Discussion

Improving Cognitive Function and Functional Outcome in Severe Mental Illness

COGNITIVE IMPAIRMENT

Dr. Tamminga: Considering some of the information on varying proportions of cognitive deficits, does every person have all of those deficits or do some patients with schizophrenia have mainly one deficit and some have mainly another? Hill et al. [*Hill SK, et al. J Clin Exp Neuropsychol 2002;24:765–780*] suggest that some clusters of patients with schizophrenia have predominantly memory or other deficits and others have global impairments or few impairments.

Dr. Green: You can always statistically find people who are below a cutoff on some domains and not others. This separation is only meaningful if it can be validated on another measure, which is where we have not been as successful. However, even if subjects test fairly well across domains, they may still be cognitively lower than where they should be.

Dr. Harvey: Cluster analysis is a particularly unstable statistical technique, and many of the cluster analytic studies have very different results. Longitudinal data on the stability of the cluster are lacking, which would be the true validator of the meaningfulness of these subtypes. Cluster analysis is being used almost entirely on an exploratory basis on single samples of patients without respect to longitudinal stability.

Dr. Marder: Of the bipolar literature presented, are the populations mostly bipolar I patients or do they include bipolar II patients as well? And is there a bias toward psychotic bipolar patients because of a more severe cognitive impairment?

Dr. Green: The authors are conscientious about describing their study populations. For example, the Finnish cohort study [*Tiihonen J, et al. Am J Psychiatry 2005;162:1904–1910*] included bipolar patients with psychotic features, whereas the Israeli cohort sample [*Reichenberg A, et al. Am J Psychiatry 2002;159: 2027–2035*] did not. Certainly, sample differences may account for differences in findings.

Dr. Harvey: One study [*Bromet EJ, et al. Schizophr Bull 1992;18:243–255*] included only psychotic patients with first-episode unipolar disorder, bipolar disorder, or schizophrenia. The results are consistent with Dr. Green's findings that patients with schizophrenia were more impaired than patients with bipolar disorder on all of the critical domains.

Dr. Newcomer: In terms of clinical management, do all patients with bipolar disorder have enough cognitive impairment to impact functional outcome, and would treating this cognitive impairment have public health value?

Dr. Green: The presence of cognitive impairments may characterize a subgroup of patients with bipolar disorder. For patients with schizophrenia, it is assumed that it will be common practice to treat everyone, even when the level of deficits is not fully established. The same assumption should not be made for bipolar disorder at this time. In bipolar disorder, first you make the diagnosis, then you should administer a cognitive test to assess the level of impairment linked to the rehabilitation problem.

Dr. Harvey: The other part of the equation is the perceived risk of drug treatment; if the risk is perceived as low, then pharmacotherapy may be beneficial. The pivotal distinction between schizophrenia and bipolar disorder is the practical aspect of treatment.

Dr. Tamminga: In schizophrenia, psychotic symptoms such as thought disorder, hallucinations, and delusions are cognitive symptoms as well. How do you conceptualize the difference between psychotic symptoms and cognitive symptoms in cognitive dysfunction in psychotic illnesses?

Dr. Green: In a surface description, the psychotic phenomenon is a sort of cognitive impairment. Cognitive deficits are measured by performance and psychotic symptoms are measured by interview. Thought disorder is a clinical phenomenon that lies between psychotic symptoms and cognitive performance.

Dr. Harvey: The neuropsychological tests that we use to measure cognitive impairment in schizophrenia were originally designed for people with disabilities such as head trauma. These tests were not developed for people with schizophrenia—they were applied to them.

Dr. Tamminga: Do we need schizophrenia-relevant assessments?

Dr. Harvey: To understand psychosis, I think we do. Some neuropsychological assessments do not accurately measure the cognitive domains that are relevant to hallu-

cinations and delusions. In people with schizophrenia who have minimal cognitive impairment, the severity of their disability is directly related to the severity of their psychosis, not cognitive impairment.

NEUROBIOLOGY

Dr. Harvey: You mentioned negative study results for cholinesterase inhibitors, and a number of these trials suggest that compounds that change brain activation—as measured by functional magnetic resonance imaging, for example—may result in brain activity that appears normal in the absence of any concurrent cognitive benefit. Some negative studies suggest that the relationship between cortical cognition circuits and performance in schizophrenia may not be as correlative as we previously thought—that you could normalize brain activity without affecting cognition. [*Sharma T. Curr Med Res Opin 2002;18(suppl 3):S13–S17*] What are your thoughts on this?

