Affective disorders have hitherto been explained in terms of neurotransmitter deficits or dysfunction. However, research in patients with bipolar disorder shows that, while neurotransmitter dysfunction is clearly important in the presentation of bipolar disorder, it is not the sole explanation for its etiology. Rather than all of the neurotransmitters being independently abnormal in bipolar disorder, perhaps there is something common that regulates all of them? This article will discuss the cellular plasticity and endophenotype models of bipolar disorders as well as the preclinical and clinical research that uses 3 of the most commonly used and effective drugs for bipolar disorder (ie, lithium, valproate, and carbamazepine) to show that bipolar disorder may be a neurologic dysfunction at the cellular level, via anomalies in intracellular signaling. The role of intracellular signaling cascades holds great interest because it may explain why so many neurotransmitter systems are involved in bipolar disorder, the frequent comorbidities with bipolar disorder, some of the physical brain changes observed (also described in this article), why structurally dissimilar drugs can all be effective in treating bipolar disorder, and the lag time between pharmacotherapy initiation and beneficial effect and well as the lag time between treatment cessation and withdrawal effect. Given the complex presentation of mood disorders and the advances in medical research technology, we now are starting to understand the true mechanisms of action of some of our older treatments as we better understand the underlying neurobiology of the disorders. We are on the verge of developing new drugs based on these cellular targets, which, if effective, will allow clinicians to address the fundamental biology of the disorder, rather than the presenting symptoms. (Adv Stud Med. 2006;6(6A):S417-S429)
reuptake inhibitors), affective disorders, in general, have been explained in terms of neurotransmitter deficits or dysfunction. However, research into the neurotransmitters affected in bipolar disorder shows that while neurotransmitter dysfunction is clearly important in the presentation of bipolar disorder, it is not the sole explanation for its etiology. Indeed, the complex clinical presentation of bipolar disorder is one of the first reasons researchers began looking beyond a single neurotransmitter hypothesis.

**The Genetics of Bipolar Disorder: Where Are We?**

Although bipolar disorder is widely regarded as a psychiatrist disorder having amongst the greatest genetic contribution, no genes have been identified definitively; however, there are many promising linkage regions include 4p16, 4q35, 6q22, 8q24, 12q24, 13q31-33, 16p12, 18p11-q12, 18q22-23, 21q22, and 22q11-13. Questions have been raised concerning the definition of genetically relevant phenotypes and the nature of the underlying, partially overlapping sets of susceptibility genes. The diagnosis of bipolar disorder, as defined by current classification schemas including DSM-IV, is based on clusters of symptoms and characteristics of clinical course that do not necessarily describe homogenous disorders, but rather reflect final common pathways of different pathophysiological processes involving genetic and environmental contributors. In addition, there is growing evidence that the boundaries between bipolar disorder and schizophrenia, and between bipolar disorder and recurrent major depression may not be as distinct as previously assumed. Indeed, the pattern of findings emerging from genetic studies shows increasing evidence for an overlap in genetic susceptibility across the traditional classification categories, including association findings at various genes. This should not be altogether surprising because there is not a 1-to-1 relationship between genes and behaviors, thus different combinations of genes (and resultant changes in neurobiology) contribute to any complex behavior (normal or abnormal; Figure 1). It is also critically important to remember polymorphisms in these genes (and those to be discovered) are simply associated with schizophrenia; these genes do not invariably determine outcome, but only lend a higher probability for the subsequent development of illness. In fact, genes will never code for abnormal behaviors per se, but rather code for proteins, that make up cells, forming circuits, that in combination determine facets of abnormal and normal behavior. With mood disorders, there is symptom overlap, thus inheritance of multiple susceptibility genes could lead to similar symptoms among the different mood disorders, with other factors (eg, epigenetic) affecting the ultimate expression of which mood disorder presents. Alternatively, different mutations in the same susceptibility genes could drive the ultimate presentation, similar to the relationship between migraine and epilepsy.

The elucidation of genotype-phenotype relationships is at an early stage, but current findings highlight the need to consider alternative approaches to classification and conceptualization for psychiatric research; as we discuss below, the endophenotype model is one such very promising model.

