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Early Intervention in Bipolar Disorder, Part II: Therapeutics

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Abstract

Recent evidence has shown that early pharmacological and psychosocial treatment dramatically ameliorates poor prognosis and outcome for individuals with psychotic disorders, reducing conversion rates to full-blown illness and decreasing symptom severity. In a companion paper, we discussed methodological issues pertaining to early intervention in bipolar disorder (BPD), reviewed clinical studies that focus on high-risk subjects as well as first-episode patients, and reviewed findings from brain imaging studies in the offspring of individuals with BPD as well as in first-episode patients.

In this article, we discuss how drugs that modulate cellular and neural plasticity cascades are likely to benefit patients in the very early stages of BPD, because they target some of the core pathophysiological mechanisms of this devastating illness. Cellular and molecular mechanisms of action of agents with neurotrophic and neuroplastic properties are discussed, with a particular emphasis on lithium and valproate. We also discuss their potential use as early intervention strategies for improving symptoms and functioning in patients in the earliest stages of BPD, as well as high-risk individuals.

6 Keywords

Early intervention; bipolar disorder (BPD); first-episode; neurotrophic effects; lithium; valproate

Introduction

As Part I of these companion papers noted, compelling recent evidence has shown that early pharmacological and psychosocial treatment dramatically ameliorates poor prognosis and outcome for individuals with psychotic disorders (1,2). The previous article discussed methodological issues pertaining to early intervention in bipolar disorder (BPD), reviewed clinical studies that focus on high-risk subjects and first-episode patients, and reviewed the findings from brain imaging studies in the offspring of individuals with BPD and in first-episode patients.

This article highlights the role of neurotrophic agents as potential treatments for the early phases of BPD. For instance, the mood stabilizers lithium and valproate, as well as new experimental treatments that target the glutamatergic system, have been shown to exert effects on cellular plasticity and resilience (3). Evidence does suggest that these neurotrophic treatments can improve symptoms and functioning, at least in some patients

who are at risk for developing BPD, and might thus be valuable therapeutic options in first-episode or high-risk individuals (4).

The field of early intervention in BPD is still in its infancy, and the conversion rate—the transition from prodromal symptoms to full-blown BPD—observed in the few prospective studies that have been conducted so far in high-risk subjects is not higher than 30% (5,6); this low conversion rate underlines the limitations of approaches that rely only on clinical presentation and family history to identify subjects who might benefit from early intervention. Furthermore, because the long-term effects of psychotropic drugs on brain development are still unknown, efforts have focused on detecting those individuals vulnerable to developing full-blown psychotic syndromes who display subthreshold symptoms, in order to avoid exposing subjects unnecessarily to the risks associated with the treatments themselves (see “Early Intervention in Bipolar Disorder, Part I: Clinical and Imaging Findings” for a more thorough discussion of this topic). There is a clear need to integrate the sparse clinical data with other biological markers to identify patients who are “truly” vulnerable to developing BPD. Such biological markers might include imaging abnormalities (see “Early Intervention in Bipolar Disorder, Part I: Clinical and Imaging Findings”) and genetic susceptibility alleles. In this regard, the recent use of whole-brain genome association approaches for studying the genetics of BPD, along with more rigorous hypothesis-testing designs (7,8), has the potential to help identify SNPs that confer significant risk for developing BPD.

Pharmacological strategies in the early phases of BPD

Few treatment trials in BPD have specifically targeted first-episode or even “new” cases of BPD. Although there is a consensus that the earlier targeted treatment begins the better, much is still unknown about the most appropriate treatments for this population and the timing of their administration (9). The timing of neurobiological changes suggests that the optimal period for neuroprotective interventions is either the prodromal phase or during the early stages of illness, when many patients achieve remission and structural and functional brain changes are, for the most part, still limited (4) (See “Early Intervention in Bipolar Disorder, Part I: Clinical and Imaging Findings” for a thorough discussion of these changes).