Dr. Tamminga: Those observations make me think we are looking for cognitive improvement either at the wrong time or in the wrong way. It is hard for me to think that you can truly normalize brain activity and not get a reasonably positive effect on cognition. The studies should include long-term treatment, different dose treatment, and measures of social functioning in addition to cognitive performance. Perhaps treatments paired with cognitive remediation would work cooperatively together.

Dr. Harvey: Yes, some of these treatments, although they cannot change cognition on their own, may very well facilitate the benefit from being in a rehabilitation program. I am encouraged by cognitive remediation results in schizophrenia studies that have shown cognitive targets to be extremely malleable. Two recent publications on cognitive remediation interventions showed substantial improvements in cognition as well as functional outcomes [*McGurk SR, et al. Schizophr Bull 2005;31:898–909; Wexler BE, et al. Schizophr Bull 2005;31:931–941*].

Dr. Marder: Does cognitive remediation actually change metabolic activity in the brain?

Dr. Tamminga: My colleagues and I are currently conducting a 4-cell design study of cognitive remediation and medication. The study is not far along, but the patients with schizophrenia like the aspects of cognitive remediation—the interaction and the computerized games—which appears to have increased their ability to function in the world, such as making grocery lists.

Dr. Green: Dementia research in Alzheimer's disease seems so far ahead of research in schizophrenia. During the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) process, we went to great lengths to separately define cognitive impairment in schizophrenia versus cognitive impairment in dementia for U.S. Food and Drug Administration (FDA) classification purposes. Furthermore, the procholinergic agents borrowed from treating dementia in Alzheimer's disease have been unimpressive in treating patients with schizophrenia. My question is: Is there nothing we can learn from dementia research, or should there be more interchange of ideas between the two fields?

Dr. Tamminga: We are beginning to define the pharmacology of normal cognition in humans, which would be comparable in a person who has a predisposition to Alzheimer's disease versus a predisposition to schizophrenia. So, in looking to enhance cognition, whether in Alzheimer's disease or schizophrenia, we need to think of what is happening specifically to learning, memory, and attention systems. We can overlook the systems compensating for neuronal cell death in Alzheimer's disease, but if drugs work in other parts of the intact systems to enhance cognition in Alzheimer's disease, I think that we can borrow those drugs for schizophrenia. I do not think cognition in Alzheimer's disease and cognition in schizophrenia are enormously different if you consider intact systems, but they are different if you examine neurodegenerated systems.

No evidence exists for neurodegeneration in schizophrenia, although there is evidence for volumetric changes in key parts of the brain that are important for cognition. When you examine the neurons in postmortem tissue, the neurons are not different from those of controls, but the dendritic arbors of the neurons are. So, there would be evidence of neuronal regression or dysfunction but not of neuronal degeneration.

Dr. Harvey: Another possibility is non–neurotransmitter-based interventions, such as those targeting myelin and other white matter abnormalities that affect circuitry. Treatments can be administered that directly affect myelin integrity and myelin deposition. Treatments being piloted in multiple sclerosis and in spinal cord injury may have a path toward non–neurotransmitter-based cognitive enhancement.

Dr. Marder: Would it be fair to say that the data on cholinesterase inhibitors are discouraging and that you would not encourage clinicians to try these in patients who have cognitive impairments?

Dr. Tamminga: There is a very modest effect in schizophrenia, perhaps the magnitude that you see in Alzheimer's disease, but that magnitude of effect is so much more important in someone with dementia than in someone without dementia. That effect might not be cost-effective in schizophrenia because it does not impact function as much.

Dr. Harvey: Patients with Alzheimer's disease do not improve when given cholinesterase inhibitors; they

just do not worsen. So, the effect in schizophrenia may be the same as in Alzheimer's disease, without the backdrop of neurodegeneration. Cholinesterase inhibitors may in some way prevent degeneration that is Alzheimer's-specific and not provide a true procognitive benefit.

Dr. Tamminga: Especially since neurodegeneration is not characteristically a factor in schizophrenia, these drugs would have a different action in Alzheimer's disease.

QUALITY OF LIFE AND RECOVERY

Dr. Marder: You made an interesting point about the relationship between subjective response, adherence, and quality of life. Is a shared decision-making process with the patient in setting treatment goals becoming an underlying tenet of recovery from serious mental illness?