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**Figure 1. The Heterogeneity and Genetics of Bipolar Disorder**

- **Environmental Factors:** Psychological stress, Sleep deprivation, Reproductive hormones, Stimulants
- **Epigenetic Events:** Early onset WMA, Reward impairment, Cognitive and attention deficits, Reduced anterior cingulate volume
- **Susceptibility Genes:** (? Location of mutation), Protective Genes
- **Modifying Genes:** Imprinting, Variable Haploinsufficiency
- **Schizoaffective, Bipolar I, II, Recurrent Unipolar (severe depression)**

WMA = white matter abnormalities. Data from Hasler et al.
WILL AN ENDOPHENOTYPE STRATEGY FOR BIPOLAR DISORDER LEAD TO A MAJOR PAYOFF?

With respect to additional conceptualizations for psychiatric research, it is becoming increasingly more clear that, although the pathways beginning with genes and then expressed through simple biological processes do not necessarily have a single quantifiable endpoint (i.e., behavior), it may be possible to assay the result of aberrant genes through more biologically “simpler” approaches.9 The term “endophenotype” was described as an internal, intermediate phenotype (i.e., not obvious to the unaided eye) that fills the gap in the causal chain between genes and distal diseases, and therefore may help to resolve questions about etiology.12 The endophenotype concept assumes that the number of genes involved in the variations of endophenotypes representing more elementary phenomena (as opposed to the behavioral macros found in the DSM) are fewer than those involved in producing the full disease.13

Endophenotypes provide a means for identifying the “upstream” traits underlying clinical phenotypes, in addition to the “downstream” biological consequences of genes. The methods available to identify endophenotypes include neuropsychological, cognitive, neurophysiologic, neuroanatomical, imaging, and biochemical measures.9 The information revised in this volume suggests that candidate brain function endophenotypes include attention deficits, deficits in verbal learning and memory, cognitive deficits following tryptophan depletion, circadian rhythm instability, and dysmodulation of motivation and reward. Moreover, reduced anterior cingulate volume and early onset white matter abnormalities represent candidate brain structure endophenotypes. Finally, symptom provocation endophenotypes may be based on bipolar patients’ sensitivity to sleep deprivation, psychostimulants, and cholinergic drugs.9

NEUROTRANSMITTER AND NEUROPEPTIDE ABNORMALITIES IN BIPOLAR DISORDER

In bipolar disorder, studies have produced a surfeit of findings implicating several major neu-
Central to the study of bipolar disorder is the understanding of the brain chemistry and comorbid illnesses. Abnormalities in neurotransmitters and neuropeptides: abnormal levels of norepinephrine, serotonin, acetylcholine, dopamine, glutamate, GABA, corticotropin releasing factor, and cortisol in cerebrospinal fluid, plasma, and/or urine in patients with bipolar disorder. Rather than all of these substances being independently abnormal, perhaps there is something common that regulates all of them? One way to approach this idea is to understand the precise biochemical targets of antimanic drugs and mood stabilizers. Three of the most effective and commonly used drugs for bipolar disorder are valproate (an 8-carbon fatty acid), lithium (a monovalent cation), and carbamazepine (an anticonvulsant with a similar chemical structure to tricyclic antidepressants).

The direct targets of these drugs are listed in the Table. Note that all 3 drugs affect enzymes or proteins involved in intracellular signaling cascades (ie, adenylyl cyclase, phospholipase A and C, cGMP phosphodiesterase, potassium channels, and calcium channels). These cascades are initiated when a membrane-bound receptor receives a signal, which activates an associated G-protein that ultimately affects gene expression, protein function, and perhaps cellular plasticity via these enzymes (Figure 2). The potential role of some of these enzymes is described later in this article.

The role of intracellular signaling cascades holds great interest because it may explain not only all of the neurotransmitter systems involved in bipolar disorder but also all of the comorbidities with bipolar disorder, and some of the physical brain changes observed. Effects on the more general role of intracellular signaling may also explain why structurally dissimilar drugs (ie, lithium, valproate, and carbamazepine) can all be effective in treating bipolar disorder and why there is a lag time between pharmacotherapy initiation and beneficial effect, which is usually several weeks. Similarly, when patients stop taking these drugs, an immediate withdrawal effect is not seen; relapse can be delayed several weeks. The role of intracellular signaling cascades in other chronic diseases have been appreciated in recent years (eg, cancer and diabetes), thus there is some precedent for their role in chronic diseases.

