New approaches to bipolar disorder

Dr. P.N. SURESH KUMAR
M.D., D.P.M., D.N.B. (Psych.), M.N.A.M.S.
Senior Lecturer
Department of Psychiatry Medical College, Kozhikode

The pharmacotherapy of bipolar disorder (BPD) is complicated by the likelihood that the mechanism underlying depression, mania and the switch to either pole are different, thus one may speak of antidepressant, antimanic and antiswitch properties of the available drugs.

An ideal mood stabilizer should have the following properties (Chengappa and Levins, 2000)-

1. It should reverse rather than suppress the basic pathophysiological mechanism.
2. It should act rapidly (in hours to days).
3. It should have a high therapeutic index with minimal short-term and long-term adverse effect.
4. It should not switch the patient to opposite pole of illness.
5. It should not induce rapid cycling.
6. It should have therapeutic and prophylactic efficacy in all phases of illness.
7. Its clinical effect should be easy to measure and should not require monitoring.

Unfortunately none of the existing mood stabilizers fulfil all these criteria.

During the last decade, however there has been an explosion of research on potential new therapies of BPD, it is possible that certain of these new therapies may in the coming years, usefully augment the psychiatrist's therapeutic armamentarium. This article is devoted to a discussion of such new and experimental methods of treatment.

Mood stabilizers for mania

Time immemorial lithium is the drug of choice for elated, grandiose mania with positive family history (Cookson, 1997).

Since the antimanic effect of valpromide was first reported by Lambert et al (1966) there has been various open and controlled studies which confirmed the efficacy of valproate for mixed, dysphoric, rapid cycling mania and in those with substance abuse comorbidity (Pope et al, 1991; Bowden et al, 1994).

Currently carbamazepine is used as the third antimanic of choice, behind lithium and valproate. Many double blind studies suggest the beneficial role of carbamazepine in acute mania as well as prophylaxis (Calabrese & Bowden, 2000). Emrich (1985)

reviewed the results of double blind multicentric trials comparing oxcar bazepine with haloperidol and lithium in acute mania and concluded that the efficacy of oxcarbazepine is comparable with haloperidol and lithium. However the value of oxcarbazepine in the prophylaxis of bipolar disorder is not established. Oxcarb azepine may be better tolerated than carbamazepine; however, the current pub lished database is small and the potential for oxcarbazepine to induce the type of serious idiosyncratic reactions occasionally associated with carbamazepine is unknown (Grant & Faulds, 1992).

Recent clinical trials have suggested lamotrigine as a potential agent in BP depression and rapid cycling either as a monotherapy or add-on therapy with other mood stabilizers especially sodium valproate (Calabrese et al, 1999; Calabrese et al, 2000).

Preliminary data suggest the beneficial role of gabapentin in the treatment of BP-II and BPD with comorbid panic disorder (Marcotte, 1997; Perugi et al, 1999). Its efficacy appears to lie in co-administration with other mood stabilizers and / or second-generation antipsychotics.

Topiramate is another newer anticonvulsant effective for rapid cycling and treatment refractory BPD (Marcotte, 1998). Tiagabine and zonisamide are other emerging newer anticonvulsants found to be effective acute mania (Mc Elroy & Keck, 2000).

Among the Calcium channel blockers verapamil may usefully augment lithium therapy, especially when these patients have failed to respond to lithium (Mallinger et al, 1997). It also has a role in BP women who are considering pregnancy for other indications (Briggs et al, 1998). Preliminary data suggests that nimodipine was also function as a mood stabilizer (Manna, 1991).

Among atypical antipsychotics clozapine appears to benefit patients with rapid cycling, treatment refractory BPD, schizoaffective disorder and those with tardive dyskinesia or intolerant to typical neuroleptics (Banov et al, 1994). Overall, the response to clozapine is better in the manic and psychotic phase than in the depressed phase. Clozapine may be used as monotherapy or in combination with other mood stabilizers (except carbamazepine as there is risk for agranulocytosis).