Dr. Harvey: Based on substance abuse treatment, the recovery model for serious mental illness first involves owning your illness and making your own decision to seek treatment. These data strongly suggest that a collaboratively developed treatment plan may result in a better outcome, both subjectively on the part of the patient and objectively in terms of recovery indicators, which appear to be determined by illness variables.

Dr. Tamminga: What do you think about the rapid changing of medications that led to high response rates and equally high relapse rates reported in the Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) study [*Lieberman JA, et al. N Eng J Med 2005; 353:1209–1223*]?

Dr. Harvey: The CATIE project was a randomized trial, and the subjects were recruited knowing that one of the goals was to switch pharmacotherapy to optimize treatment. The fact that medications changed rapidly captures clinical reality in that many patients with schizophrenia have taken several different treatments, and patients with bipolar disorder have often taken even more. Switching medications shows that treatments may need to be adjusted in individuals, but the switch should be the mutual choice of the patient and the therapist.

Dr. Green: Do you use the terms *quality of life* and *subjective life satisfaction* interchangeably?

Dr. Harvey: Because quality of life is multidimensional, studies define quality of life differently. As a result, some studies measure the quality of well-being while others examine subjective life satisfaction, and these produce very different results.

Dr. Green: The idea of working with the patient in a partnership to make treatment decisions could only be good. However, the idea that I would feel responsible for the outcome of subjective satisfaction sounds like a concept I have no control over.

Dr. Harvey: That is true. Quality of life judgments made by people with schizophrenia appear to be based on criteria different from the clinician's focus. In studies conducted by the University of California San Diego group [*McKibbin C, et al. J Nerv Ment Dis 2004;192: 405–413*], quality of well-being scores in people with schizophrenia were highly associated with the patient's subjective impression of their own disability, which was not related to others' impressions of their disability or with their ability to perform functional skills. The subjective response originates from the patient in terms of satisfaction with the decision-making, treatment, and outcome experienced to date. It is possible that people, whom clinicians would agree are optimally treated, are still unhappy. The role of the prescriber is to facilitate recovery, not be responsible for it. This notion of recovery is that the subjective response comes out of a collaborative relationship that has resulted in the best possible symptomatic and functional outcome up to that point.

Dr. Tamminga: What exactly do you mean by the term *recovery*?

Dr. Harvey: Recovery in schizophrenia and bipolar disorder aims to minimize susceptibility to relapse, keep the illness under control across multiple domains, and maintain functioning as close to optimal as current treatments allow.

Dr. Newcomer: Are there differences in syndromal relapse in functionally recovered patients versus those who have not functionally recovered?

Dr. Harvey: Now that relapse, remission (full and partial), and recovery have been better defined, quantifiable research can use the same measurement methods to assess those differences. Previous studies such as the CATIE effectiveness model are difficult to interpret because there is no way to determine whether one treatment is better than the other in terms of relapse prevention. CATIE patients were switched to new medication because that was part of the trial, not because they met some relapse or criteria.

Dr. Newcomer: So, the hypothesis is that a unique biology exists for cognitive impairments, which drive functional deficits; if patients can function at a higher level, the result is a healthier patient with better long-term outcome in terms of relapse.

Dr. Harvey: Right. Also, functional recovery is common in bipolar disorder, but it is still not the norm. When treatment options that can enhance cognition become available, patients who have not achieved functional recovery will benefit immensely. Presently, most assessments are focused on symptoms and not function.

Dr. Tamminga: Once we get drugs to improve cognition in schizophrenia or bipolar disorder, patients will become better able to participate in their own recovery.

Dr. Harvey: Participating in recovery is a problem-solving process, and many of the components of the MATRICS Neurocognitive Assessment are required in order to make complex decisions about the management of your own illness.

PHARMACOTHERAPY AND PSYCHOEDUCATION

Dr. Marder: I'm interested in the issue of impairment caused by mood-stabilizing drugs. Have there been any direct studies of the effects of valproate and lithium on cognition?

Dr. Green: There is an assumption that certain medications, typically antidepressants and anticonvulsants, are cognitively neutral, whereas lithium may or may not have a negative impact on cognition.

