



Targeting Remission:

Treating Both Emotional and Physical Symptoms Associated With Depression

A CME Audio Home Study Program

Sponsored by



Designated for 1.0 hour in Category 1 of the Physician's Recognition Award of the AMA.

Supported by an unrestricted educational grant from Eli Lilly and Company.

Accreditation

The Center for Bio-Medical Communication, Inc. is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

This CME activity was planned and produced in accordance with the ACCME Essentials.

CME Credit

The Center for Bio-Medical Communication, Inc. designates this educational activity for a maximum of 1.0 hour in Category 1 credit towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Acknowledgment

The sponsor of this program gratefully acknowledges the unrestricted educational grant from Eli Lilly and Company.

Release date: July 28, 2004

Expiration date: July 28, 2005

CME credit cannot be awarded after the expiration date.

Faculty

Robert M. Guthrie, MD
Professor of Emergency Medicine,
Internal Medicine, and Pharmacology
Associate Director of Clinical Pharmacology
The Ohio State University
Columbus, Ohio

Disclosure

Disclosure is requested when faculty members are confirmed. This educational activity may include discussion of an unlabeled use or an investigative use not yet approved for a commercial product. Therefore, it is incumbent on individuals participating in this activity to be aware of these factors in interpreting its contents and evaluating its recommendations. Every effort has been made to encourage faculty to disclose any commercial relationships or personal benefits that may be associated with their participation in this program. The following indicates the faculty and nature of their commercial relationships.

Robert M. Guthrie, MD, FAAFP, FACP, has disclosed that he is a consultant and is on the speakers bureau for AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, and Sanofi-Synthelabo, Inc. He receives grant/research support from AstraZeneca, Pfizer Inc, GlaxoSmithKline, and Boehringer Ingelheim Corporation. Dr Guthrie states that this presentation includes discussion of investigative or off-label product uses.

Targeting Remission:

Treating Both Emotional and Physical Symptoms Associated With Depression

Overview

Neurotransmitters serve many roles and have many functions in disease etiology. This audio home study program will focus on their roles in major depression.

Major depression can be a complex disease involving both emotional and physical symptoms. Indeed, physical symptoms often drive patients to seek treatment from their physicians and may mask underlying major depression. With more than 30 million people experiencing major depression in their lifetimes, it is important to define for the physician the role physical symptoms have in the disease. Unfortunately, treatment options for depression often address only the emotional symptoms, ignoring the physical ones. This can limit the patient's ability to achieve remission from the depression. Therefore, to increase physician awareness of the needs of patients with both emotional and physical symptoms associated with major depression, and to promote optimum depression therapy, the Center for Bio-Medical Communication, Inc. has created this CME audio home study program based on information from surveys, literature searches, and meetings with depression experts.

Needs Assessment

Recent estimates suggest that more than 30 million people will experience major depression in their lifetimes. Currently, the total cost of depression is estimated to be \$44 billion a year. A key component of successful treatment of the disease is alleviating all of the depressive symptoms. Major depression can be a complex syndrome, however, involving both emotional and

physical symptoms. Physical symptoms are often the driving reason patients seek treatment from their physicians. In many instances, the patient will complain only of the physical symptoms, leaving the physician unaware that underlying depression is the problem. Although several classes of antidepressants are available to treat patients with depression, only 30% to 40% of the patients treated with antidepressants achieve remission. However, many currently available antidepressants can only treat the emotional components of depression, which may explain why so many patients relapse within 1 year of treatment. Thus, it is important to clearly define for the physician the role physical symptoms have in depression.

Who Should Participate

This program is intended for primary care physicians, general practitioners, family physicians, and other healthcare providers who may treat patients with depression.

Learning Objectives

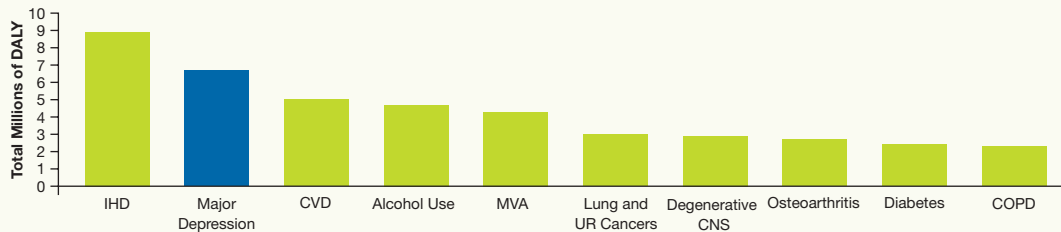
After reviewing this audio home study program, participants should be able to:

1. Explain the necessity for recognizing emotional and physical symptoms as equally important components of depression
2. Understand the importance of treating both the emotional and physical symptoms associated with depression
3. Define the difference between response and remission in depression



Facts About Depression

Major Depression Is a Leading Cause of Disease Burden¹



DALY=Disability-adjusted life years; IHD=Ischemic heart disease; CVD=Cardiovascular disease; MVA=Motor vehicle accidents; UR=Upper respiratory; CNS=Central nervous system; COPD=Chronic obstructive pulmonary disease

The Burden of Major Depression Is Growing^{2,3}

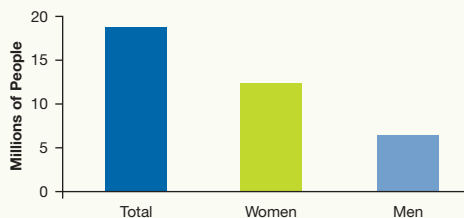
Rank Year 2000

- 1 Lower respiratory infections
- 2 Perinatal conditions
- 3 HIV/AIDS
- 4 **Unipolar major depression**
- 5 Diarrheal diseases

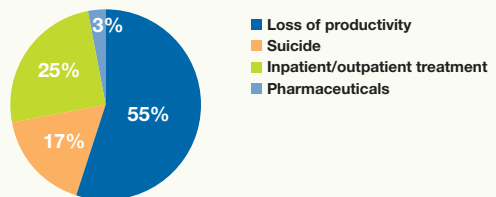
Year 2020 (Estimated)

- Ischemic heart disease
- Unipolar major depression**
- Road traffic accidents
- Cerebrovascular disease
- Chronic obstructive pulmonary disease

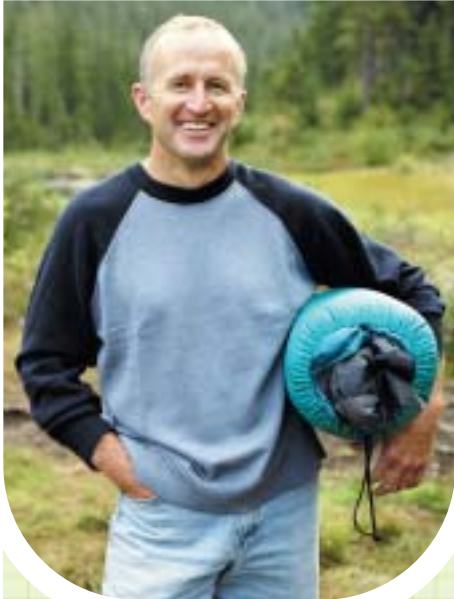
Women Are at Greater Risk for Depression Than Men⁴



Total Annual Cost of Depression: \$44 Billion⁵



1. NIMH publication 01-4586. 2001.
 2. World Health Organization. *The World Health Report. Mental Health: New Understanding, New Hope.* 2001.
 3. Adapted with permission from: Michaud et al. *JAMA.* 2001;285:535.
 4. NIMH publication 01-4584. 2003.
 5. Jain. *Addressing Both the Emotional and Physical Symptoms of Depression.* Available at www.medscape.com. Accessed July 2003.



Emotional and Physical Symptoms Associated With Depression

Depression Has a Wide Range of Emotional and Physical Symptoms¹

Emotional Symptoms

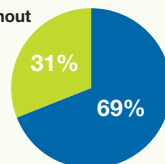
- Sadness
- Loss of interest in everyday activities
- Feelings of guilt
- Suicidal ideation
- Anxiety
- Hopelessness
- Irritability
- Difficulty concentrating
- Worthlessness

Physical Symptoms

- Fatigue – low energy
- Gastrointestinal problems
- Loss of appetite
- Vague aches and pains
 - Back
 - Headache
 - Neck
- Sleep problems

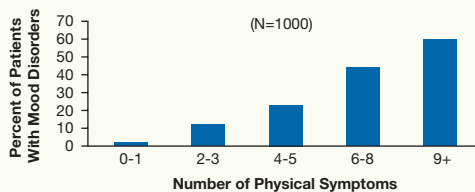
Depressed Patients Present More Frequently With Physical Symptoms²

