LEADING EXPERTS IN THE TREATMENT OF DEPRESSION EXPLORE CHRONIC DEPRESSION, ITS IMPACT, AND POSSIBLE TREATMENT STRATEGIES.

Chronic depression is difficult to manage and often represents a heavy burden to those with the disorder, their families, and even the health care system, since those with chronic depression often seek medical help for vague somatic complaints.

On September 26, 2005, Alan J. Gelenberg, M.D., Editor-in-Chief of *The Journal of Clinical Psychiatry* and an Executive Director of the CME Institute of Physicians Postgraduate Press, Inc., assembled a group of experts that included clinical psychiatrists and researchers who are specialists in the treatment of depression, especially chronic depression. Their discussion appears here.

This special Commentary is another in a series of independent projects undertaken by the CME Institute as a service to its members and the broader academic and clinical community. Visit www.psychiatrist.com/issues to listen to audio selections from this discussion.

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The State of Knowledge of Chronic Depression

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The Definition of Chronic Depression

Dr. Gelenberg: Let's begin with a discussion of the definition of chronic depression. What is the clinical relevance of the subtypes of depression in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)?[1]

Dr. McCullough: My colleagues and I have reported on 1316 patients with chronic depression.[2,3] We found no differences when a wide variety of demographic, psychosocial, and health measures were compared. For the DSM-V, we have argued that the existing subtypes do not represent qualitatively distinct entities. We have recommended a 2-by-2 table to accommodate a 4-fold classification of the unipolar disorders: mild versus moderate-to-severe severity and acute versus chronic types of episodes (Table 1). We can greatly simplify the current subtypes of chronic depression by consolidating them into a single category termed *chronic depression*.

Dr. Gelenberg: Will you define chronic depression?

Dr. McCullough: Chronic depression lasts a minimum of 2 years without at least a 2-month hiatus or a full remission. We are not suggesting the elimination of the DSM-IV categories for depressive disorders, but are recommending the deletion of distinct chronic subtypes since these subtypes do not represent qualitatively different entities.

Dr. Ninan: Perhaps we should review the current diagnostic criteria for depressive disorders. The criteria for dysthymia require depressed mood for the majority of time and 2 additional symptoms that persist for 2 years, while the criteria for a major depressive episode stipulate 5 or more symptoms, including depressed mood or anhedonia, persisting for at least 2 weeks. Dysthymia followed by a major depressive episode is frequently labeled *double depression*. In the DSM-IV, *chronic depression* is defined as the persistence of the full criteria for a major depressive episode for at least 2 years. *Major depressive disorder with incomplete recovery* occurs when enough symptoms improve that the patient no longer meets the full criteria for major depressive disorder, but still has residual symptoms of depression (i.e., subsyndromal depression). If that patient later meets the full criteria for a major depressive episode without a period of remission in between, we consider it another episode of major depression (i.e., 2 episodes with incomplete recovery in between).

Dr. McCullough: On our 2-by-2 table, we recommend maintaining dysthymia on the chronic row and in the mild severity column. Most of the disorders that Dr. Ninan just delineated would be in the moderate-to-severe column. On the acute episode row, the mild disorder would be labeled minor depressive disorder and the moderate-to-severe episode would be termed episodic major depression. Dan N. Klein, Ph.D., has

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Table 1. Proposed Classification of Unipolar Disorders[a]

Course of Illness	Mild	Moderate-to-Severe
Acute	Minor depressive disorder	Episodic major depression
Chronic	Dysthymia	Chronic major depression Double depression Recurrent major depression without complete interepisode recovery

[a]Data from McCullough et al.[2]

conducted a 10-year naturalistic prospective study comparing dysthymia and double depression with episodic major depression that has also supported a unitary category for chronic depression.[4] He argues that dysthymia is a pernicious disorder that has a 60% probability of recurrence as major depression after it remits.

Dr. Kocsis: I have the impression that dysthymia tends to emerge earlier—in childhood or early adolescence—than chronic major depression, which tends to appear in the adult years. Do the data support my impression?