**Protein Kinase C**

Protein kinase C (PKC) is present throughout the body and acts as a major regulator of neuronal excitability. It is activated by amphetamines, cocaine, and stress—factors that typically destabilize bipolar disorder—and plays a central role in phosphorylating proteins, such as neurotransmitter and neuropeptide receptors, signaling molecules, transcriptional factors, and cytoskeletal proteins. It is thought to play an important role in bipolar disorder because of its altered distribution and functioning in postmortem studies of frontal cerebral cortex and blood platelets from bipolar disorder patients. PKC also appears to be the target of lithium’s effect on bipolar mania. Very recent studies in patients with bipolar disorder show that lithium and valproate do indeed alter PKC activity and distribution and that high levels of PKC activity in prefrontal cortex markedly impair behavioral and electrophysiological measures of working memory, possibly contributing to signs of prefrontal cortical dysfunction, such as distractibility, impaired judgment, impulsivity, and thought disorder.

Only 3 PKC inhibitors are currently available for humans: tamoxifen, ruboxistaurin (now approved for diabetic retinopathy), and bryostatin-I. Tamoxifen is an estrogen receptor blocker best known for its use in breast cancer treatment; however, it also inhibits PKC at higher concentrations. Tamoxifen crosses the blood-brain barrier and has good tolerability. In animal models of mania, tamoxifen attenuates the effects of amphetamine (eg, risk-taking behavior and hedonism). A pilot study in 13 women with acute bipolar disorder in the manic phase shows that tamoxifen is able to reduce manic symptoms over 28 days (Figure 3). Current studies are also looking at a possible relationship between PKC polymorphisms and response to lithium or valproate.
**GLYCOGEN SYNTHASE KINASE-3**

Glycogen synthase kinase-3 (GSK-3) is activated by the insulin receptor and it regulates (as its name suggests) glycogen and glucose synthesis as well as nerve growth and survival, circadian rhythms, and targets in the pathophysiology of Alzheimer’s disease (ie, tau phosphorylation, presenilins, and amyloid deposition). It is present in the adult brain and is regulated by amphetamines, estrogen, and glucocorticoids. GSK-3 exerts its effects via promoting apoptosis and inducing changes in gene expression that lead to long-term changes in synaptic connections and modulation of critical neuronal circuits. GSK-3 is a clear target of lithium; in animal models, GSK-3 inhibitors produce an unusual antimanic and antidepressive phenotype. As reviewed by Gould et al, several GSK-3 inhibitors are under investigation now in clinical studies.

**AMPA RECEPTORS**

Glutamate is the major excitatory neurotransmitter and has 4 major types of receptors: N-methyl-D-aspartate (NMDA), \( \alpha \)-amino-3-hydroxy-5-methylisoxazole propionate (AMPA), kainite, and metabotropic. AMPA receptors play a major role in regulating various forms of neural and behavioral plasticity and are involved in both mood disorders and drugs of abuse. AMPA receptors may sit at the crossroads of reward pathways in the brain, which may explain the very high rates of comorbid substance abuse with bipolar disorder. AMPA receptor potentiators reduce the rate of receptor desensitization and/or deactivation in the presence of an agonist (eg, glutamate and AMPA). AMPAkines are a subclass of AMPA receptor potentiators that produce positive modulation of AMPA receptors; they are actively under investigation for the treatment of schizophrenia. Preclinical studies with an AMPAkine have shown reduced synaptic and neuronal degeneration from excitotoxic insults, with other antidepressant effects. Preclinical studies also show that lithium and valproate reduce synaptic expression of a glutamate receptor subunit, while imipramine (an antidepressant that can trigger manic episodes) increased expression of this receptor subunit. AMPAkines have also undergone preliminary evaluation in patients with schizophrenia and we are starting a study with AMPAkines in treatment of depression.

**NMDA ANTAGONISTS**

N-methyl-D-aspartate antagonists are used as anticonvulsants and are now being studied for the treatment of depression. There have been 2 studies of intravenous (IV) ketamine in depression with very exciting results. These studies in treatment-resistant unipolar major depressive disorder revealed robust and rapid antidepressant effects resulting from a single IV dose of an NMDA antagonist; interestingly, onset of antidepressant effects was seen very rapidly (occurring within 4 hours after infusion) and remained significant for 1 week.

