Pharmacological aspects

Promising avenues of therapeutics for bipolar illness
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There are multiple promising areas of clinical therapeutics in the long-term treatment of bipolar disorder. Several opportunities are readily at hand, and only require the necessary academic commitment and resources to be initiated and completed. For example, a variety of single-nucleotide polymorphism (SNP) markers are available for assessing both vulnerability to illness onset and also treatment response. Combining such a profile of 50 to 100 SNP markers with clinical attributes and other neurobiological markers, one might begin...
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to be able to treat the illness much earlier than is commonly accomplished now, and even consider the possibility of primary prophylaxis for those at the highest risk. Currently, it is very much a clinician’s best guess and a hit-or-miss proposition in assigning the optimal mood stabilizer or mood stabilizer combination for those with a definite diagnosis. If one were able to utilize this combination of SNP and other markers to more rationally assign appropriate drugs to individual patients, one might be able to ward off the very considerable morbidity and mortality associated with the early phases of the disorder, when multiple severe recurrences are common, both before and after treatment is initiated.

This is a particularly critical issue for children and adolescents with early-onset bipolar illness which, parenthetically, comprises some 55% to 60% of all bipolar illness in adults.1-3 These individuals with early onsets have the longest delays to first treatment and a more severe course of illness throughout their lives into adulthood, both as measured retrospectively and confirmed prospectively. Thus, it would appear imperative to treat these patients early and effectively in an attempt to avoid this otherwise poor prognosis. What the best treatments are for childhood bipolar illness is just beginning to be defined,4 and major new initiatives are needed, including the formation of treatment outcome networks to better define both optimal treatment and prediction of individual treatment response.3

Novel targets

Neuropeptides

Neuropeptides may provide optimal targets for therapeutics of the affective disorders in light of their longer time frame of activity and behavioral modulation compared with classical neurotransmitters. A number of companies are attempting to develop corticotropin-releasing hormone (CRH) antagonists with the hope that these will be useful in depression and anxiety syndromes. Conversely, some neuropeptides are thought to be potentially endogenous antidepressant or mood-stabilizing substances, with thyrotropin-releasing hormone (TRH) being a critical example.5,10 Thus, novel targets of drug development may be derived both from inhibition of primary pathological mechanisms, such as CRH, but also potentially enhancing endogenous secondary compensatory processes, such as TRH.11,12

Neurotrophic factors

Brain-derived neurotrophic factor (BDNF) has been implicated in the genetic and environmental vulnerability to bipolar onset, episode occurrence, and progression, and in many of the acute and long-term treatments of the illness.13 BDNF is also positive in many models of depression, and this raises the possibility of more immediate antidepressant effects being achieved by direct manipulation of BDNF, potentially with an intrathecal route of administration in order to circumvent the blood-brain-barrier.

At the same time, BDNF increases in the ventral tegmental-nucleus accumbens-dopaminergic pathway appear critical to the manifestations of both defeat stress behavior and cocaine-induced behavioral sensitization.14 There are very prominent learned components in both the manifestation of defeat stress behaviors and increased activation and responsivity to repeated doses of cocaine. Since BDNF appears to be intimately implicated in these learned associations, as it is necessary to the occurrence of long-term potentiation and long-term memory, ways of altering the substrates conveying these learned behaviors and deconditioning them might prove salutary.