Major depression without physical symptoms

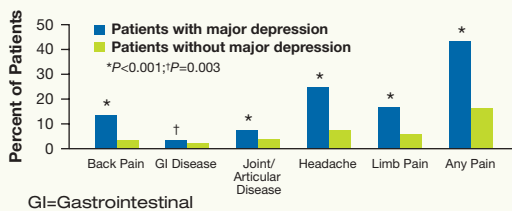


Major depression with physical symptoms

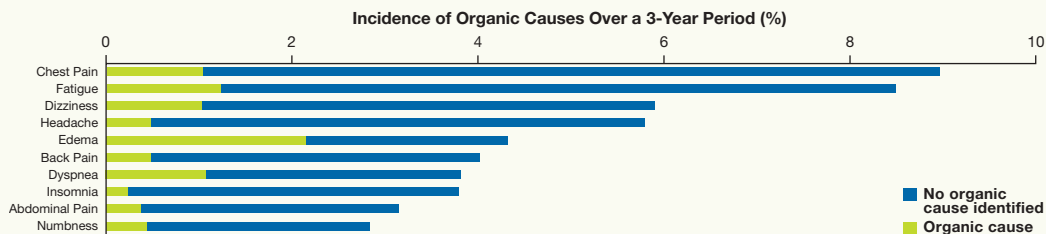
Physical Symptoms Increase Likelihood of Mood Disorders³



Relationship Between Major Depression and Physical Symptoms⁴



Most Physical Complaints Are Not Linked to an Organic Cause⁵



1. Schatzberg, Korn. *Beyond Depression: The Somatic/Affective Interface*. Available at www.medscape.com. Accessed July 2003.
 2. Simon et al. *N Engl J Med*. 1999;341:1329.
 3. Kroenke et al. *Arch Fam Med*. 1994;3:774.
 4. Ohayon, Schatzberg. *Arch Gen Psychiatry*. 2003;60:39.
 5. Adapted with permission from: Kroenke, Mangelsdorff. *Am J Med*. 1989;86:262.

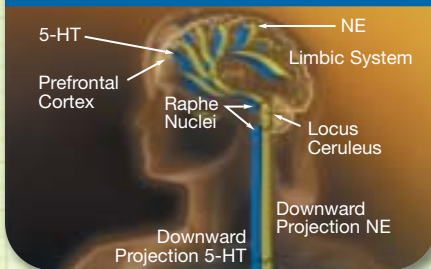
Emotional and Physical Symptoms Associated With Depression: A Common Biological Pathway



Serotonin and Norepinephrine Are Key in Many Bodily Processes

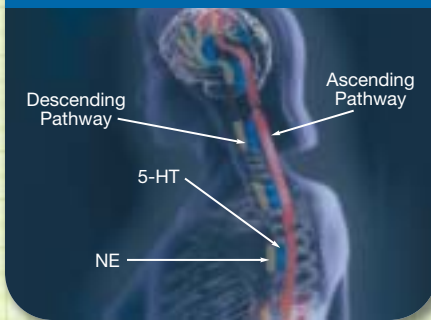


Serotonin and Norepinephrine Are Important for Emotion and Sensation



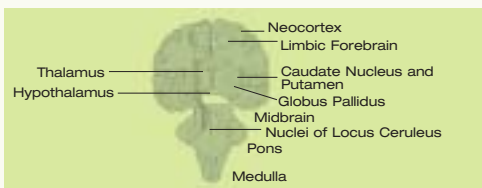
5-HT=Serotonin; NE=Norepinephrine

Serotonin and Norepinephrine Are Important in Pain Sensation

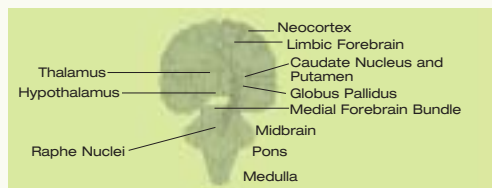


Serotonin and Norepinephrine Systems Overlap¹

Norepinephrine may play a role in motivation, energy, interest, and concentration



Serotonin may play a role in impulsiveness, appetite, and sexual function

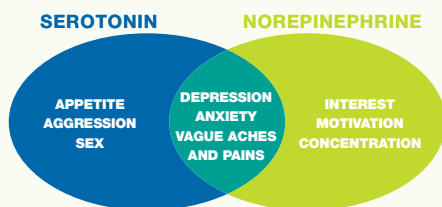


1. Reprinted with permission from: Kandel et al. *Principles of Neural Science*. 3rd ed. New York: Elsevier Science: 1991.

