# *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

*Basic scientific advances in understanding the neuropsychobiology of bipolar disorder have given us a multitude of opportunities to explore and exploit new avenues of therapeutics. Pharmacotherapeutic approaches include: neuropeptides (agonists such as thyrotropin-releasing hormone and antagonists such as corticotropin-releasing hormone), neurotrophic factors (especially brain-derived neurotrophic factor), and glutamatergic mechanisms (such as riluzole, ketamine, and antagonists of the NR-2B subunit of the glutamate receptor). Physiological interventions that would offer alternatives to electroconvulsive therapy include: repeated transcranial magnetic stimulation, especially at more intense stimulation parameters; magnetic stimulation therapy (seizures induced more focally by magnetic rather than electrical stimulation with resulting reduced meaning loss); vagal nerve stimulation, and deep brain stimulation. However, these, as well as the panoply of existing treatments, require further intensive investigation to place each of them in the proper therapeutic sequence and combination for the individual patient, based on development of better clinical and biological predictors of response. Large clinical trial networks and development of systematic research in clinical practice settings, such as that featured by the National Cancer Institute for cancer chemotherapy, would greatly accelerate the progress in incorporating new, as well as existing, agents into the best treatment strategies. The bipolar disorders, which are increasingly recognized as complex, highly comorbid conditions with a high morbidity and mortality, of which the majority start in childhood and adolescence, are not likely to respond completely to any single new treatment agent, and new public health initiatives and research strategies are needed as much as any new single treatment advance.*



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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[9] 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 dysphorogenic 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 Kalivas[15] 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.[16] Moreover, Sackeim et al[17] 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.[18] 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,[19] 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 interstimulus 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,[20] 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.[21-23] 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[24] 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,[25-27] as do other approaches to manipulating low-level magnetic fields with alterations of the parameters of magnetic resonance spectroscopic imaging (MRSI).[28] 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.[29]

**Novel mechanism of antidepressant action**

Given the ambiguity of antidepressant efficacy in bipolar depression[30] and the risks of switching or cycle accel-

eration,[31,32] 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[33] 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).[34,35] Increases in SWS have now been demonstrated in depressed patients,[36] and the receptor profile of this new antidepressant should help sleep onset, cause a phase advance in patients with circadian phase delays,[37] and synchronize biological rhythms.[38-41] The drug is also weight-neutral, and putatively does not involve the sexual dysfunction common to most selective 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,[42] light,[43] and sleep-phase alterations.[44] 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.[45] 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.[46] 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[47] 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[48] 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[49] 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.[50,51] 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.[52] As noted above, N-acetyl cysteine (NAC) is an antioxidant and a glutathione precursor. Recently, Harvey et al[53] 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. Also intriguing are the effects of NAC in decreasing cocaine intake noted above,[15,54] and in reducing pathological gambling,[55] problems not uncommon in patients with bipolar illness.

**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[56] and in a small trial for fluoxetine augmentation.[57] 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.[58] 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.[59] 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[60] 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[30] and the risks of associated switching,[61] 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 rimonabont 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.[62] 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.[63,64]

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 extraordinarily 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,[65] 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.[66] 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: neuropéptidos (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 que provoquen una 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 morbimortalidad, 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 transcranienne 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.*