Moreover, chronic cocaine administration in animals and in man increases both brain dynorphin and its sigma opiate receptor, thus accounting for some of the dysphoric and psychotomimetic effects of chronic cocaine administration that are not apparent on initial applications. Suppressing these overpotentiated dynorphinergic mechanisms thus could be a target of therapeutics, but at present it is not at all obvious how this might be accomplished. Sigma opiate antagonists may hold some promise for initial success, but would likely ultimately be associated with increases in sigma opiate receptor sensitivity, which could be counterproductive. One potential way of attempting to rebalance neural substrates associated with increased psychopathological behavior would be to combine pharmacotherapy with neurostimulatory techniques. Another approach pioneered by Kalivas15 is to reduce glutamate secretion in the nucleus accumbens that is associated with cue and stress-induced relapse in cocaine-abstinent animals. This can be accomplished with the glutathione precursor N-acetyl cysteine which acts on the cysteine-glutamate exchanger, and now has preliminary evidence of efficacy in animals and humans.
Promises of neurostimulation for clinical therapeutics in the affective disorders

Electroconvulsive therapy (ECT) has been used as a major therapeutic modality for depression and the affective psychoses for more than half a century. While highly acutely effective, recent data suggest that its long-term efficacy on mood stability is quite low, with only some 20% or less of acutely-treated patients remaining remitted at 6 months, whether or not they received continuation (prophylactic) ECT treatment. Moreover, Sackeim et al. have demonstrated that the degree of deficit in autobiographical memory is directly proportional to the number of bilateral ECT treatments. These concerns about memory loss further complicate the procedure, which has a considerable stigma based on the necessity of inducing a seizure, even under anesthesia and muscle paralysis, as performed at the present time.

Repeated transcranial magnetic stimulation (rTMS) of the brain may ultimately be able to replace ECT for a subgroup of patients; five of six studies revealed that both treatments showed equal efficacy in a small series of patients, with rTMS showing no cognitive dysfunction. However, what remains to be better delineated is the nature of the continuation and prophylactic management of acutely responsive patients to rTMS. The FDA is currently considering approval of one piece of equipment, and we look forward to delineation of the optimal parameters for individual patients with this technology for brain stimulation which does not require a seizure or anesthesia. Recent data from Mark George (personal communication, 26 September 2007) suggest excellent results in highly treatment-refractory patients with shorter inter-stimulus intervals generating 6000 to 8000 pulses per daily session, with 10 Hz over left prefrontal cortex at high intensity (130% of motor threshold).

As such, rTMS has other potential advantages, including the possibility of administering it during attempts to enhance neural circuits associated with positive adaptations (using 20Hz rTMS) and dampen overactive neural circuits associated with pathological processes and dysfunction (using 1 Hz rTMS). Extinction and deconditioning of anxiety disorders has been demonstrated with adjunctive use of the glutamate enhancer d-cycloserine, and one can similarly envision enhancing, with rTMS, glutamatergic and other neural circuits in the medial prefrontal cortex that are involved in new learning, which appears to be a critical component of habituation or desensitization. rTMS is also capable of activating BDNF and other neurotropic factors, and thus holds the possibility of reprogramming neural circuitry in a relatively regionally selective fashion during cognitive behavioral therapy or other psychorehabilitative processes.

Vagal nerve stimulation (VNS) was recently approved for treatment of refractory depression after initially being approved as an adjunctive approach to refractory epilepsy. While not yet widely endorsed or accepted by most agencies involved with reimbursement, the fact that the rate of clinical improvement appears to grow over the course of a year (in contrast to most treatments which tend to show a tolerance-like process or loss of effectiveness over time), suggests that it is likely an active treatment. Preliminary data from Marangell, Suppes, and colleagues suggest that VNS may also be useful in mood unstable and rapid cycling bipolar patients. Further studies of this modality in bipolar illness are obviously indicated in light of its promise for long-term management in an illness where the primary therapeutic target is prevention of recurrences.

Deep-brain stimulation (DBS) is a widely accepted procedure for patients with some types of refractory Parkinsonism, and data are just beginning to be accumulated about efficacy in the mood disorders. Initially, highly promising improvement in patients with refractory depression has been accomplished by Mayberg and colleagues with stimulation of area 25 in the anterior cingulate gyrus. The specificity of therapeutic effects to this location and the optimal parameters again require considerable further study and evaluation.