Dr. Thase: There is a late-onset variant of dysthymia, which appears to be distinct from early-onset mood disorder, that has been studied by Devanand and colleagues.[5] I think our discussion primarily concerns the early-onset variant of chronic mood disorder.

Dr. Gelenberg: Are the subtypes of chronic depression relevant to the clinician?

Dr. McCullough: Any practitioner who sees a depressed patient needs to ask 2 questions: (1) Is the disorder chronic or acute? and (2) Is dysthymia part of the course of illness? It is imperative to differentiate between an illness with a chronic course and one with an episodic course. If dysthymia is part of the course of illness, the disorder becomes very difficult to treat. The practitioner must make certain that the dysthymia is brought to remission. Dr. Thase's point about the existence of late-onset dysthymia is also crucial.

Dr. Kocsis: An early age at onset of chronic depression often leads to misdiagnosis as a personality disorder by clinicians—particularly nonmedical clinicians but also psychiatrists. The patients themselves often think that they have a personality disorder. Also, many patients have chronic somatic symptoms and present to primary care medical settings for treatment of insomnia or chronic pain. Once again, the depressive syndrome or the affective disorder diagnosis is missed.

Dr. Gelenberg: Which personality disorders or traits are clinicians and patients likely to consider in lieu of early-onset dysthymia?

Dr. Kocsis: Chronic depression can appear as personality traits of dependency or avoidance. These individuals often have deficits in social functioning that can be mistakenly identified as personality traits. I think cluster C personality disorder traits are the most common misdiagnosis.

Dr. Ninan: Children, in particular, often lack the cognitive capacity to make subtle distinctions between worry, which is the cognitive component of anxiety, and negative ruminations about the self, which is the cognitive component of depression. So practitioners may have difficulty distinguishing early-onset dysthymia and generalized anxiety disorder (GAD), which is also a chronic illness. Somatic symptoms are also common in GAD.

Children might also behaviorally act out their pathology or have problems in executive function. They might consequently be misdiagnosed with conduct disorder, attention-deficit/hyperactivity disorder, or a learning disability instead of chronic anxiety or depression.

Psychological Differences Between Chronic and Acute Recurrent Depression

Dr. Gelenberg: How do people with chronic depression differ psychologically from those with acute recurrent depression? Dr. McCullough, I know, has studied the influence of the type of depression on response to psychotherapy. Perhaps you could give us a succinct summary of what essentially has been a lifetime of work.

Dr. McCullough: At this point, I cannot make a distinction between these patients. I am seeing someone now who can recall 15 to 20 recurrent episodes of major depressive disorder. To me, she has chronic depression. Perhaps Dr. Thase or Dr. Kocsis can help fine-tune a distinction between a person who has many recurrent episodes and one who meets clear criteria for chronic depression.

Dr. Thase: I have noticed that people with chronic depression are disproportionately negative in the way they view themselves, their world, and their future. They are very pessimistic and unlikely to believe they have the capacity to take action to solve their problems. My colleagues and I have found that the Cognitive Behavioral Analysis System of Psychotherapy (CBASP),[6] developed by Dr. McCullough, helps patients with chronic depression make sense of their problems and learn new techniques for taking action to solve their problems.

Dr. Ninan: You raise an important point. Factors that have an impact on chronicity may differ from the factors that make one depressed. As an analogy, in panic disorder, extensive avoidance often leads to agoraphobia, which tends to persist even after the panic attacks are controlled or remitted. Similarly, there may be variables in depressed individuals that push them toward a chronic course of illness, even after the issues that led up to the acute episode have been settled. Therefore, while the same treatments may frequently be effective for both chronic and acute depression, some effective treatments for chronic depression may be different from those aimed at recurrent acute major depressive disorder.

Dr. Kocsis: Data suggest that individuals with chronic depression have more deficits in social function than those with recurrent forms of major depression.[7] I think these data make sense because chronic depression is associated with an early age at onset and a chronic course of illness. These individuals may fail to develop social learning and social skills because they lack sufficient intervals of wellness. As a result, they are left with more social deficits and disabilities than those with a more episodic course of illness.