## REFERENCES


1. Perlis RH, Miyahara S, Marangell LB, et al; STEP-BD Investigators. Long-term implications of early onset in bipolar disorder: data from the first1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry*. 2004;55:875-881.
2. Leverich GS, Post RM, Keck PE Jr, et al. The poor prognosis of childhood-onset bipolar disorder. *J Pediatr*. 2007;150:485-490.
3. Post RM, Kowatch RA.The health care crisis of childhood-onset bipolar illness: some recommendations for its amelioration. *J Clin Psychiatry*. 2006;67:115-125.
4. Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M. Child Psychiatric Workgroup on Bipolar Disorder. Treatment guidelines for children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2005;44:213-235.
5. Gary KA, Severino KA, Yarbrough GG, Prange AJ Jr, Winokur A. The thyrotropin-releasing hormone (TRH) hypothesis of homeostatic regulation: implications for TRH-based therapeutics. *J Pharmacol Exp Ther*. 2003;305:410-416.
6. Szuba MP, Amsterdam JD, Fernando AT 3rd, Gary KA, Whybrow PC, Winokur A. Rapid antidepressant response after nocturnal TRH administration in patients with bipolar type I and bipolar type II major depression. *J Clin Psychopharmacol*. 2005;25:325-330.
7. Yarbrough GG, Kamath J, Winokur A, Prange AJ Jr. Thyrotropin-releasing hormone (TRH) in the neuroaxis: therapeutic effects reflect physiological functions and molecular actions. *Med Hypotheses*. 2007;69:1249-1256.
8. Frye MA, Gary KA, Marangell LB, et al. CSF thyrotropin-releasing hormone gender difference: implications forneurobiology and treatment of depression. *J Neuropsychiatry Clin Neurosci*. 1999;11:349-353.
9. Marangell LB, George MS, Callahan AM, et al. Effects of intrathecal thyrotropin-releasing hormone (protirelin) in refractory depressed patients. *Arch Gen Psychiatry*. 1997;54:214-222.
10. Callahan AM, Frye MA, Marangell LB. Comparative antidepressant effects of intravenous and intrathecal thyrotropin-releasing hormone: confounding effects of tolerance and implications for therapeutics. *Biol Psychiatry*. 1997;41:264-272.
11. Post RM, Weiss SR. Ziskind-Somerfeld Research Award 1992. Endogenous biochemical abnormalities in affective illness: therapeutic versus pathogenic. *Biol Psychiatry*. 1992;32:469-484.
12. Post RM. Animal models of mood disorders: kindling as a model of affective illness progression. In: Schachter S, Holmes G, Kasteleijn-Nolst Trenité D, eds. *Behavioral Aspects of Epilepsy: Principles and Practice*. New York, NY: Demos Medical Publishing; 2007;19-27.
13. Post RM. Role of BDNF in bipolar and unipolar disorder: clinical and theoreticalimplications. *J Psychiatr Res*. 2007;41:979-990.
14. Berton O, McClung CA, Dileone RJ, et al. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat Stress. *Science*. 2006;10;311:864-868.
15. Kalivas PW. Neurobiology of cocaine addiction: implications for new pharmacotherapy. *Am J Addict*. 2007;16:71-78.
16. Sackeim HA, Prudic J. Length of the ECT course in bipolar and unipolar depression. *J ECT*. 2005;21:195-197.
17. Sackeim HA, Prudic J, Fuller R, Keilp J, Lavori PW, Olfson M. The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology*. 2007;32:244-254.
18. Post RM, Speer AM. rTMS and related somatic therapies: prospects for the future. In: Belmaker RH, George MS, eds. *TMS in Clinical Psychiatry*. Washington DC: American Psychiatric Press, Inc; 2007.
19. O'Reardon JP, Solvason, HB, Janicak, PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry*. 2007;62:1208-1216.
20. Davis M, Ressler K, Rothbaum BO, Richardson R. Effects of D-cycloserine on extinction: translation from preclinical to clinical work. *Biol Psychiatry*. 2006;60:369-375.
21. Rush AJ, Sackeim HA, Marangell LB, et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. *Biol Psychiatry*. 2005;58:355-363.
22. George MS, Rush AJ, Marangell LB, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry*. 2005;1;58:364-373.