Over many decades, Russians teams have claimed therapeutic effects of low-level DC (direct current) stimulation. A series of studies suggest the promise of this procedure, as do other approaches to manipulating low-level magnetic fields with alterations of the parameters of magnetic resonance spectroscopic imaging (MRSI). Should rTMS and these lesser invasive techniques of DC stimulation and low-level magnetic fields prove useful in preliminary controlled studies, further intensive study would appear warranted in light of their convenience and apparent safety. Studies in animals and man also suggest their utility in enhancing pharmacotherapy.

**Novel mechanism of antidepressant action**

Given the ambiguity of antidepressant efficacy in bipolar depression and the risks of switching or cycle acceler-
eration, one mechanistically new drug looks highly promising. Agomelatine has a novel set of actions, and proven antidepressant effects in unipolar depression and potential high effectiveness in bipolar depression, with an open study indicating about 80% response rates rather than the usual 30% to 50% rates with traditional antidepressants. Agomelatine is a serotonin (5-HT)-2c antagonist which results in the disinhibition of both dopamine and norepinephrine release, and is also a melatonin M1 and M2 receptor agonist. It is also a 5-HT-2B antagonist, like some other antidepressants and most atypicals. The 5HT-2C receptor antagonism is thought to increase slow-wave sleep (SWS). Increases in SWS have now been demonstrated in depressed patients, and the receptor profile of this new antidepressant should help sleep onset, cause a phase advance in patients with circadian phase delays, and synchronize biological rhythms. The drug is also weight-neutral, and putatively does not involve the sexual dysfunction common to most selective serotonin uptake inhibitors (SSRIs). Thus, the novel norepinephrine and dopamine disinhibition (NDDI), combined with melatonin receptor agonism and circadian phase realignment, offer potential therapeutic approaches to bipolar depression.

Altered glutamatergic mechanisms: the potential for acute onset of antidepressant effects

While most of our efficacious antidepressant treatments have typically required 2 to 4 weeks or longer for maximal therapeutic effectiveness, many different procedures indicate that results can be achieved much more rapidly. In the approximate 50% of responders to one night of sleep deprivation, therapeutic effects are apparent (literally) overnight. The critical issue is maintaining efficacy, and several attempts have shown to be effective including cotreatment with lithium, light, and sleep-phase alterations. As noted above, the antidepressant effects of TRH are also rapid in onset, but the brief duration again limits current utility. Intravenous administration of the glutamate antagonist ketamine also appears capable of inducing rapid onset of antidepressant effects and in this case, improvement can last some 3 to 5 days or longer. How to capture the acute onset of effects in the long term remains a therapeutic conundrum. One approach to this being explored is to follow ketamine administration with another glutamate-active agent, riluzole, which has shown promise in the treatment of unipolar and bipolar depressed patients. This glutamate-active agent is approved for neural protection in amyotrophic lateral sclerosis, and both the acute effects of ketamine and longer-term responses to riluzole demonstrate the potential therapeutic utility of altering glutamatergic tone as a novel approach to therapeutics. In an initial series of three highly treatment-refractory depressed patients, Charney et al reported remarkable and sustained effects of acute ketamine achieved by an additional three intermittent ketamine infusions. These data suggest a shift in therapeutic approaches toward exploring new ways of maintaining the acute onset of antidepressants induced by ketamine and related agents. For example, Preskorn et al reported rapid onset of antidepressant effects with a specific antagonist of glutamate GluR 2B subunits. The aminergic systems have proven to be effective targets of delayed onset of maximum antidepressant effects, and γ-aminobutyric acid (GABA)ergic mechanisms have been intimately implicated in anxiolytic, if not antidepressant, efficacy. Whether glutamatergic/GABAergic balance can be altered from the perspective of dampening overactive glutamatergic systems remains to be further explored. It is noteworthy, however, that Hough and colleagues have demonstrated that the mood stabilizers lithium, valproate, carbamazepine, and lamotrigine are all weak inhibitors of calcium influx through the glutamate N-methyl-D-aspartic acid (NMDA) receptor, further suggesting that modulation of this major excitatory neurotransmitter system in brain through other approaches could prove clinically useful for patients with bipolar disorder.