**GLUTAMATE RELEASE INHIBITORS**

Riluzole, a neuroprotective agent with anticonvulsant properties, was originally approved for the treatment of amyotrophic lateral sclerosis. It acts by inhibition of the glutamate release, blocking presynaptic calcium and sodium ion channels, by inhibition of the voltage-dependent sodium channels in
mammalian central nervous system (CNS) neurons, and by inhibition of postsynaptic actions by indirect mechanisms. It has been shown to have neuroprotective properties in animal models of Parkinson’s disease, dementia, ischemia, and traumatic CNS injury. It has shown some antidepressant benefit in a pilot study of 14 patients with bipolar disorder (Figure 4). Similarly, lamotrigine, which works presynaptically to regulate glutamate release, has shown significant antidepressive benefit in long-term, randomized, placebo-controlled studies in patients with refractory bipolar I depression.

**Brain Morphology and Mood Disorders**

With computed tomography and magnetic resonance imaging (MRI), we can now see morphologic changes in patients with mood disorders. Although mood disorders are not classic neurodegenerative disorders, such as Alzheimer’s disease, there is measurable brain atrophy and nerve cell loss. In 1997, Drevets et al showed using MRI quantitative loss of prefrontal cortex gray matter in the brains of unmedicated patients with bipolar and unipolar depression by 39% and 48%, respectively ($P < .0002$). Using positron emission tomography, they also showed decreased mean measures of metabolism by 16.3% and decreased mean measures of blood flow by 18.5% in this region of the brain in patients with bipolar disorder, relative to control subjects. Postmortem studies of patients with bipolar disorder also reveal decreased volume, decreases in the number of neurons, and decreases in glia in specific areas of the brain. It is not currently known if these alterations constitute developmental abnormalities conferring vulnerability to severe mood episodes, compensatory changes to other pathogenic processes, or the sequelae of recurrent affective episodes. However, a recent report showed that individuals at high risk of developing mood disorders exhibited reduced subgenual prefrontal cortical volumes, raising the possibility that this endophenotype may constitute a heritable vulnerability factor in these patients. Overall, the data reviewed clearly shows that bipolar disorder, undoubtedly a neurochemical illness, is also a disorder associated with impairments of cellular plasticity.

It has also been hypothesized that the atrophy results from fewer dendritic spine or branches, rather than actual cell death. Of note, these morphologic changes have also been observed in children with bipolar disorder. Studies have shown an association between depression duration and hippocampal volume. MacQueen et al note that reductions in hippocampal volume may not antedate illness onset, but volume may decrease at the greatest rate in the early years after illness onset.

A recent study of medicated and nonmedicated patients with bipolar disorder ($n = 36$) showed the...
extent of neuroplastic changes that may be occurring. Using MRI and voxel-based morphometry, the results showed morphometric abnormalities in brain areas known to exhibit increased metabolism in depression. These areas project to the network of prefrontal cortex and other areas (ie, amygdala, hippocampal subiculum, and ventral striatum) already identified to be altered based on postmortem studies of patients with bipolar disorder. Thus, the morphologic changes in bipolar disorder occur in an extended network of neuroanatomical structures that regulate emotional behavior.57

Preclinical studies in animal models of stress show measurable effects of valproate and lithium in neuronal cell death and expression of neuroprotective peptides. Clinical studies are measuring the effect of bipolar disorder treatments on morphometric brain changes. In a pilot study, 10 patients with bipolar disorder, who were in a depressed state, received 4 weeks of lithium treatment. MRI scans showed lithium significantly increased total gray-matter volume in 8 of 10 patients by a mean of 3%.58 In a similar study, healthy volunteers and patients with newly diagnosed bipolar disorder were treated with lithium for 8 weeks. MRI analysis showed an overall increase in gray matter volume and in specific brain areas in those patients with bipolar disorder, but not in the controls (article in preparation). Collectively, these data suggest a causal relationship between volume changes and mood disorders. However, the observed changes with treatment occur over a period of at least 4 weeks. Therefore, perhaps these treatments restore neuronal connections through which neurotransmitters, such as serotonin and norepinephrine, work. If this theory holds true, this suggests the possibility of altering the long-term trajectory of the illness if patients are treated early enough.