Interestingly, many of the neurotrophic and neuroprotective agents used to treat BPD, including antidepressants, mood stabilizers, atypical antipsychotics, and perhaps a number of experimental agents currently under investigation, exert significant effects on signaling pathways that regulate cellular plasticity. Their use early in the course of BPD presents a valuable therapeutic option as a preventive strategy and shifts the therapeutic focus from end stage-based treatment models to the emerging phase of BPD (4,10-13). Indeed, preliminary studies indicate that valproate, a commonly used mood stabilizer, and olanzapine, an atypical antipsychotic, work well for the offspring of individuals with BPD who have non-bipolar psychiatric diagnoses (14), as well as persons experiencing their first episode of an affective psychosis (15). Valproate also seems to reduce aggression in symptomatic young patients at risk for BPD (16). However, a recent study by Findling and colleagues (17) failed to show any benefit for valproate monotherapy in patients with BPD not otherwise specified (BPD-NOS) or cyclothymia who had at least one parent with BPD. Other negative evidence is provided by a study that failed to show that treatment with the mood stabilizer lithium was superior to placebo in a group of BPD patients who had a major depressive episode and a positive family history of mood disorders (18). However, lithium’s lack of efficacy in the early stages of BPD cannot be inferred from this negative finding, as the study was short (six weeks), and drug titration reached the targeted lithium levels only at week three. Moreover, the most compelling evidence about lithium’s efficacy regards its antimanic and prophylactic properties rather than its antidepressant ones (see (19) for a review).

A recent open-label study also suggests that quetiapine might be a useful early intervention strategy in high-risk populations. Quetiapine significantly reduced mood symptoms at week 12 in a cohort of 20 offspring of BPD-I patients; the offspring were diagnosed with mood disorders other than BPD-I (20).

More randomized controlled trials are needed to evaluate the potential effectiveness of drug treatment in high-risk populations. Also, because reduction of symptoms in the short-term does not guarantee functional improvement in later phases of the illness (21,22), the therapeutic effects of these drugs will need to be evaluated over the long term. Below, we review several agents that have been shown to have neuroplastic and neuroprotective properties in animal or human studies (see Table 1).

Neuroprotective and neurotrophic treatments in the early phases of BPD

Research into the effects of structurally diverse mood stabilizers such as lithium and valproate suggests that these agents share some potent neurotrophic and neuroprotective properties (23,24). Bcl-2 is a major anti-apoptotic protein that inhibits both apoptotic and necrotic cell death induced by diverse stimuli (25-27) (reviewed in greater detail below). Chronic treatment of rats with therapeutic doses of lithium and valproate has been shown to double Bcl-2 levels in the frontal cortex, an effect due primarily to a marked increase in the number of Bcl-2 immunoreactive cells in layers II and III of the anterior cingulate cortex (28-30). Interestingly, the importance of neurons in the anterior cingulate has recently been emphasized in neuroimaging studies of BPD, particularly because these areas provide connections with other cortical regions and are targets for subcortical input (31). Chronic lithium was also found to markedly increase the number of Bcl-2 immunoreactive cells in the dentate gyrus and striatum (32).

Subsequent to these findings, lithium was shown to increase Bcl-2 levels in C57BL/6 mice (28), in human neuroblastoma SH-SY5Y cells in vitro (33), and in rat cerebellar granule cells in vitro (28). Overall, the data clearly show that chronic lithium robustly increases levels of the neuroprotective protein Bcl-2 in areas of rodent frontal cortex, hippocampus, and striatum in vivo, and in cultured cells of both rodent and human neuronal origin in vitro. Furthermore, at least in cultured cell systems, lithium reduces levels of the pro-apoptotic protein p53.

Bcl-2 is a major neurotrophic protein

Bcl-2 is expressed in the rodent and mammalian nervous system and is localized to the outer mitochondrial membrane, endoplasmic reticulum, and nuclear membrane. It is now clear that Bcl-2 is a protein that inhibits both apoptotic and necrotic cell death induced by diverse stimuli ((25-27) and references therein). Several cellular mechanisms are likely involved in mediating Bcl-2's protective effects, including sequestering the proforms of caspases, inhibiting the effects of caspase activation, antioxidant effects, enhancing mitochondrial calcium uptake, and attenuating the release of calcium and cytochrome c from mitochondria (reviewed in (25,26,34,35)). A role for Bcl-2 in protecting neurons from cell death is now supported by abundant evidence; Bcl-2 has been shown to protect neurons from a variety of in vitro insults including growth factor deprivation, glucocorticoids, ionizing radiation, and oxidant stressors such as hydrogen peroxide, *tert*-butylhydroperoxide, reactive oxygen species, and buthionine sulfoxamine (25,26). In addition to these potent in vitro effects, Bcl-2 also prevents cell death in numerous studies in vivo.