Do you think chronic depression tends to respond less well to traditional cognitive-behavioral therapy (CBT) than to CBASP? If so, why?

Dr. Thase: When my colleagues and I studied CBT, we found that about 15% to 20% fewer patients with chronic depression remitted within a 12-week or 16-week interval than patients with acute illness.[8] I have always attributed this lack of response to the belief that patients with chronic depression are generally less responsive to treatment. However, that decrement was not apparent in the Keller et al. study[9] comparing CBASP and nefazodone, in which patients had about a 50% chance of responding to either monotherapy within 12 weeks.

Dr. McCullough: CBASP takes a broader approach than traditional cognitive therapy. CBASP includes skill training and looks at interpersonal issues that usually have a long, problematic history. The CBASP therapist recognizes that the origin of these interpersonal issues is usually found in the early stages of development and often involves some early trauma that stems from maltreatment by significant persons in the patient's life.

Dr. Gelenberg: One feature that distinguishes CBASP from traditional cognitive therapy is that CBASP places less emphasis on abstract cognitive concepts like catastrophic thinking and more emphasis on situational analyses, i.e., how the person began feeling passive and victimized and what practical steps the person can take to affect his or her environment.

Dr. McCullough: That is an excellent point. It is hard to feel helpless when you stare at the consequences of your behavior that you have choreographed. CBASP changes the cognitive focus to situational interpersonal consequences that are identified within a person-to-person encounter. We first teach patients the effects their behavior has on others and then show them that if they do not like the consequences, they have to change their behavior. The CBASP model has a situational orientation and includes a strong interpersonal component, which makes the approach a bit broader than traditional cognitive therapy.

Treatment of Chronic Depression

Dr. Gelenberg: Imagine a patient who has had ongoing depression for more than 2 years—one of the subtypes that Dr. Ninan described. This patient is sitting in your office. How should this patient be treated? Should the treatment differ from that given to someone who is experiencing a first or second discrete episode of recurrent major depressive disorder?

Dr. Kocsis: The 2 current options are antidepressant medications and psychotherapy. The literature supports the efficacy of various classes of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and some of the newer agents.[10]

One treatment trial showed lower response rates to antidepressant monotherapy for chronic depression than for various forms of acute recurrent major depression.[11] There is some evidence that switching nonresponders to a treatment from a different class of antidepressant may improve response, so 2 or 3 trials of antidepressant medications may be indicated.[12]

The only available research on psychotherapy as a treatment for chronic depression involves CBT, interpersonal therapy (IPT), and CBASP. Keller et al.[9] provided the best evidence for efficacy and high response rates for CBASP. One issue that remains unresolved which we need to consider is how to select the most effective specific first-line treatment for an individual patient. We have a menu of treatments that we know may work, but we know little about how to predict the best starting treatment for an individual patient.

Dr. Gelenberg: If I see a patient with a first or second episode of nonchronic, mild-to-moderate, uncomplicated major depressive disorder, I would reasonably begin by asking the patient if he or she preferred psychotherapy or medication. If that patient preferred medication, the newer antidepressants—most commonly an SSRI but possibly a serotonin-norepinephrine reuptake inhibitor—are accepted first-line treatments. If that patient chose psychotherapy, CBT and IPT are well-accepted treatments.

Following Dr. Kocsis' line of thought, if the patient had had depressive symptoms for 2 or more years and met the criteria for chronic depression, I would also start by asking for the patient's treatment preference. If the patient selected medication, I would prescribe one of the newer antidepressants. I assume that the dose would be similar to the starting dose for acute depression. If the patient preferred psychotherapy, I would start with CBASP because it has the best evidence for efficacy. What do you think?

Dr. McCullough: I would return to a point raised by Dr. Thase: age at onset. There seems to be increasing evidence in the journal literature that patients with late-onset chronic depression have a milder, healthier developmental history than patients with early onset. Patients with late-onset as opposed to early-onset chronic depression may have a better chance of remission.