**Future Directions**

Figure 5 shows 11 of the identified cellular targets in the expression of mood disorders; 7 of them are currently being investigated for therapeutic options.5 Of particular interest is the use of transcriptomics (the genome-wide study of mRNA expression levels).59 Technological advances in recent years, with techniques such as differential display and micorarray analysis (Sidebar), allow investigators to measure at a genetic level the pathophysiologic processes of mood

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**DIFFERENTIAL DISPLAY AND MICROARRAY ANALYSIS**

**Differential Display**

In differential display, mRNA from the tissue of interest is isolated and reverse transcribed to form its cDNA. The cDNA sequences are amplified by polymerase chain reaction, and the resultant products are separated on polyacrylamide gels. The bands can then be visualized, for example, by autoradiography. If a band is present in a lane representing one sample and not the other, this band is considered to represent an expressed gene and is excised and further amplified. The amplified gene product is used to screen a library to obtain a full-length cDNA, which, using sequence homology and sequencing, can be used to identify the gene of interest.59

**Microarray Analysis**

This technique builds on other standard technologies that use cDNA to probe immobilized sequences of DNA. Microarray analysis involves immobilization of the entire expressed gene content of an organism (not just a cell type or tissue) onto a large number of locations on a solid support (commonly a derivatized glass microscope slide or silicon wafer), in the form or arrays of dots. Each dot represents a unique sequence. RNA from the tissue of interest is extracted, labeled with a fluorescent dye, and hybridized to the sequences on the array. In theory, the signal detected from each spot would be proportional to the amount of that specific RNA in the original sample, so that the technique shows not only what gene is expressed but also how much. As shown in the Figure, microarray can also show which genes are expressed in response to treatments for bipolar disorder, such as lithium or valproate.59

(Continued on page 424)
disorders and the effects of current medications on these disorders. To date, these techniques have suggested that some of the genes involved in bipolar disorder are in fact classes of genes involved in neurotropy and cell survival, mitochondria function, metabolism, cytoskeleton, and cell signaling. The Sequenced Treatment Alternatives to Relieve Depression study is a multicenter study designed to evaluate the comparative effectiveness of treatments when used either as augmenting treatments or as new treatments when remission is not achieved with citalopram. Clinical outcomes include symptoms, function, side effect burden, quality of life, and participant satisfaction. We will be obtaining the DNA from about 2000 of these study patients to perform differential display and microarray analysis.

CONCLUSIONS

Our understanding of the pathophysiology of mood disorders has moved beyond simple explanations of neurotransmitter deficiencies. Given the complex presentation of mood disorders and the advances in medical research technology, we now are starting to understand the true mechanisms of action of some of our older treatments as we better understand the underlying neurobiology of the disorders. These pursuits are not strictly an academic interest. An increasing amount of data is suggesting a number of new drugs for cellular targets, which, if effective, will allow clinicians to address the fundamental biology of the disorder, rather than the presenting symptoms.

DISCUSSION

MOLECULAR MECHANISMS OF DRUGS FOR BIPOLAR DISORDER

Dr Treisman: Have you studied whether there’s a difference between lithium and valproate in terms of their antidepressant effects?

Dr Manji: Yes, but at this point it’s clearly very speculative. In some parts of the brain, we see an equivalent effect, but in the frontal cortex, lithium seems to have more of a neurotrophic effect than valproate. The longitudinal data in humans thus far are only with lithium, but it’s interesting that the left subgenual prefrontal cortex is one of the places that seems to correlate with lithium’s antidepressant response. Therefore, that may be something that dif-

(Continued from page 423)
ferentiates the 2 agents and may explain lithium’s antidepressant effects.

Dr Kaye: Do you think tamoxifen is working through cortisone, which we have historically thought is probably not good for mood, or through this PKC inhibitory effect, or are they the same?

Dr Manji: In our studies, the animal behaviors responsive to tamoxifen really do look like they’re PKC-mediated. In animals, we use PKC inhibitors (which are very clean) and show that the inhibitors mimic tamoxifen’s beneficial antimanic effects. We have not looked as much at glucocorticoids; we’ve looked more into estrogen with tamoxifen.

