain. Lynch³⁰ found that 80% of TCA studies showed a beneficial effect for pain compared with only about 36% of SSRI studies. Additionally, a calculation³¹ of the number of patients needed to treat showed SSRIs to be less effective for various types of neuropathic pain than TCAs.

In reference to depression remission, dual action antidepressants appear to also offer an advantage over the SSRIs. Clomipramine, a dual-action antidepressant, demonstrated greater remission rates than the SSRI citalopram.³² The SSRI fluoxetine combined with the noradrenergic antidepressant desipramine showed a superior rate of remission after 4 weeks compared with desipramine alone (71% vs. 14%).³³ Patients treated with the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine also had a significantly higher remission rate (45%) than those treated with the SSRIs fluoxetine, paroxetine, or fluvoxamine (35%).³⁴ Finally, the SNRI duloxetine produced a greater remission rate (43%) than the SSRIs paroxetine, sertraline, or fluoxetine (38%).³⁵

Interestingly, the SSRIs also appear to be less effective for the somatic symptoms of depression than for the emotional symptoms of depression. Greco et al.³⁶ studied depressed primary care patients during 9 months of SSRI treatment and found that, while depressive symptoms continued to gradually improve, somatic symptoms decreased most during the first month and then ceased to resolve. In the same population,³⁷ 69% of patients reported pain at baseline and 58% still reported pain after 3 months, and the odds ratio for poor treatment response was positively correlated with severity of pain.

One study³⁸ showed that venlafaxine, an SNRI, is effective for neuropathic pain, although it is not approved by the U.S. Food and Drug Administration (FDA) for this use. Patients with diabetic peripheral neuropathic pain treated with higher doses (> 150 mg/day) of extended-release venlafaxine had significantly greater mean Visual Analog Pain Relief scores than placebo by week 6 of the study, as well as significantly reduced mean Visual Analog Pain Intensity scores ($p < .001$).³⁸ Dr. Fishbain noted that when venlafaxine is used at lower doses, it acts like an SSRI, but at

Figure 1. Mean Change From Baseline in 24-Hour Average Pain Severity Score for Different Doses of Duloxetine for Diabetic Peripheral Neuropathic Pain^a



higher doses, it has more dual-action activity.

Duloxetine, an SNRI balanced in noradrenergic and serotonergic activity, is FDA-approved for the treatment of diabetic peripheral neuropathic pain as well as MDD (Figure 1).³⁹ Duloxetine has been shown to separate from placebo at week 1 for its analgesic effect and this may be secondary to its

balanced activity.³⁹ Duloxetine has also been shown to be effective for backache, shoulder pain, time in pain while awake, and interference with daily activities secondary to pain in patients with MDD.⁴⁰ Fava et al.⁴¹ found that patients whose pain responded to duloxetine had better rates of depression remission than those whose pain did not respond (39% vs. 25%).

Table 3. Treatment Plan for Depression Associated With Pain and Other Somatic Symptoms

Treat pain aggressively to make treatment of somatic symptoms easier and consequently achieve depression remission
 Target individual somatic symptoms to control them and help achieve remission of depression
 Use antidepressants with demonstrated analgesic properties such as dual-action antidepressants that make treatment of somatic symptoms easier

Conclusion

Dr. Fishbain concluded that alleviating painful physical symptoms in depression can speed remission and improve overall remission rates. Further, dual-action antidepressants are more effective at achieving remission because they are more effective in treating the painful physical symptoms of depression than SSRIs. A treatment plan for depression associated with pain and other somatic symptoms should include 3 aspects: aggressive pain treatment, the targeting of individual somatic symptoms, and the use of antidepressants that have demonstrated analgesic properties (Table 3).

Managing Treatment-Resistant Depression With Painful Physical Symptoms in Primary Care

In primary care, patients may seek treatment for depression, or for pain, or for a combination of both pain and depression, but many may not respond to initial treatment approaches, according to Ronald M. Glick, M.D.

Treatment-Resistant Depression With Comorbid Pain

Treatment resistance is a major problem in depression treatment. About 40% of patients with depression do not respond fully to adequate treatment.⁴² The STAR*D study⁴ resulted in a protocol for patients with depression who do not respond to the first medication prescribed (see Table 2). At each step of the protocol, a few more patients responded until eventu-

ally most patients responded to and tolerated their medication.⁴³ No evidence-based protocol like the STAR*D exists for treatment-resistant depression with comorbid pain.

Comorbid pain may contribute to treatment resistance and may warrant specific treatment or consultation. It is uncertain whether the data on treatment-resistant depression can be generalized to patients with comorbid pain; however, the use of dual-action medications appears to be the best strategy. Dr. Glick emphasized the importance of asking patients with treatment-resistant depression whether they have pain. Because depression is the primary concern, many patients will not mention that they suffer from pain unless asked.

