Can Psychopharmacologic Treatments That Relieve Symptoms Also Prevent Disease Progression?

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Issue: *Early treatment of numerous psychiatric disorders not only may reduce current symptoms but may even interrupt or delay symptomatic progression.*

Numerous psychiatric disorders are hypothetically linked to a vulnerable genome that can trigger illness when meeting adverse environmental experiences.[1] Some disorders may be more highly biologically endowed, such as Alzheimer's disease,[2–4] schizophrenia,[1,5–7] and bipolar disorder,[1] whereas others may be more strongly linked to environmental exposure, such as posttraumatic stress disorder (PTSD)[8,9] and other anxiety disorders,[10,11] medical and cardiac complications of stress,[12–14] substance abuse,[15] and chronic pain.[16,17] Currently, our therapeutic approach to psychiatric disorders is largely to wait until symptoms are overtly expressed and, once symptoms interfere with social or occupational functioning, to treat them, usually reducing but not removing symptoms. Treatments can thus be conceptualized as symptom suppressors that are discontinued by patients or their providers once symptoms have been reduced, especially early in the course of the illness, only to be reinstituted whenever symptoms recur.

Relapse Prevention

We have begun to change this scenario. We have learned that once symptoms have occurred in a number of illnesses, from major depression to bipolar disorder, schizophrenia, and numerous anxiety disorders, the risk of recurrence can be reduced by continued treatment. We also know that complete suppression of symptoms to attain remission, at least in depression, is associated with better functional outcomes and less chance of relapse.[18] Since the more relapses that have occurred, the more will occur, preventing second and third relapses to prevent a chronic relapsing and remitting illness is important. Thus, early identification to achieve treatment at the time of the first episode may be particularly important in preventing future relapses and the best opportunity to do so.

Presymptomatic Treatment

A new and somewhat controversial concept takes these ideas to another level, namely, to prevent or delay the first episode of illness by treating those with subsyndromal symptoms or even those at risk for a psychiatric illness but with no current symptoms. Thus, treatment of those with mild memory loss but not dementia might prevent the evolution of these symptoms into Alzheimer dementia.[2–4] Whether the current cholinergic treatments for Alzheimer dementia have the appropriate mechanism to delay disease progression at the stage of mild cognitive impairment is not yet known. Nevertheless, early treatment of mild cognitive impairment is an exciting concept since it may be easier to prevent disease progression than to reverse neurodegeneration caused by amyloid deposits.[4] Potentially disease-modifying therapies for Alzheimer dementia, such as beta secretase inhibitors that might inhibit amyloid formation, are on the horizon.[4] However, this strategy is vitally dependent upon accurate ways to diagnose who is at risk, and this information is not yet available.

A related idea is to treat presymptomatic individuals at risk for schizophrenia or "odd" individuals who have negative but subsyndromal symptoms in the hope that an atypical antipsychotic may prevent the development of schizophrenia.[6,7] Since the onset of schizophrenia is in adolescence or early adulthood, this approach necessarily involves treating relatively young, otherwise healthy people. Accurate identification of at-risk individuals and treatments that are safe when administered over a lifetime are crucial.

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Take-Home Points

- The pathophysiology of numerous psychiatric disorders may proceed from a silent but vulnerable presymptomatic stage to a prodromal early symptomatic stage and then to an active stage characterized not only by acute symptoms, but also by progressive neurobiological events that may culminate in new symptoms, relapses, and treatment resistance.
- Various hypotheses link Alzheimer's disease, schizophrenia, substance abuse, posttraumatic stress disorder, and chronic pain among others to this pathophysiologic theme.
- Evidence is accumulating that suppression of symptoms early in the course of such disorders may also prevent or mitigate the molecular sensitization and possible neurodegeneration that accompany these disorders. Such actions may interrupt symptomatic progression and therefore be "disease modifying." If so, continuing treatment may interfere with the formation of new symptoms, relapse of old symptoms, and development of treatment resistance.

Currently, we lack adequate markers of vulnerability to schizophrenia to support this approach. Whether atypical antipsychotics, which are capable of suppressing some symptoms in patients with schizophrenia, would be capable of interfering with the pathophysiologic process that leads to the full schizophrenia syndrome is, as yet, unclear.

Treatment at the first inkling of anxiety, or even prior to symptom onset after exposure to trauma, could theoretically prevent the development of PTSD.[8,9] Whether such "inoculation" or "molecular debriefing" would be effective will require better ways to identify who is and is not at risk for developing PTSD symptoms after such environmental exposures. Similarly, treatment that anticipates or reduces subsyndromal symptoms of anxiety from early childhood stressors may also prevent evolution of a full-blown affective or anxiety disorder or a comorbid mixture of the two.[10–12] It is already possible that relieving symptoms of anxiety and depression in adults exposed to chronic environmental stressors may prevent cardiac complications such as myocardial infarction and sudden death.[13,14] Prevention of psychiatric complications by early intervention would be equally useful.

Molecular Sensitization

How do symptoms beget symptoms in so many psychiatric disorders? Theoretically, the pathophysiology of chronic symptom maintenance in psychiatric disorders is linked to molecular events within the CNS that perpetuate symptoms long after the stressor that precipitated them is over. Thus, the CNS appears to react in some cases by altering synaptic "strength" so that specific circuits are more likely to be triggered with lower and lower levels of provocation, to the point of firing spontaneously.[8] This may be the case in the evolution of worry into anticipatory anxiety into provoked and unprovoked panic attacks.[8,9] It may also explain the evolution of chronic pain states in the absence of apparent continuing tissue injury.[16,17] Molecular sensitization also could explain some elements of addiction and substance abuse, including craving and recidivism.[15] The goal is to identify those disorders in which molecular sensitization may perpetuate symptoms and disability and then to intervene to suppress symptoms in the hope of interrupting the process and thus prevent long-lasting and potentially irreversible molecular changes in the nervous system. One troubling change that may accompany chronic symptoms of anxiety and depression is brain atrophy, particularly in the hippocampus.[9] Whether early symptomatic interventions can prevent such atrophy and the neurodegeneration that it may represent is an important issue to resolve.

Error of Commission or Omission?

Removal of current symptomatic suffering in psychiatric disorders may not be merely merciful. It may also preserve the brain's functioning and alter the course of illness and therefore be "disease modifying." If so, treatment interventions may be able to interrupt the natural history of untreated psychiatric illnesses that would otherwise lead to relapse, exacerbation, comorbidity, and treatment resistance. Although we are uncertain that our treatments can in fact alter the course of illness, given the stakes at hand, erring on the side of overtreatment—an error of commission—might be preferable to erring on the side of undertreatment—an error of omission. ◆

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