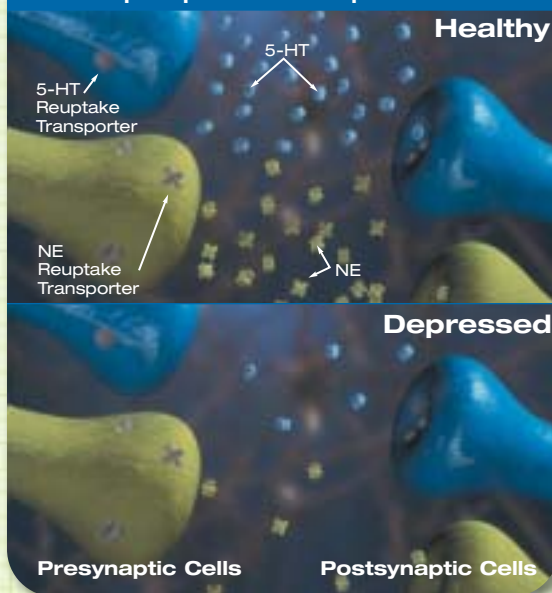


Treating the Emotional and Physical Components Associated With Depression

Serotonin and Norepinephrine Mediate a Broad Spectrum of Depressive Symptoms



The Role of Serotonin and Norepinephrine in Depression



5-HT=Serotonin; NE=Norepinephrine

Treating the Broad Spectrum of Depressive Symptoms¹

- The prognosis is less favorable when emotional and physical symptoms present together than when either disorder appears alone
- Treating either the emotional or physical symptoms alone reduces the likelihood of remission in the majority of treated patients

Current and Future Antidepressants

Tricyclic Antidepressants

Imipramine (Tofranil®)
Desipramine (Norpramine®, Pertofrane®)
Amitriptyline (Elavil®)
Trimipramine (Surmontil®)

SSRIs

Fluoxetine (Prozac®)
Paroxetine (Paxil®)
Sertraline (Zoloft®)
Citalopram (Celexa®)
Escitalopram (Lexapro®)

SNRIs

Venlafaxine (Effexor®)
Duloxetine (Cymbalta®)*

Piperazinoazepines

Mirtazapine (Remeron®)
Nefazodone (Serzone®)

Aminoketones

Bupropion (Wellbutrin®)

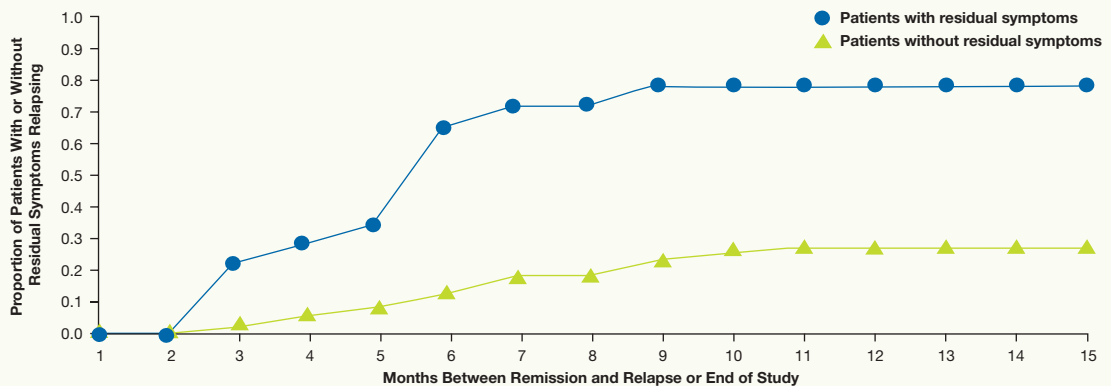
SSRI=Selective serotonin reuptake inhibitor; SNRI=Serotonin and norepinephrine reuptake inhibitor

*As of the release of this program, Cymbalta is not yet approved by the FDA.