Case reports and open clinical trials have documented the efficacy of risperidone especially younger age, shorter duration of illness and the diagnosis of BPD or schizoaffective disorder (Keck et al, 1995). Interestingly, there have been several reports of risperidone induced mania and risperidone – induced worsening of manic symptoms (Dwight et al, 1994; Tomlinson, 1996; Koek & Kessler, 1996).

Olanzapine is the first FDA approved atypical antipsychotic for mania. Short-term data suggest that olanzapine is effective in patients with rapid cycling BP mania (Tollefson et al, 1997).

Quetiapine is a balanced $5HT_2/D_2$ blocker either alone or in combination with mood stabilizers may also be helpful in difficult to treat BPD. It has been approved for use in schizophrenia and schizoaffective disorder (Small et al, 1997). Ziprazidone has also a role in BPD especially for patients who had gained weight on other medications.

All other atypical antipsychotics have lower risk for EPS, elevated serum prolactin

and muscarinic adverse effects. The role of atypical antipsychotics as add-on treatment and as primary mood stabilizer in different phases of BPD is an important current research area.

Conventional antipsychotics are first line adjuvant agents for psychotic mania and for patients who have failed to respond to one or two atypical antipsychotics. Depot conventional antipsychotics are effective for the treatment of non-compliant patients (Sachs et al, 2000).

Adenyl cyclase inhibitor such as democycline (DMC) is a tetracyclic derivative, which blocks the action of antidiuretic hormone (ADH) in the kidney like lithium. DMC has been found useful in acute excitement (Roitman et al, 1998). Minocyclin is a more promising antimanic agent as it enters the CNS more readily than DMC. A case report has suggested the efficacy of minocycline in depression (Levin et al, 1996).

Among the Protein Kinase Inhibitors (PKC) tamoxifen citrate, a nonsteroidal compound with antiestrogenic effect has been found to be effective for acute mania (Bebehuk et al, 1998). Lithium valproate and verapamil also inhibits PKC isoenzymes in humans.

Dietary supplements such as inositol may benefit patients with major depression, break through BP depression and BPD with comorbid OCD or panic disorder (Levin et al, 1995; Chengappa et al, 1998). It is commercially prepared from corn-steep liquor. Choline an essential nutrient in humans, a precursor of the neurotransmitter acetylcholine and as a precursor of phospholipids in the cell membranes of neurons and glia has been found to be effective in rapid cycling patients who do not respond to lithium (Stoll et al, 1996). Sporadic reports are available regarding the efficacy of omega 3 fatty acids BPD (Skoll et al, 1999).

Repetitive transcranial magnetic stimulation (RTMS) is a noninvasive procedure which creates rapidly changing focal magnetic field over the scalp and in the underlying brain tissue there by depolarizing neurons and their projections. Double blind controlled studies (Pascual-Leone et al 1996; George et al, 1997) have shown the efficacy of RTMS administered to left prefrontal cortex in patients with major depression and right prefrontal cortex in patients with mania. RTMS is suggested to induce long-term synaptic depression and to have an anticonvulsant effect in a specific model. This is also suggested to induce an early gene expression in restricted brain areas, especially in the thalamic paraventricular nucleus (Schleapfer et al, 1997).

In the case of refractory BPD, the following agents are also suggested, although there are only few studies that address the use of these agents empirically (Sachs, 2001).

- Anticonvulsants – Tiagabine, acetozolamide, pregabaline.
- Calcium channel blockers - nifedipine, amlodipine.
- Adrenergic blocking agents – clonidine, proparanolol, guanfacine.
- Hormonal medications – thyroxin, ostrogen/progesteron.
- Others - Tryptophan, donepezil.

Bipolar depression

The lack of data on depression in BPD makes it a difficult topic to discuss (Montgomery et al, 2000). Experts in

In adjuvant antipsychotics therapy, if there is no response within a week, it is the time to try a second antipsychotic. Combination of typical and atypical antipsychotics is another recommendation in treatment resistant BPD according to evidenced based clinical guidelines (Sachs et al, 2000).

Regarding the acute phase dose of antidepressants the recommendation is to start slow, go slow, but to aim eventually the same maximum doses as in non-BP depression. It should be tapered 2 to 6 months after remission. There are few research data on dosing and duration of antidepressant treatment in BPD.