Pain With Comorbid Depression

Dr. Glick noted that some patients seeking traditional treatment for chronic pain may be reluctant to acknowledge psychological symptoms, but patients seeking more integrative approaches may recognize an association between their painful symptoms and depression.

Patients with chronic pain, particularly when they have comorbid depression, tend to become increasingly passive because activity increases their pain. Dr. Glick encourages patients to take a more active role in their pain management through exercise, diet, and stress management. Almost all patients with pain and/or depression could benefit from increased activity.

Thirty minutes of aerobic exercise per day, whether it is walking at a brisk pace or something more rigorous, has analgesic and antidepressant effects.⁴⁴⁻⁴⁶ Physical therapy or a pain rehabilitation program can be helpful for patients with a chronic pain syndrome⁴⁷ or with a specific musculoskeletal cause for their pain.⁴⁸ Being overweight can contribute to pain. Counseling encourages patients to reduce portion size, increase intake of fruits and vegetables, shift away from red meat and saturated fats, and shift toward foods with more omega-3 fatty acids such as coldwater fish and plant sources of fat.

Treatments that alleviate stress also seem to reduce pain. Sometimes patients are resistant to the idea that their pain may have a psychological component because they think that the physician does not believe their pain is real, so the idea of stress management is more palatable to these patients. Dr. Glick suggested that activities such as yoga, meditation, and other mind-body approaches may have a role in pain management. However, a patient whose life has been taken over by pain may benefit most from working individually with a psychologist who is knowledgeable about treatment of pain.

Given the prevalence of chronic pain, primary care physicians are experienced in addressing a wide array of general health and musculoskeletal conditions that result in pain. However, it is important to recognize when to refer patients with pain and comorbid depression or with treatment-resistant depression with pain to a psychiatrist, a psychologist, or to a pain management program. Warning signs that a referral is appropriate include suicidality, bipolar features (especially if there is a strong family history of bipolar disorder or prominent mood lability), irritability, substance use issues, prominent interpersonal or Axis II personality disorder features, full chronic pain syndrome in which the pain takes over and functioning continually declines, and cases in which standard methods of care have not helped.

Table 4. Steps for Managing Primary Pain With Comorbid Depression

1. Identify and treat specific pain syndromes such as diabetic neuropathy, fibromyalgia, or headache
2. Encourage active patient self-management through exercise, dietary change, and stress management
3. Prescribe SNRIs that can help both pain and depression and choose appropriately energizing or sedating medications
4. Treat sleep problems including sleep apnea
5. Seek psychiatric, psychological, or pain management consultation if appropriate
Abbreviation: SNRI = serotonin-norepinephrine reuptake inhibitor.

Medication Choices

In patients primarily concerned with depression, addressing pain may help manage treatment-resistant depression. Dr. Glick supported the use of agents that boost both serotonin and norepinephrine such as venlafaxine and duloxetine.⁴⁹ Higher doses of duloxetine (120 mg/day) may produce a better analgesic effect than lower doses.^{39,50,51} In Dr. Glick's clinical experience, at least 150 mg/day of venlafaxine are needed to achieve an analgesic effect. Dr. Glick recommended the TCA nortriptyline for pain and depression, dosed in an antidepressant range of 50 to 75 mg/day, but also cautioned that the dose should be reduced in older patients because of the risks of sedation, falls, and heart arrhythmia.⁵²

Duloxetine carries a specific indication for use in neuropathic pain conditions such as diabetic neuropathy, but can be helpful for patients with fibromyalgia and other chronic pain states.^{39,50,51} Dr. Glick stated that specifically for fibromyalgia or neuropathic pain, a higher dose (120 mg/day or 60 mg p.o. b.i.d.) may provide a greater benefit than the reduced dose of 60 mg/day most commonly used for depression. Similarly, the anticonvulsant pregabalin produces a better analgesic effect at a dose of 600 mg/day t.i.d.⁵³ Pregabalin does not have a specific antidepressant effect but can be used in patients primarily presenting with pain,⁵⁴ either alone or in concert with an antidepressant.