23. Marangell LB, Martinez M, Jurdi RA, Zboyan H. Neurostimulation therapies in depression: a review of new modalities. *Acta Psychiatr Scand*. 2007;116:174-181.
24. Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment-resistant depression. *Neuron*. 2005;3;45:651-660.
25. Holcomb RR, Worthington WB, McCullough BA. McClean MJ. Static magnetic field therapy for pain in the abdomen and genitals. *Pediatr Neurol*. 2000;23:261-264,
26. McLean MJ, Engstrom S, Holcomb RR. *Magnetotherapy: Potential Therapeutic Benefits and Adverse Effects*. New York, NY: TFG Press; 2003.
27. Segal NA, Toda Y, Huston J, et al. Two configurations of static magnetic fields for treating rheumatoid arthritis of the knee: a double blind clinical trial. *Arch Phys Med Rehabil*. 2001;82:1453-1460.
28. Rohan M, Parow A, Stoll AL. Low-field magnetic stimulation in bipolar depression using an MRI-based stimulator. *Am J Psychiatry*. 2004;161:93-98.
29. McLean MJ, Holcomb RR, Wamil AR, Pickett JD, Cavopol AV. Blockage of sensory neuron action potentials by a static magnetic field in the 10 mT range. *Bioelectronmagnetics*. 1995;16:20-32.
30. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med*. 2007;26;356:1711-1722.
31. Post RM. Kindling and sensitization as models for affective episode recurrence, cyclicity, and tolerance phenomena. *Neurosci Biobehav Rev* 2007;31:858-873.
32. Post RM, Leverich GS. The role of psychosocial stress in the onset and progression of bipolar disorder and its comorbidities: The need for earlier and alternative modes of therapeutic intervention. *Dev Psychopathol*. 2006; 18:1181-1211.
33. Calabrese JR, Guelfi JD, Perdrizet-Chevallier C; Agomelatine Bipolar StudyGroup. Agomelatine adjunctive therapy for acute bipolar depression: preliminary open data. *Bipolar Disord*. 2007;9:628-635.
34. Mouret,J, Lemoine P, Minuit MP, Benkelfat C, Renardet M. Effects of trazodone on the sleep of depressed subjects-a polysomnographic study. *Psychopharmacology (Berlin)*. 1988;95(suppl):S37-S43.
35. Smith MI, Piper DC, Duxon MS, Upton N. Effect of SB-243213, a selective 5HT2c receptor antagonist on the rat sleep profile: a comparison to paroxetine. *Pharmacol Biochem Behav*. 2002;71:599-605.
36. Quera Salva MA, Vanier B, Laredo J, et al. Major depressive disorder, sleep EEG and agomelatine: an open-label study. *Int J Neuropsychopharmacol*. 2007;10:691-696.
37. Lewy AJ, Emens J, Jackman A, Yuhas K. Circadian uses of melatonin in humans. *Chronobiol Int*. 2006;23:403-412.
38. Racagni G, Riva MA, Popoli M. The interaction between the internal clock and antidepressant efficacy. *Int Clin Psychopharmacol*. 2007;22 (suppl 2):S9-S14.
39. Fuchs E, Simon M, Schmelting B. Pharmacology of a new antidepressant: benefit of the implication of the melatonergic system. *Int Clin Psychopharmacol*. 2006;21(suppl 1):S17-S20.
40. Varcoe T, Kennaway DJ, Voultsios A. Activation of 5HT2c receptors acutely induces Per gene expression in the rat suprachiasmatic nucleus at night. *Mol Brain Res*. 2003;119:192-200.
41. Kennaway DJ, Moyer RW. Serotonin 5HT2C agonists mimic the effect of light pulses on circadian rhythms. *Brain Res*. 1998;806:257-270.
42. Baxter LR Jr, Liston EH, Schwartz JM, et al. Prolongation of the antidepressant response to partial sleep deprivation bylithium. *Psychiatry Res*. 1986;19:17-23.
43. Benedetti F, Dallaspezia S, Fulgosi MC, Barbini B, Colombo C, Smeraldi E. Phase advance is an actimetric correlate of antidepressant response to sleep deprivation and light therapy in bipolar depression. *Chronobiol Int*. 2007;24:921-937.
44. Vawter MP, Rollins B, Morgan L, et al. The effect of total sleep deprivation on transcript expression in peripheral blood from health controls and mood disorder. Paper presented at: ACNP 46th Annual Meeting. Boca Raton, Fl; 2007.
45. Zarate CA Jr, Singh JB, Carlson PJ, et al A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006;63:856-864.