To the extent that the ostensibly opposing behaviors and symptomatology exhibited in depression versus mania are attributable to excess activity in either inhibitory or excitatory neural substrates, one could envision how dampening neural excitability could be of potential use in both phases of the illness. Among the anticonvulsants, the sodium-channel blockers, which inhibit glutamate release, appear to be among those best demonstrating antimanic efficacy compared with agents which enhance GABAergic mechanisms (gabapentin, tiagabine, topiramate) which, with the exception of valproate, do not appear to exhibit acute antimanic efficacy. Thus, modulation of glutamate mechanisms both to dampen overexcitability in both depression and mania, and potentially enhance glutamatergic tone for new learning and decon-
ditioning, would appear to be valuable new potential approaches to the therapeutics of bipolar disorder. Considerable evidence implicates alteration in cytokine levels and functioning in the affective disorders. Preliminary attempts at using anti-inflammatory approaches, such as with antagonists of tumor necrosis factor, have been successful, and suggest a whole new approach to therapeutics in the future. Decreases in BDNF and increases in oxidative stress have also been seen during episodes of both mania and depression. As noted above, N-acetyl cysteine (NAC) is an antioxidant and a glutathione precursor. Recently, Harvey et al have shown significant effects of NAC over placebo in preventing bipolar episodes, particularly depressive recurrences in a 1-year double-blind study. As an agent with few side effects and having the major asset of preventing depressive episodes, this compound holds considerable therapeutic promise, both in its own right and as a stalking horse for a new class of therapies.

Vitamins, fatty acids, and other augmenting agents

Megavitamin therapy has not been proven to be effective in controlled clinical trials, but specific substances remain promising. For example, augmentation with folic acid (1 mg/day) is now widely recommended in refractory depression, based on a series of positive controlled trials in unipolar depression and in a small trial for fluoxetine augmentation. Moreover, it decreases levels of homocysteine, which is increased in bipolar patients with cognitive deficits and in those not recovering between episodes, as well as those being treated with valproate. As a major cardiovascular risk factor in an illness with a significantly increased risk of myocardial infarction and stroke, perhaps homocysteine should be a routine target of therapeutics with folate and other approaches. A mixed, but generally positive, literature supports the effectiveness of omega-3 fatty acids in the treatment or prevention of depressive episodes. Even in a negative study of 6 g of eicosapentaenoic acid (EPA) per day in bipolar patients, younger patients did better on active treatment, while older persons did better on placebo. Given the growing recognition of childhood onset bipolar illness in the US, further study of this safe and generally well-tolerated strategy would have considerable merit.

Another extremely promising augmentation strategy for residual depression, fatigue, and poor concentration in bipolar illness is that of modafinil. Frye et al found highly significant improvement with modafinil compared with placebo on these symptom measures, and this was achieved without an increase rate of switch into mania. Given the increasing evidence of the inadequacy of traditional antidepressant augmentation and the risks of associated switching, modafinil augmentation looks very promising. Moreover, exploration of its nonstimulant mechanism of action may also provide a new target of therapeutics.