In the absence of pharmacological means of increasing CNS Bcl-2 expression (until recently), all the studies have hitherto used transgenic mouse models or viral vector mediated delivery of the Bcl-2 gene into the CNS. In these models, Bcl-2 over-expression

has been shown to prevent motor neuron death induced by facial nerve axotomy and sciatic nerve axotomy, to save retinal ganglion cells from axotomy-induced death, to protect cells from the deleterious effects of MPTP or focal ischemia, and to protect photoreceptor cells from two forms of inherited retinal degeneration; interestingly, neurons that survive ischemic lesions or traumatic brain injury in vivo show upregulation of Bcl-2 ((27,35-40), and references therein).

Overexpression of Bcl-2 has also recently been shown to prolong survival and attenuate motor neuron degeneration in a transgenic animal model of amyotrophic lateral sclerosis (ALS) (41). Not only does Bcl-2 overexpression protect against apoptotic and necrotic cell death, it can also promote *regeneration* of axons in the mammalian CNS, leading to the intriguing postulate that Bcl-2 acts as a major regulatory switch for a genetic program that controls the *growth* of CNS axons (37). Because Bcl-2 has also recently been shown to promote neurite sprouting, increasing CNS Bcl-2 levels may represent a very effective therapeutic strategy for the treatment of many neurodegenerative diseases (37).

Mood stabilizers also regulate GSK-3, another major neuroprotective cascade

Another major pathway likely to be involved in lithium's neuroprotective effects is the inhibition of the glucose synthase kinase-3 signaling cascade (GSK-3), a major regulator of apoptosis and cellular plasticity and resilience (see (42) for a review). While older literature suggests that lithium interacts with glycogen synthase, it was not until 1996, when Klein and Melton made the seminal observation that lithium inhibited the action of GSK-3, that the direct inhibition of this enzyme by lithium was identified (43). GSK-3 is now known to regulate diverse functions in the adult mammalian brain, and to exert major cytoprotective effects (reviewed in (44-46)). Indeed GSK-3 is one of the kinases responsible for the aberrantly hyperphosphorylated form of the microtubule-associated protein, *tau*, a major constituent of neurofibrillary tangles (47). GSK-3 has also been shown to play a major role in amyloid deposition (48); thus GSK-3 inhibition regulates the two major pathways implicated in long-term disease progression in degenerative diseases.

Lithium exerts robust neuroprotective effects in preclinical paradigms

In view of their major effects on Bcl-2 and GSK-3, it is not surprising that recent studies have investigated lithium and valproate's potential neuroprotective effects in a variety of preclinical paradigms, demonstrating robust neuroprotective properties against a number of insults (reviewed in (33,44,49)). Notably, lithium pretreatment has been demonstrated to protect cultured brain neurons from glutamate-induced, N-methyl-D-aspartate (NMDA) receptor-mediated apoptosis (reviewed in (49)). Excessive NMDA throughput is likely involved in stress-induced hippocampal atrophy, and has been implicated in the pathogenesis of a variety of neurodegenerative diseases such as stroke, Huntington's disease, ALS, spinal cord injury, brain trauma, and cerebellar degeneration. In cultured neurons, lithium-induced neuroprotection against glutamate excitotoxicity occurs within the therapeutic concentration range of this drug and requires five to six days of pretreatment for maximal effects. The lithium neuroprotection requires BDNF induction and activation of its receptor TrkB, and is associated with upregulation of Bcl-2, downregulation of the pro-apoptotic proteins p53 and Bax, and inhibition of caspase-3. Treatment of cultured neurons with other GSK-3 inhibitors or transfection with GSK-3 siRNA mimics the neuroprotective effects of lithium (50), again suggesting a critical role of GSK-3 in mediating neuroprotection.

Lithium also shows beneficial effects in a number of animal models of neurodegenerative diseases. For example, pre- or post-insult treatment with lithium suppresses cerebral ischemia-induced brain infarction, caspase-3 activation, and neurological deficits in rats, and

these neuroprotective effects are associated with induction of heat shock protein 70 and decreased expression of Bax (51,52). Several independent studies demonstrated that lithium has neuroprotective effects in animal and cellular models of Alzheimer's disease, Huntington's disease, Parkinson's disease, retinal degeneration, spinal cord injury, and HIV infection (reviewed in (49)). Notably, Phiel and colleagues (2003) demonstrated that therapeutic concentrations of lithium, by acting on GSK-3, blocked the production of A β peptides by interfering with amyloid peptide precursor protein (APP) cleavage at the γ -secretase step. Furthermore, lithium also blocked the accumulation of A β peptides in the brains of mice that overproduce APP (48).