Dr. Keck: The studies of lithium were not controlled and were primarily long-term, naturalistic studies of large groups of people. Most of the studies found a subset of people who allegedly had some cognitive problems on lithium, but the cognitive impairment was often self-reported and not assessed by neuropsychological or cognitive measures. A potentially dangerous assumption exists that anticonvulsants and antidepressants are cognitively neutral. These are heterogeneous groups. Anecdotally, patients will periodically report subjective cognitive problems with selective serotonin reuptake inhibitors (SSRIs), the most widely prescribed antidepressants. Naturalistic reports suggest that some anticonvulsants, such as carbamazepine, may have more cognitive side effects than others, such as divalproex or lamotrigine, which may be truly cognitively neutral for most patients.

Dr. Marder: In your clinical experience, have you seen high-functioning patients who have actually complained that mood-stabilizing drugs impaired their functioning?

Dr. Keck: A majority of patients do not complain of that. In a dose-related fashion, lithium and valproate can be associated with cognitive complaints [*Jamison KR. An Unquiet Mind: A Memoir of Moods and Madness. New York, NY: Vintage; 1997*]; however, therapeutic levels offer symptomatic control without producing negative cognitive side effects. Some of the atypical antipsychotics have potentially more beneficial effects on aspects of cognitive function than the typical agents in patients with schizophrenia, which has not been demonstrated in bipolar illness research. Anecdotally, the atypicals with the fewest subjective cognitive complaints have been those that are also the least sedating, such as ziprasidone and aripiprazole.

Dr. Harvey: The association between higher levels of depression and greater sensitivity to cognitive limitations is appearing in studies of other neuropsychiatric conditions. It would seem that patients with bipolar disorder whose moods tend to be changeable might also have the potential for variability in their ability to actually index their own cognitive limitations.

Dr. Keck: Many studies used patients' self-report as the global outcome measure, but neglected whether mood state and symptoms had an impact on that assessment. On the issue of insight, which I think cuts across several cognitive domains, some studies indicate that insight in bipolar disorder is often the first cognitive aspect to degenerate. Many patients begrudgingly take their medication and comply with treatment, but are not fully convinced that they have an illness or are unable to examine their own behavior, especially in manic or hypomanic states.

Dr. Marder: Is loss of insight characteristic of a manic episode?

Dr. Keck: I think it is one of the most insidious symptoms of mania or hypomania. This lack of insight leads to difficulties in people getting help earlier rather than later in the course of an episode.

Dr. Harvey: This suggests that vulnerability toward self-initiated discontinuation of medication would be more likely to occur during hypomania as opposed to depression.

Dr. Keck: So, the questions are: do patients lose insight and then stop medication, or stop medication because of some side effect and then lose their insight?

Dr. Marder: In schizophrenia, educating patients and families about the illness decreases relapse rates relatively consistently. Has psychoeducation been tried much in bipolar disorder?

Dr. Keck: In fact, much of the research that has been done in bipolar psychoeducation has been imported and modified from groundbreaking schizophrenia research [*Miklowitz DJ, Goldstein MJ. Bipolar Disorder: A Family-Focused Treatment Approach. New York, NY: Guilford Press; 1997*]. I think it has become *the* platform now, not only in mental illness, but also in medical illness so that patients can be involved in self-management.

Dr. Tamminga: What is the relationship between insight dysfunction and certain cognitive deficits? Is lack of insight merely a type of cognitive deficit, a combination of cognitive deficits, or something different?

Dr. Green: Insight can refer to the awareness of one's own cognitive capacity and one's own cognitive performance, although it may mean knowledge of one's illness and the need for treatment. A review published by the Association for Psychological Science (APS) [*Dunning D, et al. Psychol Sci Public Interest 2004;5: 69–101*] found that even nonclinical samples were poor

at monitoring their job performance. In clinical samples that have cognitive deficits, the capacities necessary to perform tasks are probably those capacities needed to evaluate one's own performance on that task. This leads to fairly pessimistic conclusions.

Dr. Harvey: Right. A discussion in the field has centered on whether or not insight—awareness of one's illness and the need for treatment—is simply a proxy for executive functioning. But, one of the findings by the APS is that people with depression are more accurate appraisers of their situation, whereas those who switch into mania have an unrealistically optimistic state.

Dr. Tamminga: How do you accurately assess and improve a patient's lack of insight?

Dr. Harvey: It is important to keep in mind that many patients with poor insight are completely capable of evaluating the plausibility of a statement as it applies to other people, but when it comes to applying those standards to themselves, their judgment is lost.