Dr. Thase: Psychiatrists are partial to combining psychotherapy and pharmacotherapy, but there is no strong

evidence that combining treatments is more beneficial than monotherapy for patients with a first episode of mild depression. However, I think combining psychotherapy and pharmacotherapy is clearly the first-choice treatment for chronically depressed patients.

Dr. Gelenberg: So the combination of an antidepressant medication and the targeted CBASP form of psychotherapy would provide a chronically depressed patient with the most robust chance for recovery and remission. Of course, the patient's insurance coverage would also probably play a role in the choice of treatment.

Dr. Thase: In the Keller et al. study[9] in which we all participated, the average patient given the combination of an antidepressant and CBASP had a 20% greater likelihood of responding or remitting than the average patient given one or the other therapy alone. That effect is as large as the typical drug-placebo differences in clinical trials and provides evidence of an advantage for combined treatment in chronic depression.

Dr. Gelenberg: To summarize: (1) The combination of an antidepressant and CBASP psychotherapy has the best evidence for a high remission rate. (2) The antidepressants appear to have similar response and remission rates, but most clinicians choose newer antidepressants first for reasons of convenience and safety. (3) Among the various forms of psychotherapy, there seems to be preferential evidence in favor of CBASP.

Dr. Ninan: What were the comparative response and remission rates in the imipramine versus sertraline study?[12]

Dr. Gelenberg: There were no statistical differences in either the intent-to-treat or observed-cases analysis. The response rate was about 50%.

Dr. Ninan: Can we make a general statement that the response and remission rates with pharmacology are about 5% to 10% lower in chronic depression studies than in nonchronic depression studies?

Dr. Kocsis: They may be even lower.

Dr. Gelenberg: The rates for chronic depression may be affected by a lower floor of the placebo effect in most chronic depression studies. Dr. Thase, didn't you find similar response rates in a study of sertraline in dysthymic disorder?

Dr. Thase: Yes. The study[13] included a placebo arm, and the placebo response rate was only about 20%. I agree the rate of response to antidepressant monotherapy in chronic depression is around 45% to 50%.

Dr. Gelenberg: Would it be fair to say that the overall response rate is lower in chronic depression, but the treatment effect size may be comparable to that in studies of nonchronic depression by virtue of a lower placebo response rate in those studies that include placebo?

Dr. Kocsis: I think that is correct. A 1988 study[14] that my colleagues and I conducted supports your argument. The placebo response and remission rates were quite low, but the magnitude of difference between the active drug and the placebo was comparable to the effect in the Thase et al. study.[13]

Dr. Ninan: So we are suggesting that patients with chronic depression are not necessarily treatment resistant, because a substantial number of them respond and remit to treatment with the first antidepressant as well as to specific forms of psychotherapy, but the absolute number of responders is slightly fewer than with nonchronic depression treatments.

Dr. Gelenberg: Yes, with the corollary that failure on the first round of treatment still gives someone roughly a 50-50 chance of responding to the second round of treatment. A patient who does not respond to the first antidepressant has a reasonable chance of responding to a second antidepressant or psychotherapy.

Dr. Kocsis: We are all currently involved in a National Institute of Mental Health (NIMH) chronic depression study. One question we are asking is whether patients with chronic depression are inherently treatment resistant. About 700 patients are currently enrolled in this study. Approximately 75% have not failed previous antidepressant trials, so there is clearly a difference between having chronic depression and being treatment resistant. Many patients with chronic depression do not have a history of treatment resistance.

Dr. McCullough: In the NIMH study from the early 1980s,[15] almost one fourth of patients with acute episodic depression did not remit and went on to develop a chronic course. I wonder if part of the treatment resistance we see comes from patients like those.

Long-Term Course and Treatment Response in Chronic Depression

Dr. Gelenberg: Dr. Kocsis, will you discuss long-term course and treatment response in a chronically depressed population?