Similarly, lithium administration has been shown to significantly lower levels of phosphorylation at several epitopes of *tau* known to be hyperphosphorylated in Alzheimer's disease and to significantly reduce levels of aggregated, insoluble *tau* (53). Furthermore, levels of aggregated *tau* correlated strongly with degree of axonal degeneration, and lithium-treated mice showed less degeneration if administration was started during early stages of tangle development. Most recently, it has been demonstrated that lithium is neuroprotective in APP transgenic mice (54). Thus, mice treated with lithium displayed improved performance in the water maze, preservation of the dendritic structure in the frontal cortex and hippocampus, and decreased *tau* phosphorylation (54). Chronic lithium treatment also protects against neurodegeneration and improves spatial learning deficits in rats perfused with A β fibrils (55).

Human studies supporting lithium's neuroprotective effects

Human studies have also provided indirect evidence for the neurotrophic effects of lithium. Chronic lithium treatment at therapeutic levels was associated with a five percent increase in N-acetylaspartate (NAA) levels in BPD patients and in healthy controls; the NAA increase was correlated with an increase in total brain grey matter content (56). Chronic lithium has further been shown to induce a three percent increase in grey matter volume in patients with BPD, suggesting that some of its long-term therapeutic effects might be mediated by its neurotrophic properties (57). In addition, Drevets and colleagues (1997) found that reduced subgenual prefrontal cortex volume in patients with familial mood disorders was apparent in subjects treated with SSRIs but not in those treated with lithium (58), thus implying that lithium might prevent the cellular atrophy underlying these volumetric abnormalities. Furthermore, several independent cross-sectional studies have now demonstrated that lithium-treated patients with BPD show greater gray matter volumes than BPD patients not treated with lithium (59-62). More recently, it was found that gray matter volume in the prefrontal cortex and left subgenual prefrontal cortex was increased in BPD subjects treated with chronic lithium for four weeks, and that the increase in gray matter volume was more pronounced in lithium responders (Moore and colleagues, unpublished data).

Valproate

Valproate has been shown to induce hippocampal neurogenesis and to promote neuronal maturation in mice (reviewed in (63)). Moreover, as discussed above, chronic treatment with valproate increases Bcl-2 expression in the frontal cortex, the striatum, and the hippocampus (28,30). In view of the important role that the extracellular receptor coupled kinase (ERK) signaling cascade plays in mediating long-term neuroplastic events, a series of studies were undertaken to investigate the effects of lithium and valproate on this signaling cascade (64,65). These studies showed that lithium and valproate, at therapeutically relevant concentrations, robustly activate the ERK MAPK cascade in human neuroblastoma SH-SY5Y cells (64,65). Recent follow-up studies showed that, similar to the effects observed in neuroblastoma cells in vitro, chronic lithium and valproate also robustly increase the levels

of activated ERK in areas of the brain that have been implicated in the pathophysiology and treatment of BPD—the anterior cingulate cortex and hippocampus (64).

Valproate also shows neuroprotective properties against oxidative stress (66), intracerebral hemorrhage (67), and glutamate-induced neurotoxicity (68). Other downstream targets of valproate include the GSK-3 signaling cascade, on which valproate exerts an inhibitory effect that might be mediated by both direct and indirect mechanisms (42), and that might thus be relevant to valproate's neurotrophic properties.

Notably, a recent study showed that valproate upregulates the expression of glial cell line-derived neurotrophic factor (GDNF) as well as BDNF from astrocytes (69), suggesting that neuronal-glial cell interplay might be a major target for current and future drug development in BPD. BDNF is a secretory neurotrophin that is critical for neuronal survival and differentiation. Extensive experimental evidence has implicated BDNF in affective disorders, anxiety disorders, and the mechanism of action of antidepressants (see (70) for an excellent review of BDNF).

Nevertheless, evidence for valproate's neuroplastic/neurotrophic properties in humans remains unproven. Silverstone and colleagues (2003) failed to show greater NAA levels in euthymic patients with BPD treated chronically with valproate compared to healthy controls, although lithium-treated patients had NAA levels that were significantly higher than healthy controls (71). However, because this study suffered from some limitations (MRS spectra were acquired just once), further studies are needed to determine valproate's neurotrophic effect in humans.