Dr. Tamminga: So, you would put a lack of insight into the category of psychosis, more than into the category of cognitive dysfunction?

Dr. Green: Insight and cognition probably do not have a linear relationship. A certain amount of cognition is necessary to have some insight, but high levels of cognition could also be associated with coping mechanisms, which may reduce insight. Therefore, I would put insight into a category by itself.

MECHANISM OF ACTION AND ADDITIVE EFFECTS

Dr. Marder: Do mood stabilizers such as lithium and valproate have mechanisms of action that would produce additive effects when used adjunctively with antipsychotics, such as weight gain?

Dr. Newcomer: We do not know the exact mechanisms of action. For antipsychotics, histamine type I receptor binding affinity explains much of the variance in weight gain over short-term intervals. However, lithium does not bind significantly to H_1 receptors; that is not its primary mechanism of action.

We also do not know if these agents promote weight gain by increasing appetite or by decreasing activity level. Sedation is a common occurrence with many of these agents, which has an impact on caloric expenditure. Most of our caloric expenditure during the day is just standing up, holding yourself upright, and fidgeting and moving around. So, if we sedate somebody who was previously perhaps psychotically pacing and walking inordinate amounts, the result is a rather significant drop in total caloric expenditure for a day.

Dr. Harvey: Cognitive impairment decreases the ability to reduce health risk factors. For example, patients with schizophrenia who have substantial working memory abnormalities do not respond well to smoking cessation interventions [*George TP, et al. Neuropsychopharmacology 2002;26:75–85*]. Likewise, healthy lifestyle promotion and weight reduction programs would probably be less accessible to people whose cognitive impairments are greater.

Dr. Newcomer: I think that is a very important point about cognition, but motivation is also important—both having the ability to process what the task is in terms of weight reduction strategies and then being motivated enough to stick with it.

Dr. Harvey: Should weight gain be considered treatable via medication switch rather than through an intervention program? That is, if weight loss is so difficult for the general population, why would it work in people with schizophrenia?

Dr. Newcomer: Empirical studies are being conducted to ascertain the effectiveness of diet and exercise interventions in patients with schizophrenia; however, studies of these interventions in nonpsychiatric populations are unimpressive. So, the question is, what level of behavioral intervention will it take in this population? My guess is that it can work but it will have to be a more intensive and perhaps a more costly intervention.

Dr. Harvey: Are behavioral interventions going to be affordable in a community health setting?

Dr. Newcomer: This is a current public health debate. According to a recent report from the Institute of Medicine [*http://www.iom.edu/CMS/3809/19405/30836.aspx*] on primary care, mental illness, and metabolic syndrome, major service reconfigurations are going to have to be made in order for these interventions to be cost-effective.

Dr. Marder: Some people with schizophrenia are anxious and willing to improve their health when provided with the information. So, from a clinical standpoint, I think that we should inform the patients and ask them if they want an intervention.

Dr. Newcomer: Right. Large effect sizes can be seen in a minority of patients with a modest offering of tools. On a tiered or stepped approach, the next level of intervention would have more successful completers, and the highest level of the most expensive and aggressive interventions would be reserved for those patients who really need it.

Dr. Green: I would think that the mechanism by which glucose and insulin interact with the brain and cognition would affect all neuronal activity, but is it only in specific domains?

Dr. Newcomer: A popular hypothesis is that there are regional differences in the expression of insulin receptors and in the activity of insulin degrading enzyme. Work from Harvard [*Vekrellis K, et al. J Neuroscience 2000;20:1657–1665*] focused on the idea that differences in the activity of the insulin degrading enzyme enhance bad lipoproteins, contributing to risks

for patients with a predisposition for illnesses such as Alzheimer's disease.

COGNITIVE ASSESSMENT AND REMEDIATION

Dr. Tamminga: What do you consider to be the effective component of the MATRICS process [*http://www.matrics.ucla.edu/*] that facilitated change within the field?

Dr. Marder: A couple of ideas made it successful. One was the inclusiveness of the project. Wayne Fenton, M.D., and Ellen Stover, Ph.D., of the National Institute of Mental Health emphasized this and provided the resources to bring large numbers of people from industry, the FDA, and academia, so many people felt included in the process. The other component was having the route to consensus in the beginning so that the process was well-defined.

Dr. Green: There was also a level of connection and constant communication that I had never encountered before at both the local and national level.