Managing special problems (Sachs et al, 2000)

Weight gain

Associated with mood stabilizers.

- Continue the present medication
- Dietary restriction / exercise
- Switch to a different mood stabilizer (CBZ/LTG)
- Add topiramate Associated with atypical antipsychotics
- Dose reduction
- Switch to another atypical antipsychotic like ziprazidone or risperidone.
- Add topiramate

Improving drug compliance

- If on lithium or divalproex, use once-daily dosing
- Encourage use of compliance enhancing aids (eg: - Weekly pill boxes, daily mood charting)
- Ask family members to monitor/ supervise medications
- Use of depot antipsychotics

Comorbid Psychiatric conditions

Panic disorder	- Divalproex/gabapentin
Alcohol/other substance abuse	- Divalproex
PTSD	- Divalproex

Prominent features of the episode

Marked insomnia	- Divalproex/atypical antipsychotic.
Marked psychomotor agitation.	
Marked aggression/ violence	- divalproex.
Marked psychomotor retardation	- Lithium.

Comorbid medical problems

Heart disease / Stroke / head injury with secondary mania- Divalproex

Renal problems	- Divalproex Atypical antipsychotic Carbamazepine
Liver disease	- Lithium

Reproductive issues

Trying to get pregnant	- conventional antipsychotic
First trimester	- do
Second trimester	- Lithium /conventional / atypical antipsychotic

Age related issues

Prepubertal	- Lithium
Adolescent girl	- do
Adolescent boy	- Divalproex / Lithium
Elderly patient with dementia	- Divalproex/atypical antipsychotic

References

- American Psychiatry Association (1994). Practice guidelines for the treatment of

patients with bipolar disorder. American Journal of Psychiatry 151(Suppl): 1-36.

- Amsterdam J (1998). Efficacy and safety of venlafaxine in the treatment of bipolar II major depressive episode. Journal of Clinical Psychopharmacology 18: 414-417.
- Angst J and Stabl M (1992). Efficacy of moclobemide in different patient groups: a metanalysis of studies. Psychopharmacology 106: S 109 – S 113.
- Banov MD, Zarate CA, Tohen M et al (1994). Clozapine therapy in refractory affective disorders: Polarity predicts response in long-term follow up. Journal of Clinical Psychiatry, 55: 295-300.
- Bebcuk JM, Arfken CL, Dolan-Manti S et al (1998). A trial of the protein kinase C inhibitor tamoxifen in the treatment of acute mania. New Research Program Abstracts, American Psychiatry Association Annual Meeting, Toronto.
- Benazzi F (1999). Prevalence and clinical features of atypical depression in depressed outpatients: a 467 case study. Psychiatry Research 86: 259 – 65.
- Brady KT and Sonny SC (1995). The relationship between substance abuse and bipolar disorder, Journal of Clinical Psychiatry, 569 suppl.3): 19-24.
- Briggs GG, Freeman RK and Yaffe SJ (1998). Drugs in pregnancy and lactation, 5th ed., Baltimore: Williams and Wilkins, 1104 – 5.
- Brown ES, Dilsaver SC, Shaib AM et al (994). Depressive mania: response to residual depression to bupropion. Biological Psychiatry 35: 493 – 94.
- Calabrese JR and Bowden C (2000) Lithium and anticonvulsants in bipolar disorder. http://WWW.acnp.org/G4/GN 401000106/CH.html.
- Calabrese JR, Bowden CL and Mc EIvoy SL et al (1999a). Lamotrigine in treatment refractory bipolar disorder. American Journal of Psychiatry, 156, 1019-1023.
- Calabrese JR, Bowden CL, Sachs GS et al (1999b). A double blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Journal of Clinical Psychiatry 60: 79 – 88.
- Calabrese JR, Suppes T, Bowden CL et al (2000). Double blind, placebo-controlled, prophylaxis study of lamotrigine in rapid cycling bipolar disorder. Journal of Clinical Psychiatry 61: 841 – 50.
- Chengappa KMR, Levine J, Gershon S et al (1998). Inositol for bipolar depression. Abstracts, Annual New Clinical Drug Evaluation Unit Program (NCDEU) Meeting, Boca Raton.
- Chengappa KMR and Levine J (2000). Biological treatments for bipolar disorder: Recent strategies. In advances in Psychiatry (eds. Andrade.C) Oxford University Press, 215 – 240.
- Cookson J (1997) Lithium: Balancing risks and benefits. British Journal of Psychiatry, 171: 10 – 14.
- Deuborsky SL, Buzan Rd 91997). Novel alternatives and supplement to lithium and anticonvulsants for bipolar affective disorder. Journal Clinical Psychiatry 58: 224 – 42.