Glutamatergic modulating agents

Recent preclinical and clinical evidence suggests that the glutamatergic system is involved in the pathophysiology of both BPD and major depressive disorder (MDD), and that abnormalities of glutamatergic transmission may underlie the impairment in brain neuroplasticity and cellular resilience observed in BPD (72-74). Glutamatergic excitotoxicity is likely a major contributor to volumetric and neuropathological abnormalities in BPD (see "Early Intervention in Bipolar Disorder, Part I: Clinical and Imaging Findings" for a more thorough discussion of this topic). Recently, several promising agents that modulate the glutamatergic system have been evaluated as potential neurotrophic/neuroplastic drugs. Although none have been tested specifically in first-episode BPD populations, these agents have been investigated in clinical trials as antidepressant and mood stabilizing agents for patients with various mood disorders.

Lamotrigine—Lamotrigine is an anticonvulsant with antidepressant properties that is currently approved by the Food and Drug Administration (FDA) as a maintenance treatment for BPD-I. Several randomized controlled trials have shown that lamotrigine is effective in treating patients with bipolar depression and those with rapid cycling. One of the most important mechanisms of action for lamotrigine's therapeutic effects is the inhibition of glutamate release through sodium and calcium channel blockage (75). Lamotrigine has shown neuroprotective properties in animal models of ischemia (76) and kainate-induced neurotoxicity (77). However, a recent study found that lamotrigine had no antiapoptotic activity mediated by the ERK/MAPK pathways, suggesting that other mechanisms likely contribute to its therapeutic effects (78). In vivo evidence of the neurotrophic effects of lamotrigine in humans is lacking.

Riluzole—Riluzole is a neuroprotective agent with anticonvulsant properties that easily crosses the blood-brain barrier and is approved by the FDA for the treatment of ALS. It inhibits glutamate release and enhances AMPA trafficking (79). Riluzole showed

antidepressant properties in open-label trials for both MDD (80) and bipolar depression (81), and appears to be an effective augmentation strategy in treatment-resistant MDD (82). It is neuroprotective in animal models of Parkinson's disease, NMDA receptor hypofunction, neurotoxicity, ischemia, and traumatic CNS injury (reviewed in (83)).

Because it increases the expression of BDNF, riluzole also appears to have neurotrophic properties. A single intraperitoneal injection of riluzole raised BDNF levels localized in dentate granule neurons, the hilus, and the stratum radiatum of the CA3 region in rats (84). Furthermore, repeated injections of riluzole resulted in prolonged elevation of hippocampal BDNF, and were associated with increased numbers of newly generated cells in the granule cell layer in rats (84). Recent spectroscopic studies of patients with ALS showed that both chronic (three weeks) and acute (one day) treatment with riluzole significantly increased NAA levels in the precentral gyrus (85,86). Another recent study showed that riluzole increased hippocampal NAA in patients with generalized anxiety disorder who respond to riluzole's anxiolytic effects (87). Taken together, these studies suggest that riluzole positively modulates neuronal viability.

Other glutamatergic agents—Several NMDA receptor complex antagonists with neurotrophic/neuroplastic properties have been evaluated as potential treatments in mood disorders, including memantine, MK-801, and NR-2B antagonists. All these agents show antidepressant properties in animal models of MDD, and below we review some of the data regarding their utility in humans. Most of this work, however, has focused on MDD, and further data are needed to evaluate whether glutamatergic system modulators can play a therapeutic role in BPD.

Memantine has been shown to exert neuroprotective effects against ischemia and CNS traumas (reviewed in (88)), however, a randomized controlled trial of memantine failed to show superiority over placebo in patients with MDD (88). In contrast, a small (N=8) subsequent open-label trial with memantine showed good antidepressant efficacy in patients with MDD (89). Differences in baseline clinical severity of the current episode, including treatment resistance, or the fact that in the latter study a flexible-dosage of memantine was allowed, might explain the inconsistency of these two findings. The effectiveness of memantine as an antidepressant treatment should be further investigated in future studies.

A recent clinical trial showed that the non-selective NMDA antagonist ketamine exerts a robust antidepressant effect within two hours in patients with severe, treatment-resistant MDD (90). The antidepressant effect lasted up to seven to 10 days. Ketamine's antidepressant effects are likely to be initiated by antagonism of the NMDA receptor complex, but are ultimately determined by an increase in glutamatergic transmission on non-NMDA receptors, such as AMPA receptors (91). Because ketamine's psychotomimetic effects limit its use as a chronic antidepressant agent, more selective NMDA receptor antagonists are currently under study.