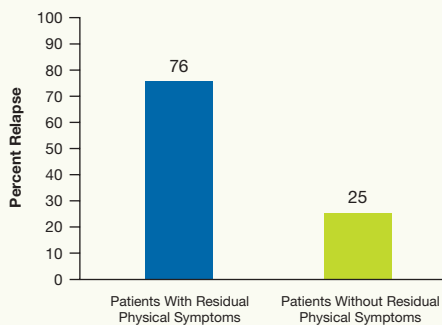


Remission Is the Goal in the Treatment of Depression

Residual Symptoms Lead to Relapse¹



Residual Depressive Symptoms Are Associated With Greater Risk of Relapse²



Dual Monoamine Reuptake Inhibitors Treat the Duality of Depression

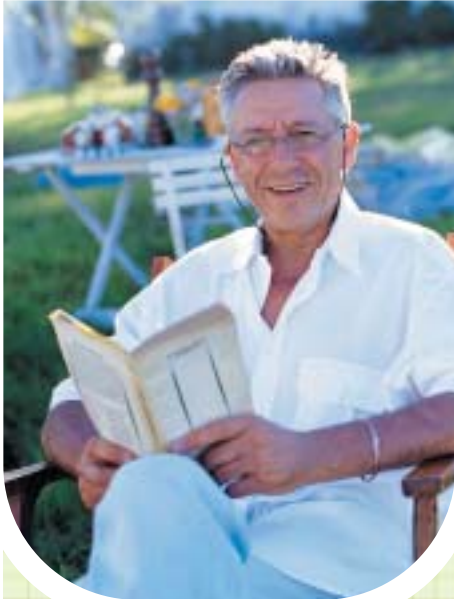
- SNRIs treat both the emotional and physical symptoms associated with depression
- New class of agents includes
 - Venlafaxine: Effexor®
 - SNRI at higher doses
 - SSRI at lower doses
 - More adverse events at higher doses
 - Duloxetine: Cymbalta®*
 - SNRI at starting dose

Likely Benefits of SNRIs Over Other Antidepressants

- Address the emotional and physical symptoms associated with depression
- Offer higher probability of achieving remission

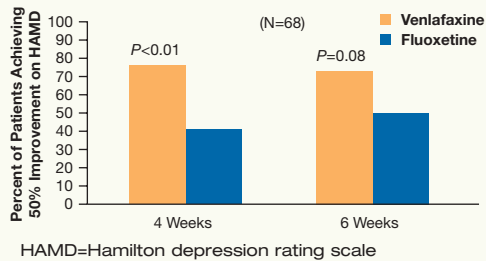
1. Adapted with permission from: Paykel et al. *Psychol Med.* 1995;25:1171.
 2. Paykel et al. *Psychol Med.* 1995;25:1171.

*As of the release of this program, Cymbalta is not yet approved by the FDA.

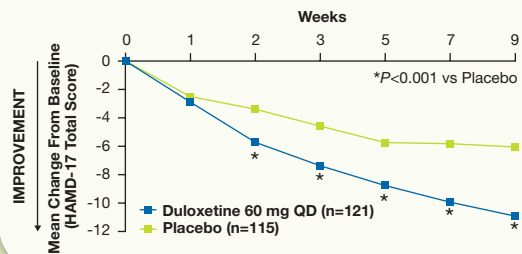


SNRIs Improve Both Emotional and Physical Symptoms Associated With Depression

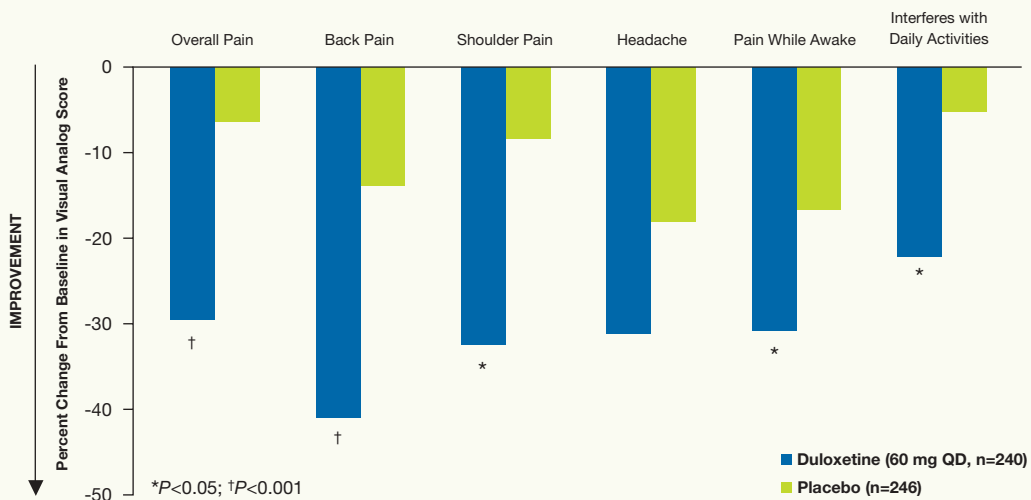
Depressed Patients Respond Better With SNRIs¹