Dr. Harvey: I think the MATRICS did an excellent job of paving the regulatory path in order to establish a process through which a drug may be approved. Due to the MATRICS Neurocognitive Consensus Battery, the FDA has agreed that the right cognitive assessments combined with the right functional outcomes assessments can lead to approval. The MATRICS opened a door for researchers in all areas of medicine, which will stay open until drugs start getting approved.

Dr. Marder: The FDA welcomed and embraced this process. The fact that they were there from the beginning brought industry into the process.

Dr. Tamminga: Dr. Marder, in your discussion of treatment for cognition, it seems that clinicians ought to give serious thought to combining drug treatment for cognition with remediation for cognition.

Dr. Marder: Yes, and I wonder if certain medications have an effect that becomes measurable only after patients have received cognitive training. For example, a patient can acquire a new cognitive ability from medication but need instruction on how to use it.

Dr. Green: Also, older studies of cognitive remediation were not well controlled. Studies from the past few years have produced more substantial results [*Bell M, et al. Arch Gen Psychiatry 2001;58:763–768; Hogarty GE, et al. Arch Gen Psychiatry 2004;61:866–876*; *Wykes T, et al. Schizophr Res 2003;61:163–174*].

Dr. Harvey: One of the most important aspects about some intervention programs is that these interventions can be delivered by paraprofessionals to groups of patients, a practical alternative to assigning a full-time psychologist to every patient [*McGurk SR, et al. Psychiatr Serv 2003;54:1129–1135*; *Medalia A, et al. Psychiatr Serv 2003;54:1219–1220*].

Dr. Marder: Can you think of any psychosocial treatments that have actually shown effects on negative symptoms?

Dr. Harvey: Patterson [*Am J Geriatr Psychiatry 2003;11:17–23*] has shown psychosocial interventions having direct effects on functional capacity measures using the functional adaptation skills training (FAST) intervention. So, you can treat functional capacity like you can treat cognition—with a structured intervention [*Leff J, et al. Br J Psychiatry 2000;176:217–223*]; however, I'm not aware of structured intervention trials that measured negative symptoms.

Dr. Newcomer: What is the sequence or the proper combination of treatments? These have been established in other areas of medicine, such as cardiovascular disease.

Dr. Harvey: The analog for treating schizophrenia would be to start a pharmacologic intervention, wait a certain amount of time, and then add the behavioral intervention if needed because it is more labor intensive.

Dr. Green: Besides psychopharmacologic and psychosocial interventions, cognitive remediation should also be included. The 2 nonpsychopharmacologic interventions may be substantially different from one another.

Dr. Tamminga: I think of cognitive remediation in terms of plasticity—what you want the brain to do—whereas skills retraining opens up opportunity for actual use of the brain's cognitive capacity.

Dr. Harvey: If that's true, pharmacologic interventions aimed at promoting plasticity would work with retraining interventions but might not work on their own.

Dr. Marder: It also suggests that cognitive remediation should come as early in the illness as possible, when the skills have been recently lost and new skills can be developed quickly.

Dr. Harvey: We often triage patients backwards in schizophrenia. We treat a first-episode college student and send him or her back to school, and then the student fails out. The opposite intervention may be required—giving more intensive cognitive remediation and psychosocial skills interventions to younger, higher functioning people early in their illness course who are much closer to reaching successful outcomes, rather than to people who have got 12 standard deviations to overcome before they can reach such success.

Dr. Newcomer: I agree. Further, early interventions are necessary to positively impact the overall health risks and metabolic risks and the long-term course of the illness, which can prevent much of the costly medical care.

Dr. Marder: Yes, an intervention may be more powerful in patients who are within normal weight, in which relatively small behavioral changes may give them better control over their health, as opposed to someone with a body mass index of 40, although that person de-

serves treatment, too. Clinicians should monitor small early changes in patients and intervene when health parameters are violated. Weight gain affects not just health but social interactions and rehabilitation motivation.

Dr. Newcomer: Exactly. People who are overweight or obese are treated differently, may not succeed in relationships, and earn less money in the job arena. When patients experience this stigmatizing physical condition, this becomes an extra hurdle in achieving an optimal functional outcome.

Drug Names: aripiprazole (Abilify), carbamazepine (Carbatrol, Tegretol, and others), divalproex (Depakote), lamotrigine (Lamictal and others), lithium (Eskalith and others), ziprasidone (Geodon).

Disclosure of off-label usage: The authors of this article 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.