As with the primary management of depression, when treating depression with comorbid pain the choice of medication can be influenced by the

desire for an energizing effect or for a sedating effect. Some patients with pain and depression have prominent lethargy, but others have prominent insomnia. Dr. Glick explained that in his clinical experience, venlafaxine has had energizing effects at higher doses, similar to bupropion; whereas trazodone, nortriptyline, mirtazapine, and amitriptyline have had sedating effects. Mirtazapine and amitriptyline are also associated with weight gain and sluggishness. Because of the risk of metabolic syndrome, atypical antipsychotics should be avoided unless the patient has comorbid bipolar disorder or psychotic illness.⁵⁵ However, physicians should note that atypicals may have analgesic properties.⁵⁶

To combat insomnia, Dr. Glick recommended that patients avoid caffeine after the middle of the day, avoid exercise late in the day, and practice stress management approaches. Patients may also take 3 to 9 mg of melatonin at bedtime to promote sleepiness. For patients with sleep difficulties associated with myofascial pain or fibromyalgia, Dr. Glick recommended 2 to 4 mg of the muscle relaxant tizanidine at bedtime, although liver function should be monitored. If insomnia does not improve with behavioral approaches and monotherapy, particularly in the presence of obesity, Dr. Glick suggested screening for sleep apnea. Often, once sleep is improved, patients report both better mood and less pain.

Dr. Glick advised caution with combined serotonergic agents, such as the SSRI escitalopram and the pain medication tramadol, because of potential serotonin syndrome. Serotonin syndrome can cause hyperarousal

symptoms such as tachycardia, irritability, anxiety, tremor or shakiness, and seizures.⁵⁷ Medication should be stopped if even mild symptoms of serotonin syndrome occur.

Conclusion

Dr. Glick summarized steps for treating patients with primary pain and comorbid depression (Table 4). First, identify specific syndromes to treat,

e.g., prophylactic agents for recurrent migraine. Next, help the patient shift to an active self-management strategy. Prescribe medications that treat both pain and depression, and select appropriately energizing or sedating medications. Polypharmacy will probably be necessary for adequate control of pain combined with depression. Then, if needed, use whatever consultation is available in the community.

typically not enough to treat depression and pain.

In a study³⁶ of primary care patients taking SSRIs, the treatment effect sizes on depression symptom clusters were measured; painful physical symptoms had the lowest effect size, while nonsomatic depressive symptoms had the greatest effect size. As Dr. Kuritzky elaborated, the SSRIs were effective for affective symptoms, but much less so for pain. In another study,⁶⁸ severity of pain at baseline predicted treatment response to SSRI therapy for depression; patients with the least pain had the best remission rate, supporting the concept that SSRIs are most efficacious in patients without comorbid pain.

Successfully Managing Depressed Patients With Pain

Louis Kuritzky, M.D., remarked that most clinicians can readily anticipate that patients with chronic pain disorders often subsequently develop comorbid depression; however, it may come as a surprise that patients with depression can have painful symptoms that result from the depression itself. The impact of pain on treatment outcomes of depression deserves more attention, according to Dr. Kuritzky. Pain as a symptom of depression has been overlooked in diagnostic criteria⁵⁸ but is now being recognized as an important component with serious implications.⁵⁹ When patients have multiple unexplained physical symptoms, depression should be high on the list of possible diagnoses.^{1,60,61}

“Depressalgia” and Treatment Outcomes

Dr. Kuritzky referred to the pain of depression as “depressalgia” because it does not necessarily fit into any specific pain category (e.g., migraine or osteoarthritis) but rather appears to be part of depression itself. One study⁶ showed that 76% of patients who received a diagnosis of depression had initially reported somatic symptoms. Dr. Kuritzky noted that unexplained musculoskeletal pain and back pain in particular should alert clinicians to suspect depression. In a study⁶² of primary care patients with depression, 43% had nonspecific musculoskeletal complaints and 39% had back pain.

Depression is likely to persist if pain is present and vice versa. Patients who were referred to a neurology outpatient clinic were more likely to still have depression at 3 months and at 12 months if pain symptoms were persistent than were patients without persistent pain symptoms, and similarly, patients were more likely to have continued pain if depression was present than they were if depression was not present.⁶³

The presence of unresolved pain in patients with depression has 3 predictable consequences: (1) delay in time to depression remission,²⁶ (2) decreased likelihood of depression remission, and (3) increased likelihood of relapse.⁴¹ The consequences of failing to achieve full remission in depression are decreased quality of life, social disability, increased use of medical resources, greater risk of suicide, and increased risk of relapse.⁶⁴⁻⁶⁶

Treating Depression With Pain

Dr. Kuritzky stressed the importance of recognizing that not all agents that are effective for depression have an impact on pain in depression. A meaningful connection between serotonin and norepinephrine has been recognized in modulation of pain.⁶⁷ Dr. Kuritzky explained that combined serotonin and norepinephrine modulation may be the endogenous pain-damping system from the central nervous system: serotonin modulation alone is