SNRIs Demonstrate Robust Efficacy in Treating Emotional Symptoms²



SNRIs Demonstrate Robust Efficacy in Treating Painful Physical Symptoms³



1. Clerc et al. *Int Clin Psychopharmacol*. 1994;9:139.
 2. Adapted with permission from: Detke et al. *J Clin Psychiatry*. 2002;63:308.
 3. Fava et al. *Does the Alleviation of Painful Physical Symptoms Associated With Depression Lead to Higher Remission Rates?* Presented at the 2003 Meeting of the American Psychiatric Association.

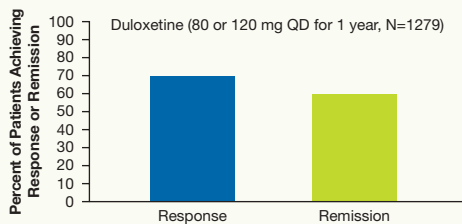


Benefits of SNRIs: Higher Remission Rates and Faster Onset of Action

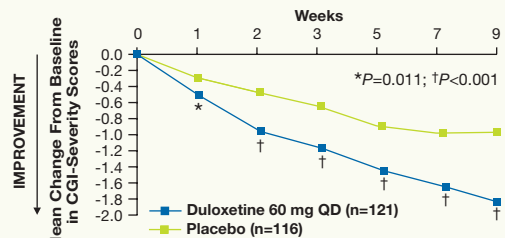
Response vs Remission: They Are NOT the Same

- Treating depression to remission is the primary goal
- Only 30%–40% of patients taking antidepressants will achieve full remission
- Not all depressive symptoms are likely to subside with initial response
- Improvements in one set of symptoms may mask other residual symptoms
- Remission is treating patients to minimal/no symptoms of depression and restoration to normal function

Treating Symptoms With SNRI Leads to Remission Rates That Approach Response Rates¹

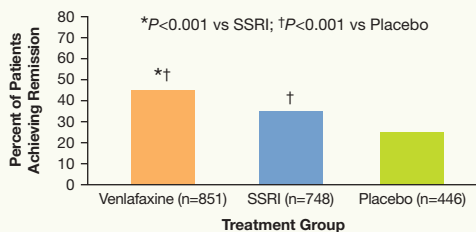


Duloxetine Significantly Improves CGI-Severity Scores by 1 Week²

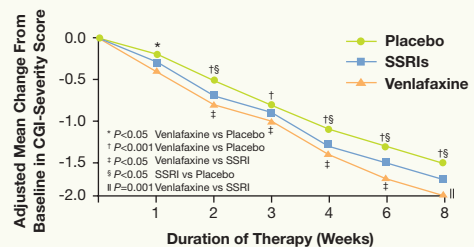


CGI=Clinical Global Impressions scale

Venlafaxine Treatment Leads to Significantly Higher Remission Rates Compared With SSRI³



Venlafaxine Significantly Improves CGI-Severity Scores More Quickly Than SSRI⁴



CGI=Clinical Global Impressions scale

1. Raskin et al. *Duloxetine in the Long-Term Treatment of Major Depressive Disorder*. Presented at the 2003 Meeting of the American Psychiatric Association.
 2. Data on file. Lilly Research Laboratories.
 3. Thase et al. *Br J Psychiatry*. 2001;178:234.
 4. Adapted with permission from: Stahl et al. *Biol Psychiatry*. 2002;52:1166.