- Dilsaver SC, Swann AC, Chen YR et al (1996). Treatment of bipolar depression with carbamazepine: results of an open study. Biological Psychiatry 40: 935 – 37.
- Dilsaver SC, Swann AC, Shaib AM et al (1993). Depressive mania associated with nonresponse to antimanic agents. American Journal of Psychiatry 150 (1): 1548 – 1551.
- Dwight MM, Keck PE, Stanton SP et al (1994). Antidepressant activity and mania associated with risperidone treatment of schizoaffective disorder. Lancet 344: 554 – 5.
- Emrich HM (1985) The use of sodium valproate, carbamazepine, and oxcarbazepine in patients with affective disorder. A preliminary report. Pharmacology Biochemistry and behaviour 19,369-372.
- Folkerts HW, Michael N, Toll R et al (1997). Electroconvulsive therapy vs. paroxetine in treatment resistant depression – a randomized study. Acta Psychiatrica Scandinavica 96: 334 – 342.
- Frances AJ, Kahn DA, Carpenter D et al (1998). The expert consensus guidelines for treating depression in bipolar disorder. Journal of Clinical Psychiatry 59 (Suppl 4): 73 – 79.
- Franchini L, Zanardi R, Gasperini M et al (1998) Fluvoxamine and lithium in long-term treatment of unipolar subjects with high recurrence rate. Journal of Affective Disorder 38: 67-9.
- George MS, Wasserman EM, Kimbrell TA et al (1997). Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo controlled cross over trial. American Journal of Psychiatry 154: 1752 – 56.
- Grant SM and Faulds D (1992) Oxcarbazepine. A review of its pharmacology and therapeutic potential in epilepsy, trigeminal neuralgia and affective disorders. Drugs 43 (6): 873-888.
- Keck PE Jr, Mc Elvoy SL, Tugral KC et al (1993). Valproate oral loading in the treatment of acute mania. Journal of Clinical Psychiatry 54: 304- 8.
- Keck PE, Wilson DR, Strakowski SM et al (1995). Clinical predictors of acute risperidone response in schizophrenia, schizoaffective disorder, and psychotic mood disorder'. Journal of Clinical Psychiatry 56: 466 – 70.
- Koek RJ and Kessler CC (1996) Probable induction of mania by risperidone. Journal of Clinical Psychiatry 57: 174-5.
- Lambert PA, Caraz G, Borselli S et al, (1766). Action neuropsychotroped'um nouvel antiepileptique : Le depamide. Annals of Medical Psychology, 1: 707-710.
- Levin J, Cholestoy A, Zimmerman J (1996). Possible antidepressant effect of minocycline. American Journal of Psychiatry 153: 582.
- Levin J, Rapaport A, Lev L et al (1993). Inositol treatment raises CSF inositol levels. Brain Research 627, 168-70.
- Mallinger AG, These ME, Hasket R et al (1997). "Verapamil treatment of lithium nonresponsive mania". Poster Abstracts, American Psychiatric Association Annual Meeting, Toronto.