**46.** Zarate CA Jr, Quiroz JA, Singh JB, et al. An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. *Biol Psychiatry*. 2005;15;57:430-432.
**47.** Charney DS. Rapid Antidepressant strategies: mechanism of action. Paper presented at: ACNP 46th Annual Meeting. Boca Raton, Fl; 2007.
**48.** Preskorn, Baker, Omo, Kolluri, Menniti, Landen. A placebo-controlled trial of the NR2B specific NMDA antagonist CP-101, 606 plus paroxetine for treatment resistant depression (TRD). Paper presented at: 160th Annual American Psychiatric Association Meeting. San Diego, CA; 2007.
**49.** Hough CJ, Irwin RP, Gao XM, Rogawski MA, Chuang DM. Carbamazepine inhibition of N-methyl-D-aspartate-evoked calcium influx in rat cerebellar granule cells. *J Pharmacol Exp Ther*. 1996;276:143-149.
**50.** Quinones, MP. Inflammation may play an important role in the pathogenesis of pediatric bipolar due to its negative effects on the structure and function of the prefrontal cortex. Paper presented at: CNP 46th Annual Meeting. Boca Raton, Fl; 2007.
**51.** Kim YK, Jung HG, Myint AM, Kim H, Park SH. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. *J Affect Disord*. 2007;104:91-95.
**52.** Kapczinski F, Vieta E, Andreazza AC, et al. Allostatic load in bipolar disorder: implicartions for pathophysiology and treatment. *Neurosci Biobehav Rev*. 2008;32:675-692.
**53.** Harvey BH, Joubert C, du Preez JL, Berk M. Effect of chronic N-acetyl cysteine administration on oxidative status in the presence and absence of induced oxidative stress in rat striatum. *Neurochem Res*. 2008;33:508-517.
**54.** Baker DA, McFarland K, Lake RW, Shen H, Toda S, Kalivas PW. N-acetyl cysteine-induced blockade of cocaine-induced reinstatement. *Ann N Y Acad Sci.* 2003;1003:349-351.
**55.** Grant JE, Kim SW, Odlaug BL. N-acetyl cysteine, a glutamate-modulating agent, in the treatment of pathological gambling: a pilot study. *Biol Psychiatry*. 2007;62:652-657.
**56.** Coppen A, Bolander-Gouaille C. Treatment of depression: time to consider folic acid and vitamin B12. *J Psychopharmacol*. 2005;19:59-65.
**57.** Coppen A, and Bailey J. Enhancement of the antidepressant action of fluoxetine by folic acid: a randomised, placebo controlled trial. *J Affect Disord*. 2000;60:121-130.
**58.** Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry*. 2002;159:477-479.
**59.** Keck PE Jr, Mintz J, McElroy SL, et al. Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. *Biol Psychiatry*. 2006;60:1020-1022.
**60.** Frye MA, Grunze H, Suppes T, et al. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. *Am J Psychiatry*. 2007;164:1242-1249.
**61.** Post RM. What is an ideal mood stabilizer? *Clin Approaches Bipolar Disord*. 2006;5:14-21.
**62.** Antelman SM, Caggiula AR, Kiss S, Edwards D J, Kocan D, Stiller R. Neurochemical and physiological effects of cocaine oscillate with sequential drug treatment: possibly a major factor in drug variability. *Neuropsychopharmacology*. 1995;12:297-306.
**63.** Belmaker RH, Shapiro J, Vainer E, Nemanov L, Ebstein RP, Agam G. Reduced inositol content in lymphocyte-derived cell lines from bipolar patients. *Bipolar Disord*. 2002;4:67-69.
**64.** Nierenberg AA, Ostacher MJ, Calabrese JR, et al. Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, orrisperidone. *Am J Psychiatry*. 2006;163:210-216.
**65.** Pazzaglia PJ, Post RM, Ketter TA, et al. Nimodipine monotherapy and carbamazepine augmentation in patients with refractory recurrent affective illness. *J Clin Psychopharmacol*. 1998;18:404-413.
**66.** Miklowitz DJ, Otto MW, Frank E, et al. Intensive psychosocial intervention enhances functioning in patients with bipolar depression: results from a 9-month randomized controlled trial. *Am J Psychiatry*. 2007;164:1340-1347.