Dr. Kocsis: Data from the few existing studies of maintenance treatment of chronic depression including SSRIs, TCAs, and some of the newer agents suggest that patients who respond to treatment—whether it's with antidepressant medication or CBASP psychotherapy—tend to do well and remain well as long as they continue their treatment.[10] When treatment is discontinued, the recurrence rate is substantial (more than 50% over 1 to 2 years),[16] so long-term treatment is indicated for many patients with chronic depression.

There does appear to be a subpopulation of patients with chronic depression who will respond to a 6-month course of treatment and remain well when treatment is discontinued. I recommend that patients continue treatment for at least 6 to 12 months. Then, if they elect to discontinue treatment—either medication or psychotherapy—they should be followed closely. I recommend restarting treatment if symptoms recur.

Dr. McCullough: The Keller et al. study[9] included a cell with a substantial group of patients who received CBASP only. The survival rate (meaning lack of symptom recurrence or relapse) in that cell was 90%.

Dr. Ninan: Was the survival rate substantially different for patients who continued taking medication?

Dr. McCullough: The comparison is different because of the size of the cells. About 55% of the placebo-treated patients relapsed during the maintenance phase, and 75% of the medication-treated patients were maintained without recurrence or relapse.

One reason that patients may not maintain the benefits of psychotherapy after discontinuation is that they forget the skills they have learned. The danger is that patients will get out of practice and simply forget to do the work of psychotherapy. I do not know if there is a comparable issue with medication treatment.

Dr. Gelenberg: There appears to be benefit in chronic depression from ongoing CBASP sessions since, in the absence of booster sessions, patients often slip back into their old patterns of passivity and pessimistic thinking.

Dr. McCullough: From the beginning, I have tried to describe CBASP as an acquisition learning methodology.

Dr. Ninan: Perhaps we should clarify our terms. Once something has been learned—particularly at an emotional level—it can seldom be wiped out. The neurobiological literature uses the term *extinction*, where new learning counters the previous learning. However, such previous patterns may return in a new context or under stressful conditions. Therefore, the psychotherapist and the patient must craft a context that tilts toward what has been learned in therapy against the old depressive patterns.

One could argue that the situation analysis is what differentiates CBASP from traditional CBT. Situation analysis is true exposure, since the patient is encouraged to face the situations that contribute to the maintenance of depression. Then he or she learns new techniques for handling these situations; the new techniques counter the cognitive schemas and behaviors that might maintain the depression. In traditional CBT, learning is not necessarily translated into behaviors, so we could argue that the maintenance value of CBASP lies in the patient continuing to challenge problematic interpersonal situations. When he or she starts avoiding such situations, it is easy to slide back into a previous depressive pattern.

Dr. McCullough: Dr. Ninan's description is excellent. Patients with chronic depression are often under a lot of stress for a variety of reasons. There may be a parallel between extinction and stopping medication. Perhaps patients with chronic depression are not armed with adequate neurotransmitters for handling stress, which may explain why stopping medication can potentiate the recurrence or relapse rate.

Effect of Childhood Abuse on the Course of Depression

Dr. Gelenberg: There is a growing body of literature about the effect of early life stress on the course of depression. Dr. Ninan, what is the effect of childhood abuse on treatment response in chronic depression?

Dr. Ninan: Early adversity, including childhood abuse, can have an influence on the developing brain that might be qualitatively and quantitatively greater than adversity in adulthood when the brain is more completely developed. Nature wants to be able to sculpt the developing brain beyond the imprint provided by genes. This sculpting is based on early experiences since such environmental experiences are often predictive of later experiences. Early experiences calibrate brain responses to stress and thus strongly influence adult responses to stress. So, someone who is born into a stressful environment develops a strong stress response, whereas an infant who is born into a relatively low-stress environment does not need to calibrate a powerful response to stressors.

Toning the stress response to a high level might make the individual more vulnerable to the later development of depression. Research that has looked at adults with depression has shown a greater likelihood of a history of early abuse than the general population.[17] The pattern of depression in this population is associated with increased activation of the hypothalamic-pituitary-adrenal axis, which is the prototypical stress axis. This conclusion is supported in animal models of depression.