Agents targeted to the multiple comorbidities of bipolar illness

The typical patient with bipolar illness will have other Axis I and III comorbidities. Therapeutic approaches to these symptoms have been largely ignored, as many of the more common and complicated patients are excluded from the traditional randomized controlled trials. Nevertheless, therapies directed at these critical areas of symptomatology are necessary for long-term remission and well-being. In contrast to lithium, the anticonvulsant mood stabilizers, valproate, lamotrigine, and carbamazepine, and the atypical antipsychotics are also effective in many of the anxiety disorder comorbidities and are useful “two-for-one” medication approaches to both biphasic mood and anxiety symptoms. On the other hand, some medications are not effective antimanic treatments, but may be useful in treating comorbid disorders. This would include topiramate, which is likely effective in alcohol and cocaine abstinence, migraine prevention, post-traumatic stress disorder, bulimia, and weight loss; and gabapentin, which is effective in social phobia and panic disorders, sleep disturbances, pain syndromes, and alcohol abstinence. Finding new approaches to the common comorbidities of bipolar illness, which would not exacerbate primary mood symptoms, would thus be of considerable clinical interest and benefit. For example, baclofen and rimonabant have been suggested as assisting in cocaine avoidance and weight loss, respectively, but both have been shown to exacerbate depression, such that these agents which are effective in the primary comorbid condition would not appear to have utility in patients with bipolar disorder.
Animal models of biphasic mood alterations

While there are a number of useful models for acute antidepressant and antimanic efficacy, the field suffers from a lack of models representing biphasic alterations in mood and behavior, and the inherent cyclicity or mood phase reversal and recurrence of the disorder. One of the few exceptions to this is Antelman’s model of intermittent stressors or cocaine administration, which appears to be associated with inductions of alterations in hyperactive and inhibited behavior. Interestingly, in this model, inositol appears to improve and stabilize both the behavioral and neurochemical alterations evident in this model. Examination of the efficacy of inositol in acute depression has led to equivocal results and perhaps deserves further exploration as a potential long-term therapeutic tool.

One of the more intriguing features of bipolar illness is its potential for recurrence and behavioral oscillation to opposite poles at almost any frequency from intermittent and infrequent episodic recurrences to more rapid, ultrarapid, and even ultradian cycling, wherein mood can fluctuate numerous times within a single 24-hour period. Thus, examination of mechanisms involved in this extraordinary wide range of temporal manifestations of opposing mood and behavior in bipolar disorders would be a fruitful avenue of investigation beyond the phenomena that show regular and invariant cyclicity in a given time domain. Thus, studies of diurnal alterations in circadian rhythms have been a primary focus of theoretical and empirical inquiry directed at therapeutics of bipolar disorder, but may not be adequate to deal with the extraordinary variability and aperiodicity that can be manifest in the illness. The dihydropyridine L-type calcium channel blocker nimodipine has shown preliminary success in some patients with ultrafast (ultradian) mood switches, and this class of compounds deserves further exploration, even though a new dihydropyridine did not differ from placebo.

Overview

There are obviously a multiplicity of novel potential approaches to the therapeutics of bipolar illness, as briefly outlined here. While each requires much further exploration in order to validate its potential utility, such exploration is also likely to yield many surprises, and some approaches will be developed much more rapidly than we can currently anticipate and envision. We have only preliminarily dealt with the issue of psychotherapy in conjunction with other approaches, but emphasize that there is a rich controlled clinical trial literature demonstrating the effectiveness of several different types of psychotherapeutic and psychoeducational approaches to bipolar illness. These too may be further honed and revised for much more optimal short- and long-term approaches to the complexities of bipolar illness in particular.

We look forward to the emergence of many innovative treatments and surprising developments in the realm of novel therapeutics, but remain chastened by the experience to date that research funding in bipolar disorder lags considerably behind that of the other major mental disorders. Major new initiatives are needed to begin to address the complexities of the illness and its multiple comorbidities in a timely fashion. New powerful treatments only introduced late in the course of illness and without appropriate integration with other therapeutic modalities may not fare as well as those more optimally utilized.