Atypical antipsychotics—Neuroprotective properties have also been demonstrated for the atypical antipsychotic olanzapine against various insults, such as oxidative stressors (92,93) and ischemia (94). Olanzapine also upregulates the expression of Bcl-2 in rat frontal cortex and the hippocampus, as well as the expression of BDNF in the hippocampus (95,96).

Moreover, a recent study showed that olanzapine increases NAA in the prefrontal cortex of adolescent patients with mania who remitted compared to nonremitters (97). Although suggestive of a possible in vivo neurotrophic effect, this finding needs further replication, as the primary aim of the study—a NAA increase following olanzapine treatment, independent from clinical change—was negative. In fact, it is possible that the NAA increase seen in

responders might be more related to the improvement in mood per se than to olanzapine's neurotrophic properties. Despite its therapeutic potential, the metabolic side effects of olanzapine, which seem to be even more pronounced in younger populations (98), put into question its risk/benefit ratio as a useful early intervention strategy in patients at risk for BPD (99). Moreover, the long-term consequences of weight gain and metabolic side effects due to atypical antipsychotics on brain development and cerebral maturation in young populations are essentially unknown; thus, safety data need to be carefully evaluated for each individual drug before testing its clinical efficacy.

Studies have suggested that other atypical antipsychotics, such as risperidone and quetiapine, have neuroprotective properties that might be relevant to their clinical efficacy in patients with psychotic disorders (100,101). For instance, one study found that the effects of stress-induced decreases of BDNF could be prevented by pre-treatment with quetiapine (102). Thus, these agents might be worth investigating for early intervention in BPD.

Non-pharmacological interventions

Non-pharmacological strategies can also be considered as useful adjuncts to pharmacological early intervention in high-risk populations. Several studies have highlighted the impact of various psychosocial stressors on the onset, recurrence, and outcome of patients with BPD (103). Cognitive behavioral therapy, psychoeducation, and interpersonal therapy might thus be useful interventions to reduce the vulnerability to developing BPD in subjects with a high genetic loading. The role of these psychotherapies in ameliorating course of illness in patients with BPD has been firmly established in the last decade (104-108); however, they still need to be validated in high-risk samples. Also, repetitive transcranial magnetic stimulation (rTMS), which shows putative neurotrophic properties in patients with MDD (109,110), is another somatic treatment option that might be worth testing as an early intervention strategy in BPD.

Summary of neurotrophic/neuroplastic drugs for early intervention in BPD

Several agents have shown neuroplastic and neuroprotective properties in animal paradigms; lithium, valproate, riluzole, and olanzapine have also shown indirect neurotrophic properties in humans and might be valuable therapeutic options in high-risk patients. However, very few treatment studies in subjects at high risk for developing BPD have been conducted. Efficacy data, as well as tolerability and side effect profiles, warrant investigation in patients who are at risk for BPD or are experiencing their first episode of illness. In fact, adolescent and young adult patients might be particularly at risk for potential endocrine and metabolic adverse effects of psychiatric medications (111).

Moreover, some of the therapeutic properties of agents with neurotrophic/neuroplastic factors discussed above are likely to be mediated, at least in part, by the effects of genes involved in major signaling pathways cascades targeted by these agents. For example, associations between treatment response to lithium and polymorphisms involving some CREB and GSK-3 SNPs have been recently identified (112,113). Future studies are warranted to identify susceptibility alleles and biomarkers of treatment response, not only in patients with full-blown BPD, but also in high-risk and prodromal patients.

Future perspectives

BPD is associated with considerable mortality, morbidity, and poor psychosocial outcome (114-116). Although individuals with BPD were long believed to recover completely between episodes, there is accumulating evidence of enduring neuropsychological and functional deficits in patients with BPD, and evidence of structural abnormalities in neuroimaging studies, particularly related to treatment-resistant patients (117). This has led

both clinicians and researchers to focus on the earliest stages of the illness to study psychopathological prodromes and biological developmental abnormalities that could guide new treatment algorithms in high-risk populations.