In the human studies, it’s obviously very difficult. We only chose tamoxifen because it’s available for humans and happens to be a PKC inhibitor, even though it is used for its estrogen receptor blockade. We’re seeing just as good an effect in men as in women, but that doesn’t answer your original question. With tamoxifen, we’re talking about estrogen receptor blockade, not circulating estrogen, thus it doesn’t necessarily tell you that it’s not an estrogen receptor effect. Most of our studies suggest that this antimanic effect is, in fact, due to PKC inhibition, but you’ll only know for sure when you give one of the cleaner PKC inhibitors. We’re working with the National Cancer Institute on this right now. Anecdotally, we’ve heard about many women with bipolar disorder who develop breast cancer, go on tamoxifen, and that tends to destabilize the bipolar illness.

Dr Kaye: Do any of our current drugs affect GSK-3 and are there any differences between currently available agents?

Dr Manji: The only drug that’s a direct GSK-3 inhibitor is lithium. That’s one of the reasons it may be tried as a modifier of disease progression in Alzheimer’s disease. GSK-3 inhibitors and lithium have a dramatic effect on Alzheimer’s disease pathophysiology in animal models of Alzheimer’s disease. Lithium is the only direct GSK-3 inhibitor, but it’s looking like many other compounds can affect GSK-3, such as valproate. Recent studies have suggested that atypical antipsychotics may also have some effect on GSK-3, but overall antipsychotics have not been as well studied in this area. In some of our studies, clozapine behaves more like lithium than olanzapine or risperidone, or other antipsychotics.
**Dr Leibenluft:** One of the big trends in treatment of bipolar disorder has been greater use of atypical antipsychotics. Do these drugs show any of the same GSK-3 inhibitory effects as lithium and valproate?

**Dr Manji:** It has some of the same effects, but not all. I am somewhat hesitant to say, as others are saying, that any antipsychotic is more than just antimanic. The data suggest that some of them have more than an antimanic effect, and we still need to see those data. Olanzapine does appear to have a modest antidepressant effect, but is it more than just an antimanic effect? We're starting to do some studies with quetiapine, which has so far stood out, in our opinion, as possibly having more than just antimanic effects. It may also be useful as monotherapy for depression.

**Dr Leibenluft:** There's also the issue about prophylaxis. To be truly a mood stabilizer, it would have to prevent mood episodes. Are you saying that perhaps there's been a bit too much labeling of atypical antipsychotics as mood stabilizers? Do you think that jumps ahead of where the treatment data really are? And, from a mechanistic perspective, what are your thoughts on atypical antipsychotics with regard to the different pathophysiological pathways you've talked about?

**Dr Manji:** We can certainly show many effects. PKC inhibition does appear to be a common effect of many antipsychotics, typical or atypical. You can categorize compounds as to which are antimanic and which are promanic, and they separate along those lines in their effects on PKC. In some of these neurotrophic signaling cascades, we don't see as robust a distinction. Our approach hasn't been to try and catalog every drug with these effects. The flip side would be that not every drug has to work on regulating plasticity. Its effect may be due to a common downstream mechanism. You can get there multiple ways.

**Pathological Mechanisms**

**Dr Adams:** You had mentioned that when patients stop taking their antidepressant, the relapse is not immediate; it's delayed. I've probably seen that at least 100 times where the patient has stopped the antidepressant and said, “I was okay, and thought I didn't need it anymore,” and they relapse. And, it's not just because the half-life of their medication was long.

**Dr Manji:** That's exactly what we intend to show. This is, in fact, a cascade. There is a lag period; if the patient discontinues the medication, the cascade has to unravel before they get worse. In fact, when they discontinue medication, often they feel better because they don't have side effects. But, then the cascade unravels and they relapse. That's one of the biggest challenges we face with compliance: patients linking medication cessation and worsening of symptoms. It's not like missing the insulin dose. The whole cascade has to unravel.

I don't want to oversell some of these neurotrophic effects because we need many more studies, but some of these treatments may be providing neuroprotective effects. We may not know until we have the 20-year longitudinal data to show that the drugs are providing some protection against the ravages of the illness. Perhaps we can use that information to help increase compliance, to explain to patients that although the medications have side effects, they need to keep taking them to avoid some of the other long-term complications, as we have found with treating diabetes.