One can hope, as new therapeutic approaches evolve and come to fruition, that this in itself will accelerate progress in earlier and more sustained treatment of this illness, and, in turn help enhance further research funding.
Prometedoras líneas terapéuticas para la enfermedad bipolar

Los avances de las ciencias básicas en la comprensión de la neuropsicobiología del trastorno bipolar han entregado una multitud de oportunidades para explorar y explotar nuevas líneas terapéuticas. Las aproximaciones farmacoterapéuticas incluyen: neuropeptidos (agonistas como la hormona liberadora de tirotropina y antagonistas como la hormona liberadora de corticotropina), factores neurotróficos (especialmente el factor neurotrófico derivado del cerebro) y mecanismos glutamatérgicos (como riluzole, ketamina y antagonistas de la subunidad NR-2B del receptor de glutamato). Las intervenciones fisiológicas que ofrecerían alternativas a la terapia electroconvulsiva incluyen: estimulación magnética transcraneal repetida, especialmente con los parámetros de estimulación más intensos; terapia de estimulación magnética (crisis convulsivas inducidas focalmente más por estimulación magnética que eléctrica y menor pérdida de conciencia); estimulación del nervio vago y estimulación cerebral profunda. Sin embargo, todas estas intervenciones como la panoplia de tratamientos existentes requieren de futuras investigaciones en profundidad para situar a cada uno de ellos en la secuencia y combinación terapéutica adecuada para cada paciente, basándose en el desarrollo de los mejores predictores de respuesta clínica y biológica. Extensas redes de ensayos clínicos y el desarrollo de investigación sistemática en la práctica clínica, como el que ha caracterizado al Instituto Nacional del Cáncer para la quimioterapia del cáncer, podrían acelerar bastante el progreso en la incorporación tanto de nuevos agentes como de los ya existentes a mejores estrategias terapéuticas. Los trastornos bipolares, que cada vez son más reconocidos como complejos, con alta comorbilidad, alta morbilidad, y cuyo inicio en la mayoría de los casos ocurre en la niñez y adolescencia; es probable que no respondan completamente a nuevos agentes terapéuticos específicos, y se requiera de nuevas iniciativas de salud pública y estrategias de investigación tanto como del avance de nuevos tratamientos individuales.

Voies thérapeutiques prometteuses pour la maladie bipolaire

Les avancées scientifiques dans la compréhension des mécanismes neuropsychobiologiques des troubles bipolaires nous ont offert de nombreuses possibilités d’exploration et d’exploitation de nouvelles voies thérapeutiques. Les approches pharmacothérapeutiques comprennent : les neuropeptides (agonistes comme la thyrotropin-releasing hormone ou TRH, et antagonistes comme la corticotropin-releasing hormone ou CRH), des facteurs neurotrophiques (surtout le brain-derived neurotrophic factor ou BDNF) et des mécanismes glutamatergiques (comme le riluzole, la kétamine et les antagonistes de la sous-unité NR-2B du récepteur au glutamate). Parmi les alternatives physiologiques susceptibles de remplacer l’électroconvulsivothérapie, on trouve : la stimulation magnétique transcrânienne répétée, surtout à des paramètres de stimulation intensifs ; le traitement par stimulation magnétique (les crises induites sont plus localisées avec la stimulation magnétique qu’avec la stimulation électrique et la perte mnésique est donc moindre) ; la stimulation nerveuse vagale et la stimulation cérébrale profonde. Il faut cependant des études supplémentaires sur ces techniques et les traitements existants afin de trouver pour chaque patient les meilleures association et séquence thérapeutique en développant de meilleurs facteurs prédictifs de réponses cliniques et biologiques. De rapides progrès pourraient être faits dans ce domaine sur la base de grandes études cliniques mises en commun et le développement d’une recherche systématique en pratique clinique, comme le fait le National Cancer Institute pour la chimiothérapie anticancéreuse. Il est peu probable que les troubles bipolaires, de plus en plus reconnus comme complexes, très comorbides avec une mortalité et une morbidité élevées, dont la majorité débute pendant l’enfance ou l’adolescence, répondent complètement à un seul nouveau médicament ; la recherche et des initiatives nouvelles de santé publique sont aussi nécessaires que toute avancée thérapeutique pour un nouveau médicament.
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