Agents that modulate both norepinephrine and serotonin have been shown to have a favorable impact on pain in patients with or without depression. The TCAs amitriptyline and desipramine and the SSRI fluoxetine were tested in patients with painful diabetic neuropathy. Moderate or greater relief of pain was found in 74%, 61%, and 48% of the treatment groups, respectively. The TCAs were found to be as effective in patients with depression as without, but the SSRI was effective only in patients with depression, suggesting an affective component to the measured pain reduction, rather than a direct pain relief effect independent of depression.⁶⁹ The SNRI venlafaxine, which modulates both norepinephrine and serotonin, was also shown to produce a statistically significant reduction in painful diabetic neuropathy versus placebo.³⁸

Nemeroff et al.^{41,70} reviewed 6 double-blind, controlled trials of the SNRI duloxetine for MDD and found that in 4 studies, duloxetine was significantly superior to placebo in reducing mean HAM-D total scores. As part of these trials,^{41,70} pain scores were obtained, and duloxetine was also significantly superior to placebo on pain measures; in accordance with the commentary above, these duloxetine trials⁴¹ demonstrated that patients who

had a greater than 50% decrease in painful symptoms had a rate of remission from depression twice that observed for pain nonresponders.

Conclusion

Dr. Kuritzky concluded that unexplained physical symptoms, particularly pain, are commonplace in depressed patients and may delay an appropriate diagnosis and adequate treatment. The goal for treatment of depression is remission, which is correlated with a reduction in painful symptoms. When pain fails to remit, resolution of depressive symptoms, likelihood of attaining complete remission, time to remission, and likelihood of relapse are all altered unfavorably. Because of the interrelatedness of depression and pain, clinicians would do well to recognize which agents among the therapeutic choices for depression may also favorably impact pain.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), nortriptyline (Pamelor and others), paroxetine (Paxil, Pexeva, and others), pregabalin (Lyrica), sertraline (Zoloft and others), tizanidine (Zanaflex and others), tramadol (Ultram and others), venlafaxine (Effexor and others).

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 article.

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Answers to Pretest: 1. a 2. d

Commentary

pp. 287–294

1. Research on exercise in patients with depression has found that the intensity of exercise has no effect on the outcome, but that distributing the exercise over fewer days diminishes efficacy.

- a. True
- b. False

2. When prescribing exercise to a patient, the clinician should do all of the following *except*:

- a. Identify individuals at high risk for stroke or heart attack
- b. Recommend that patients start at a high intensity in order to reap more benefits early on
- c. Suggest using a step counter and incorporating more steps into daily life
- d. Emphasize short-term benefits such as improved sleep quality and concentration

3. In clinical trials of exercise, patients with both depression and anxiety have often reported improvement in:

- a. Depression and anxiety
- b. Depression only
- c. Anxiety only
- d. Neither depression nor anxiety

4. Before clinicians readily prescribe exercise for the treatment of depression, they should wait until the mechanism of action has been explained.

- a. True
- b. False

5. Clinicians could use all of the following strategies when prescribing exercise as treatment for depression *except*:

- a. Encourage goal-setting
- b. Provide supportive follow-up
- c. Offer sample exercise dose calculations by weight
- d. Conduct regular neuroimaging

ACADEMIC HIGHLIGHTS

pp. 295–302

6. According to research cited by McCarberg, about ____% of patients with depression reported only somatic symptoms.

- a. 5
- b. 30
- c. 70
- d. 90

7. Fishbain stated that physical symptoms associated with depression are likely to be linked with all of the following *except*:

- a. Less severe depression
- b. Other psychiatric comorbidities
- c. Relapse of depression
- d. Nonremitting depression

8. Glick suggested that patients with chronic pain and comorbid depression may benefit from all of the following self-management activities *except*:

- a. Exercising late at night
- b. Reducing food portion size
- c. Practicing mind-body techniques such as yoga
- d. Having caffeine only before the middle of the day

9. Glick recommended all of the following considerations when choosing medication for patients with pain and depression *except*:

- a. Certain agents may need higher or lower doses for analgesic effect
- b. Patients may need treatment targeted at either lethargy or insomnia
- c. Serotonin syndrome may occur when serotonergic agents are combined
- d. Atypical antipsychotics are a safe alternative in this population

10. Kuritzky cited research that found that selective serotonin reuptake inhibitors:

- a. Have the same effect size against painful physical symptoms as against nonsomatic depressive symptoms
- b. Are more effective for nonsomatic depressive symptoms than for painful physical symptoms
- c. Are more effective than tricyclic antidepressants in patients with pain and depression
- d. Can treat depression and pain via serotonin modulation alone



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Circle the one correct answer for each question.

- 1. a b c d
- 2. a b c d
- 3. a b c d
- 4. a b c d
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