Summary

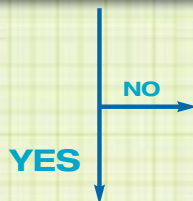


- The spectrum of depression includes both emotional and physical symptoms
- Patients with depression often complain only about physical symptoms
- Serotonin and norepinephrine are equally important pathways in the pathology of depression and perception of pain
- Treating emotional and physical symptoms associated with depression improves remission rates
- SNRIs have a faster onset of action than SSRIs

Patient Presents With Physical Symptoms



Assess for Depression



Pursue Other Options

Treat With SNRI

Instructions for Receiving CME Credit

The following examination provides the opportunity to assess your knowledge and understanding of the material presented in the audio home study program.

To obtain 1.0 hour of Category 1 CME credit, you must:

- Complete the following CME Posttest by circling the correct responses on the answer sheet on page 14
- Answer the Program Evaluation questions
- Provide the requested personal information
- Mail or fax the Answer Sheet/Evaluation to the program sponsor by July 28, 2005

Center for Bio-Medical Communication, Inc.
433 Hackensack Avenue, 9th Floor
Hackensack, NJ 07601
Attn: Depression Posttest
Fax: 201-342-7555

- If you would prefer to submit your Answer Sheet/Evaluation electronically, please visit:
<http://www.cbcbiomed.com/event/selfstudy/DEP6245071.asp>
or follow the instructions provided on the CD-ROM.

Tests will be graded, and in approximately 6 weeks, a CME certificate will be mailed to each participant who achieves a score of 70% or greater.

For technical assistance with this audio home study program, please send an e-mail request to techhelp@cbcbiomed.com. Be sure to include "Depression audio home study" in the subject line.

Expiration date: July 28, 2005

Targeting Remission:

Treating Both Emotional and Physical Symptoms Associated With Depression

CME Posttest

- Major depression is a leading cause of disease burden.**
 - True
 - False
- Serotonin and norepinephrine are important chemical modulators of**
 - Sadness
 - Pain perception
 - Vasoconstriction
 - Gastrointestinal motility
 - All of the above
- Serotonin and norepinephrine are important neurotransmitters in depression because they**
 - Control separate and contrasting processes in the brain
 - Control both emotional processes and physical sensation in an overlapping array in the brain and spinal cord
 - Are located in many different areas of the spinal cord
 - Are produced in excess in several regions of the brain in patients with depression
- Physical symptoms in depression are rare.**
 - True
 - False
- Serotonin and norepinephrine are important neurotransmitters in the perception of pain because**
 - They reduce the intensity of the pain in the periphery and prevent it from reaching the spinal cord
 - Serotonin antagonizes the influence of norepinephrine
 - Norepinephrine inhibits the further release of serotonin
 - Both serotonin and norepinephrine block the transmission of painful messages at the level of the spinal cord from ascending into the brain
- SNRIs have the following advantages over other antidepressants**
 - They antagonize many more postsynaptic receptor systems than other antidepressants
 - They reduce the availability of serotonin and norepinephrine at the synapse with more efficiency than other agents
 - Increasing both serotonin and norepinephrine at the synapse treats more of the symptoms of major depression
 - They are the least selective of all the antidepressants
- Treatment response indicates that all symptoms are gone.**
 - True
 - False
- The emotional and physical symptoms associated with depression are connected because**
 - Increasing both serotonin and norepinephrine reduces symptomology better than increasing either neurotransmitter individually
 - The serotonin and norepinephrine neurotransmitter systems overlap anatomically and functionally in the brain and spinal cord
 - Treatment remission rates increase when both neurotransmitter systems are addressed
 - They are likely due to reduced availability of synaptic serotonin and norepinephrine
 - All of the above
 - None of the above
- Many patients fail to achieve remission because**
 - Painful physical symptoms often linger even after treatment response
 - Most patients with depression do achieve remission
 - Remission cannot be achieved in most patients with depression
 - Remission and response are the same
- Remission rates for depression can be improved by**
 - Increasing the dosage of any antidepressant
 - Treating both the emotional and physical symptoms as a single disease component of depression with a single agent
 - Prescribing more than one antidepressant
 - Remission is not an achievable goal

Depression Program Evaluation

Please evaluate this CME Audio Home Study Program using the following scale:

1 = poor 2 = fair 3 = average 4 = good 5 = excellent

1. How successfully did this program meet its stated learning objectives?
 Explain the necessity for recognizing emotional and physical symptoms as equally important components of depression
 1 2 3 4 5
 Understand the importance of treating both the emotional and physical symptoms associated with depression
 1 2 3 4 5
 Define the difference between response and remission in depression
 1 2 3 4 5
2. How would you rate the clinical usefulness of this program?
 1 2 3 4 5
3. How well did this learning format work with your learning style?
 1 2 3 4 5
4. Overall, how satisfied were you with this activity?
 1 2 3 4 5
5. Accredited CME programs must be “free from commercial bias for or against any product.” In this regard how would you rate this program?
 1 2 3 4 5
6. Do you expect to make any changes in your practice or attitudes as a result of this activity?
 Yes No
 If yes, please explain _____

7. Suggestions for future audio home study programs

CME Posttest Answer Sheet

- | | | |
|--------------------------|-------------------------------|----------------------|
| 1. a b | 5. a b c d | 9. a b c d |
| 2. a b c d e | 6. a b c d | 10. a b c d |
| 3. a b c d | 7. a b | |
| 4. a b | 8. a b c d e f | |

Name _____ Degree _____
 Signature _____ Specialty _____
 Date _____ Institution/Affiliation _____
 Address _____ City _____
 State _____ Zip _____ E-mail _____

Targeting Remission:

Treating Both Emotional and Physical Symptoms Associated With Depression

Bibliography

Clerc GE, Ruimy P, Verdeau-Paillès J, for the Venlafaxine French Inpatient Study Group. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. *Int Clin Psychopharmacol*. 1994;9:139-143.

Detke MJ, Lu Y, Goldstein DJ, Hayes JR, Demitrack MA. Duloxetine, 60 mg once daily, for major depressive disorder: A randomized double-blind placebo-controlled trial. *J Clin Psychiatry*. 2002;63:308-315.

Fava M, Wohlreich MM, Mallinckrodt CH, Watkin JG, Detke MJ. Does the alleviation of painful physical symptoms associated with depression lead to higher remission rates? Poster presented at the 2003 meeting of the American Psychiatric Association, San Francisco, California, May 17-22, 2003.

Jain R. Addressing both the emotional and physical symptoms in depression. Available at www.medscape.com. Accessed July 2003.

Kandel ER. In: Kandel ER, Schwartz JH, Jessell TM, eds. *Principles of Neural Science*. 3rd ed. New York, NY: Elsevier Science Publishing, Co., Inc. 1991:853-868.

Kroenke K, Mangelsdorff AD. Common symptoms in ambulatory care: Incidence, evaluation, therapy, and outcome. *Am J Med*. 1989;86:262-266.

Kroenke K, Spitzer RL, Williams JBW, et al. Physical symptoms in primary care. Predictors of psychiatric disorders and functional impairment. *Arch Fam Med*. 1994;3:774-779.

Michaud CM, Murray CJL, Bloom BR. Burden of disease – implications for future research. *JAMA*. 2001;285:535-539.

National Institute of Mental Health (NIMH). *The numbers count. Mental disorders in America*. Washington, DC. January 2001; revised May 2003. NIMH Publication No. 01-4584.

National Institute of Mental Health (NIMH). “...the burden of psychiatric conditions has been heavily underestimated.” *The impact of mental illness on society*. Washington, DC. January 2001. NIMH Publication No. 01-4586.

Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. *Arch Gen Psychiatry*. 2003;60:39-47.

Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A. Residual symptoms after partial remission: an important outcome in depression. *Psychol Med*. 1995;25:1171-1180.

Raskin J, Goldstein DJ, Mallinckrodt C, Wohlreich MM, Ferguson MB. Duloxetine in the long-term treatment of major depressive disorder. Poster presented at the 2003 meeting of the American Psychiatric Association, San Francisco, California, May 17-22, 2003.

Sartorius N. Physical symptoms of depression as a public health concern. *J Clin Psychiatry*. 2003;64(Suppl 7):3-4.

Schatzberg AF, Korn ML. Beyond depression: The somatic/affective interface. Available at www.medscape.com. Accessed July 2003.

Simon GE, VonKorff M, Piccinelli M, Fullerton C, Ormel J. An international study of the relation between somatic symptoms and depression. *N Engl J Med*. 1999;341:1329-1335.

Stahl SM, Entsuah R, Rudolph RL. Comparative efficacy between venlafaxine and SSRIs: A pooled analysis of patients with depression. *Biol Psychiatry*. 2002;52:1166-1174.

Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry*. 2001;178:234-241.

World Health Organization (WHO). *The World Health Report. Mental health: New understanding, new hope*. Geneva, Switzerland. 2001.