**Dr Ostacher:** I use the analogy of going to the gym. When you go to the gym to lift weights, the first day you do it, you're just tired, not stronger. But, if you do it regularly for a month, you're much stronger at the end of that month, and just because you didn't lift weights one day doesn't mean you're not going to be strong that day. Patients can get their heads around that without understanding the molecular biology of it. It often helps people to understand that stopping the drug will lead to diminishing of this effect over time.

**Dr Treisman:** On the other hand, sometimes if you make an analogy like that people will ignore you, but if you use the actual scientific terms, such as glutamate, dopamine, acetylcholine, and PKC, people will pay attention.

**Dr Leibenluft:** The literature on lithium and memory is murky. Do you not believe the literature that lithium has an adverse impact on memory? Is that based on your findings, which argue the reverse? Or is it because there are many different kinds of memory?

**Dr Manji:** I think some patients do experience some of this memory deficit; I view it as a side effect that is occurring separate from the beneficial effects. PKC in the hippocampus has certainly been implicated in learning and memory. The memory problems occurring here and now may potentially have nothing to do with the long-term neurotrophic effects.

We've also attempted to find out whether you need the full antimanic dose to have the neurotrophic
effects. In the Alzheimer’s disease study and in the schizophrenia study, they’re actually using low doses. We find that, in animals, plasma levels that are about 50% to 33% of what we traditionally think of as therapeutic levels are enough to upregulate some of these growth factor cascades and bring about some of these long-term changes. Therefore, it may well be that if you’re using it mainly for neurotrophic benefit (and not immediate treatment of mania), you can get away with using lower doses and not have some of the side effects. That’s why they’re looking at lower doses in the clinical studies in other disorders, as a way of making these drugs more tolerable.

COMORBIDITIES

Dr Adams: You were talking about the intracellular signaling cascades, and the fact that there are shared pathways between different illnesses. We often wonder why we can use an antidepressant to treat migraines, chronic pain, and depression. That may be a way that we could explain it to patients, if that was borne out.

Dr Manji: I think that will ultimately be the case; that the comorbidities we see are not by accident. There may be a shared pathophysiology and the same may be true of the treatments. In fact, with these drugs, you’re targeting some of these intracellular cascades, which play a role in multiple illnesses, and that’s how you’re getting some of the benefits, not just as a nonspecific sedating agent. We are also trying to go further with the genetic studies, with patients who have both bipolar disorder and migraines. We’re looking to see if they have white matter hypointensities on MRI. Are they a subpopulation that has some common pathophysiology? Researchers are now asking those kinds of questions to see if they can tease apart pathways that may be shared. That’s become more relevant in the area of drug abuse (ie, that there is some reward pathway disturbance that predisposes to developing bipolar disorder and drug abuse), and the AMPA receptor trafficking is one of the areas that’s looking quite interesting.

We are working with Jules Angst, MD, to see if naturalistic lithium treatment for 30 years has any effect on the likelihood of developing Alzheimer’s disease. It’s a “dirty study.” People are treated with lithium and with many other types of drugs (eg, antipsychotics and antidepressants), but when you control for all of those other factors, the lithium-treated group tends to have a lower incidence of Alzheimer’s disease. And, it’s not just restricted to the lithium-responsive patients.

Dr Angst has data looking at all-cause mortality with lithium treatment in patients with bipolar disorder. We see in patients with unipolar depression a reduction in suicides but not in all-cause mortality.

Dr Ostacher: In the Swedish study, the excess mortality in unipolar depression was almost all due to unnatural causes (ie, accidents and suicides), and in bipolar depression it was almost all due, except in the first few years, to natural causes.44

Dr Manji: As we are using atypical antipsychotics more as mood stabilizers, we are seeing the deleterious effects (dyslipidemia and metabolic abnormalities), but there’s some reason to believe that some of our agents, such as lithium, may also reduce all-cause mortality. They do have cardioprotective effects. We don’t want to overgeneralize, but because we are seeing this protection, we’re asking is it simply because there is reduced stress or are these drugs targeting some fundamental process that has beneficial effects beyond the brain.

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