Pharmacological treatments with neuroprotective and neurotrophic agents hold the promise to slow the neurodevelopmental/neurotrophic brain abnormalities already evident in the early stages of BPD and to prevent or even reverse the impairment in neuroplasticity and cellular resilience that is evident from the beginning of the illness. Furthermore, there is increasing evidence that existing and well-established agents—such as lithium and valproate—have significant neuroprotective properties. What remains unclear is the extent to which their neuroprotective processes are directly related to the emergence of BPD (4).

Given the varied nature of presentation and variability in course of BPD, separating and appropriately treating at-risk individuals constitutes a serious challenge. Careful selection of the subjects who might benefit from early intervention and appropriate study designs to correctly evaluate outcome, though ongoing, are still needed. Prospective large-scale studies of high-risk populations with appropriate biological markers, such as volumetric or spectroscopic measures could help identify “real” high-risk subjects and develop new treatment algorithms. Moreover, the primary outcome measure of randomized controlled trials should be not only syndromic resolution, but also functional and psychosocial recovery, along with cognitive improvement. The results from studies conducted with high-risk subjects will eventually help identify clinical prodromes and biological markers in subjects from the general population as well.

As these two companion papers have highlighted, the future of early intervention in BPD depends on our ability to identify individuals at risk for developing BPD, and the capacity to provide targeted treatment that specifically prevents onset or recurrence of episodes. It should be emphasized that we are not advocating the widespread treatment of children with symptoms that may not be specific for BPD (including irritability, hyperactivity, and impulsivity). Rather, we are advocating for research to identify those individuals truly at risk for BPD. Hopefully, the identification of these subjects will be guided by an integrated approach that includes both clinical symptoms and biological markers and that has high specificity and sensitivity. Though such work will not easily be put into practice, we now have significant clues about not only disease onset and progression, but about the tools we need to help implement successful early intervention in BPD.

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Table 1**Neurotrophic and neuroprotective effects of lithium, valproate, glutamatergic agents, and atypical antipsychotics****Lithium***Demonstrates the following effects:*

- Is neuroprotective against glutamate and NMDA toxicity, calcium toxicity, thapsigargin toxicity, β -amyloid toxicity, aging-induced cell death, growth factor and serum deprivation, glucose deprivation, and other insults (radiations, ischemia)
- Promotes hippocampal neurogenesis
- Increases Bcl-2 in the frontal cortex, the striatum, and the hippocampus
- Activates ERK/MAP kinase pathway
- Inhibits GSK-3 in vitro and in vivo

Demonstrates the following effects in human brain:

- Increases gray matter volume in lithium-treated patients with BPD
- Increases N-acetylaspartate (NAA) levels in lithium-treated patients with BPD
- Larger anterior cingulate and prefrontal cortex volumes in lithium-treated patients with BPD
- Protects against reduced glial numbers or glia:neuron ratio in the amygdala

Valproate*Demonstrates the following effects:*

- Is neuroprotective against oxidative stress, intracerebral hemorrhage and glutamate-mediated excitotoxicity
- Induces hippocampal neurogenesis and promotes neuronal maturation
- Increases Bcl-2 in the frontal cortex, the striatum, and the hippocampus
- Activates ERK/MAP kinase pathway
- Inhibits GSK-3 in vitro and in vivo
- Upregulates GDNF and BDNF in astrocytes

Demonstrates the following effects in human brain:

- No evidence about NAA increase or volumetric changes following valproate administration

Glutamatergic agents*Demonstrate the following effects:*

- Lamotrigine protects brain cells from ischemia and glutamate-mediated excitotoxicity
- Riluzole is neuroprotective in animal models of Parkinson's disease, ischemia, traumatic brain injury, and NMDA receptor hypofunction
- Riluzole promotes neurogenesis in the hippocampus and increases BDNF expression
- Memantine has neuroprotective properties against ischemia and CNS trauma

Demonstrate the following effects in human brain:

- Riluzole increases NAA both acutely and chronically in patients with ALS

Atypical antipsychotics*Demonstrate the following effects:*

- Olanzapine is neuroprotective against oxidative stressors and ischemia
- Olanzapine upregulates Bcl-2 expression in the frontal cortex and the hippocampus
- Quetiapine inhibits microglial activation that might be toxic and reduces neurogenesis

- Quetiapine attenuates stress-induced BDNF decreases in the hippocampus
- Risperidone is neuroprotective against ischemia

Demonstrate the following effects in human brain:

- Olanzapine increases NAA in treatment-responders with BPD
-