An important question is whether early adversity predicts the likelihood of benefit from medications compared with psychotherapy like CBASP. The one study[18] that examined this question found that a higher proportion of chronically depressed patients with a history of early life stress were more likely to achieve remission with CBASP compared with nefazodone, the antidepressant medication used.

Dr. Gelenberg: So a patient who has both chronic depression and a history of childhood abuse, neglect, or trauma may be differentially likely to respond to CBASP compared with medication.

Dr. Ninan: That is correct. The likelihood of achieving remission in 3 months is about 10% higher with CBASP than with nefazodone.

Conclusion

Dr. Gelenberg: As we conclude, do you have other comments?

Dr. Thase: When we began studying chronic depression more than 15 years ago, we were shocked to discover that the vast majority of patients with chronic depression had never received treatment, and treatment for most of the rest was inadequate, i.e., low doses of antidepressant medications, short duration of treatment, and exposure to counseling but not professional psychotherapy.

Even though we are saying the prognosis for chronic depression is poor, the fact remains that many patients with chronic depression are still not receiving proper treatment. With proper treatment, particularly a combination of psychotherapy and pharmacotherapy, patients have a strong chance of getting well relatively quickly.

Dr. Gelenberg: We can end with a message of optimism. We have at least one form of effective psychotherapy, and medication is often beneficial. If the first round of treatment is not effective, a second treatment trial may help. Many patients who have been told they have a personality disorder may, in fact, have chronic depression, which can be treated.

Dr. Ninan: Sometimes the initial choice of treatment may be based on factors other than efficacy, such as cost and availability of a professional psychotherapist with experience in CBASP. Pharmacology might be less costly than intensive CBASP in the short term, but the issue of cost must be factored into the longitudinal value of CBASP in terms of greater protection from recurrence.

Dr. Gelenberg: And we can take some encouragement from the fact that Dr. McCullough is in the process of training psychotherapists around the country in CBASP.

Dr. McCullough: If the appropriate diagnosis is made early (and I think Dr. Kocsis pointed out how important it is to make an accurate diagnosis), the prognosis is optimistic.

Dr. Gelenberg: It is nice to leave our discussion of a disorder characterized by pessimism with the feeling that we, as clinicians, have a growing sense of optimism that is informed by science, and our body of knowledge is growing every day.

Drug names: imipramine (Tofranil and others), sertraline (Zoloft).

Disclosure of off-label usage: The authors have determined that, to the best of their 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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Faculty disclosures: 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) occurring within the 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. Gelenberg** has received grant/research support from Pfizer and Wyeth; has been a consultant for Eli Lilly, Pfizer, Vela, Best Practice, Bristol-Myers Squibb, AstraZeneca, Wyeth, GlaxoSmithKline, Cyberonics, Roche, ZARS, Express Scripts, and Zynx Health; has been on the speakers' bureau for Wyeth, Cyberonics, and Pfizer; and has stock options in Vela. **Dr. Kocsis** has been a consultant for Pfizer; has received grant/research support from Wyeth, Forest, Organon, and Pfizer; and has received honoraria from and been on the speakers/advisory board for Wyeth, Pfizer, and AstraZeneca. **Dr. Ninan** has been a consultant for Cephalon, Cyberonics, Forest, Janssen, UCB Pharma, and Wyeth; has received grant/research support from Cephalon, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, NIMH, Pfizer, UCB Pharma, and Wyeth; and has been a member of the speakers bureau for or received honoraria from Cephalon, Cyberonics, Forest, GlaxoSmithKline, Janssen, Pfizer, and Wyeth. **Dr. Thase** has been a consultant for AstraZeneca, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Novartis, Organon, Pfizer, and Wyeth and has been a member of the speakers bureau for AstraZeneca, Eli Lilly, GlaxoSmithKline, Organon, and Wyeth. **Dr. McCullough** has no significant commercial relationships to disclose relative to the presentation.

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