- Manna V (1991). "Disturbi affectivi bipolar e ruolo del calcio intraneuronale. Effeti terapeutici del trattamento con cali di lito e/o Calcio antagonista in pazients con rapid a inversione di polarita", Menerva Med 82: 757 – 63.
- Marcotte DB, Fogelman L and Wolfe N et al (1997) Gabapentin: An effective therapy for patients with bipolar affective disorder. APA New Research Programs and Abstracts 138, Abstract NR 261.
- Marcotte, DB (1998). Use of topiramate a new antiepileptic, as a mood stabilizer. Journal of Affective Disorder, 50, 245 – 254.
- Mc Elroy S and Keck Jr PE (1993). Treatment guidelines for valproate in bipolar, schizoaffective disorders. Canadian Journal of Psychiatry 38: 562 – 566.
- Mc Elroy SL and Keck PE Jr.(2000) Pharmacologic agents for the treatment of acute bipolar mania.Biologocal Psychiatry 48 (60): 539-557.
- Montgomery SA, Schatzberg AF, Guelfi JD et al (2000) Pharmacotherapy of depression and mixed states in bipolar disorder. Journal of Affective disorder 59: 539 – 556.
- Mukherjee S, Sackeim HA, Schnurr DB (1994). Electroconvulsive therapy of acute manic episodes: a review. American Journal of Psychiatry 151: 249-76.
- Nemeroff CB (1999). Evolutionary trends in the pharmacotherapeutic management of depression. Journal of Clinical Psychiatry 55(Suppl): 3- 15.
- Pascual–Leone A, Rubio B, Pallardo F et al. Beneficial effect of rapid-rate transcranial magnetic stimulation on the left dorsolateral prefrontal cortex in drug – resistant depression. Lancet 348: 233 –7.
- Perugi G, Toni C, Ruffolo G et al (1999). Clinical experience using adjunctive gabapentin in treatment – resistant bipolar mixed states. Pharmacopsychiatry 32 (4): 136 – 11.
- Pope HG Jr, MC Elvoy SH, Keck PE Jr et al (1991). Valproate in the treatment of acute mania: A placebo controlled study. Archives of General Psychiatry, 48: 62-68.
- Prien RF, Kupfer DJ, Mansky PA et al (1984). Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Report of the NIMH collaborative study group comparing lithium carbonate, imipramine and a lithium carbonate –imipramine combination. Archives of General Psychiatry 41: 1096-104.
- Roitman G, Levine J, Belmakder RH (1998). An adenylate cyclase inhibitor in the treatment of excited psychosis. Human Psychopharmacology 23: 121-5.
- Sachs G (2000) New approaches to bipolar disorder. Http:// WWW.medscape.com / Medscape / psychiatry/treatment / update / 2000 / tu05 / public / toc-tu05.html
- Sachs GS, Lafer B, Stoll AL et al (1994). A double-blind trial of bupropion versus desimipramine for bipolar depression. Journal of Clinical Psychiatry 55 (9): 391 - 93.

- Sachs GS, Printz DJ, Kahn DA et al (2000). The expert consensus guideline series. Medical Treatment of Bipolar Disorder 2000. A Postgraduate Medicine Special Report, MC Grow – Hills.
- Scheapfer TE, Rupp F, Ji R-R (1997). Effects of rTMS and electroconvulsive stimulation on expression of immediate early genes. Abstracts, American College of Neuropsychopharmacology Annual Meeting, Hawaii.
- Small JG, Hirch SR, Arvanitis LA et al (1997). Quetiapine in patients with schizophrenia: A high and low dose comparison with placebo. Archives of General Psychiatry 54: 549 – 57.
- Small JG, Millstein V, Small IF (1991). Electroconvulsive therapy for mania. Psychiatric Clinic of North America 14(4): 887 – 903.
- Stoll AL, Sachs GS, Cohen BM et al (1996). Choline in the treatment of rapid cycling patients. Biological Psychiatry 40: 382 – 8.
- Stoll AL, Severus WE, Freeman MP et al (1999) Omega 3 fatty acids in bipolar disorder: a preliminary double blind, placebo-controlled trial. Archives of General Psychiatry 56: 407 – 12.
- Swann AC, Bowden CL, Morris D (1997). Depression during mania. Archives of General Psychiatry 5: 37-42.
- Tollefson GD, Beasley CM, Tran PV et al (1997). Olanzapine versus haloperidol in the treatment of schizophrenia, schizoaffective and schizophreniform disorders: results of an international collaborative trial. American Journal of Psychiatry 154: 457 – 65.
- Tomlinson WC (1996) Risperidone and mania. American Journal Psychiatry 153: 132 – 3.

■