South African Family Practice 2014; 56(4):19-20

S Afr Fam Pract
ISSN 1608-4356 EISSN 1727-9835

Review

Evidence that changes the way you practice Bipolar disorder: mania and depression explained

Outhoff K, MBChB, MFPM(UK)

Senior Lecturer, Department of Pharmacology, University of Pretoria, Pretoria
Correspondence to: *Kim Outhoff, e-mail: kim.outhoff@up.ac.za*
Keywords: *bipolar disorder, depression, mania*

Abstract

Bipolar disorder is characterised by alternating discrete episodes of depression and mania. Rational pharmacotherapy necessitates an appreciation of these different phases and of the possible underlying pathophysiology. A greater understanding of the pathogenesis of bipolar disorder has boosted awareness of how anti-bipolar drugs work, and vice versa. This bidirectional relationship has amplified knowledge in both disciplines.

Introduction

Bipolar disorder is characterised by alternating discrete episodes of depression and mania.[1] Rational pharmacotherapy necessitates an appreciation of these different phases and of the possible underlying pathophysiology. A greater understanding of the pathogenesis of bipolar disorder has boosted awareness of how anti-bipolar drugs work, and vice versa.[2] This bidirectional relationship has amplified knowledge in both disciplines.

Bipolar disorder is highly heritable and genome-wide association studies have uncovered significant insights into the biological mechanisms involved in its development. Potential genetic variants implicated in disease aetiology include *CACNA1C,* that encodes the alpha subunit of brain L-type voltage-gated calcium ion channels, and *ANK3,* that encodes an adaptor protein essential for the assembly of voltage-gated sodium channels.[3] Some mood stabilisers, such as lithium, valproate and lamotrigine, stabilise neuronal conduction by modulating these channels.[4] In addition, valproate has been shown to enhance neuroinhibitory gamma amino butyric acid effects,[5] while possibly attenuating neuroexcitatory glutamate's effects by upregulating the calcium chaperone protein, glucose-regulated protein (GRP) 78.[6]

The intracellular actions of lithium and valproate that may also be relevant to their actions in bipolar disorder include stimulating cell survival pathways and increasing levels of neurotrophic factors to improve cellular resiliency.[7-9] Both agents inhibit proapoptotic glycogen synthase kinase-3 beta and increase antiapoptotic protein Bcl-2 levels in the frontal cortex, ultimately resulting in downstream regulation of gene expression and neuroprotection.[10,11]Recent genome-wide association study results have implicated a risk locus which encodes ADCY2, a protein that is involved in cyclic adenosine monophosphate signal transmission within neurons, and a locus containing MIR2113 and POU3F2, which are thought to play a role in neurodevelopmental processes, lending further support to the importance of neuronal integrity in bipolar disorder.[12] Interestingly, valproate has effects on DNA histone acetylation, and may thereby regulate epigenetic phenomena as well.[13]

Thus, the pathophysiology and treatment model of mood disorders has expanded to include anomalies of neuroplasticity, or the brain's ability to form new neural connections in response to environmental changes, including injury. Structural and functional neuroimaging studies have re-enforced this neuronal injury hypothesis and have highlighted heritable changes in cortical and corpus callosum volumes, abnormal myelination in several brain regions implicated in bipolar disorder, as well as hippocampal cell damage and loss.[14-17] The hypothesis supports the clinical observation that the more episodes that a person experiences, the more he or she will have in the future, underscoring the need for long-term maintenance treatment.[18] Besides lithium, valproate or lamotrigine, recommended maintenance monotherapy includes second-generation antipsychotic medications (SGAs); olanzapine, aripiprazole, quetiapine and risperidone long-acting injection.[1,19,20]

Because serotonin, noradrenaline and dopamine are strongly implicated in the pathophysiology of mania, pharmacological strategies include gradually discontinuing conventional antidepressants and stimulants that increase the levels of any of these neurotransmitters. Agents that antagonise serotonin and dopamine receptors, including olanzapine, aripiprazole, quetiapine, risperidone, paliperidone and ziprasidone, have demonstrated excellent antimanic efficacy when used alone. Lithium or valproate are also valuable first-line options. The combination of either, with one of the above SGAs, confers additive efficacy presumably because different sites are targeted.[1,19]

There is insufficient evidence for conventional antidepressants in bipolar depression, possibly indicating an aetiology that is sufficiently distinct from major depressive disorder. These agents may also trigger mania.[20] Instead, first-line monotherapy options for severe bipolar I depression include the neuronal stabilising and protective agents; lithium, valproate or lamotrigine, and paradoxically, the atypical antipsychotics; quetiapine or olanzapine.[19] Their mechanism of antidepressant action is speculative.[6] Olanzapine and quetiapine antagonise the 5-hydroxytryptamine $(5HT)_{2A}$ receptors while stimulating the $5HT_{1A}$ receptors, and this is thought to contribute to their

Table I: South African treatment guidelines for bipolar disorder[19]

Maintenance monotherapy	Acute mania	Bipolar I* depression	Bipolar II** depression
	First-line monotherapy	**First-line monotherapy**	**First-line monotherapy**
Lithium	Lithium	Lithium	Quetiapine
Valproate	Valproate	Valproate	
Lamotrigine	Olanzapine	Lamotrigine	
Olanzapine	Quetiapine	Olanzapine	
Quetiapine	Aripiprazole	Quetiapine	
Aripiprazole	Risperidone		
Risperidone LAI	Paliperiodone		
	Ziprasidone		
	Drugs that may trigger mania	**Drugs that may trigger depression**	**Drugs that may trigger depression**
	Antidepressants, such as SSRIs and SNRIs alone or with mood stabilisers	Antipsychotics, such as chlorpromazine antihypertensive agents and corticosteroids	Antipsychotics, such as chlorpromazine antihypertensive agents and corticosteroids

SNRIs: norepinephrine reuptake inhibitors, SSRIs: selective serotonin reuptake inhibitors

*: Bipolar I is characterised by one or more episodes of mania, with or without major depressive episodes, usually leading to severe impairment of social or occupational function

**: Bipolar II disorder is characterised by one or more episodes of hypomania, as well as at least one major depressive episode with no psychotic features, and usually no major impairment of function

antidepressant effects. In addition, the prefrontal cortical dopamine levels are indirectly elevated by this $5HT_{1A}$ partial agonistic mechanism. Rapid dissociation of quetiapine from the dopamine D_2 receptors, as well as altered expression of glutamate receptor subunits, may also contribute to its antidepressant efficacy in bipolar disorder.[6] Incidentally, quetiapine is recommended first line for the milder depression associated with bipolar II.[1,19] Based on drug responsiveness studies and a wider appreciation of its pathophysiology, rational second-line options for bipolar I depression include adjunctive risperidone, olanzapine and fluoxetine combinations, or lithium combined with either valproate, lamotrigine or an antidepressant.[19]

Table I highlights the South African treatment guidelines for bipolar disorder.[19]

References

1. Goodwin GO. Evidence-based guidelines for treating bipolar disorder: revised 2nd ed – recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2009;23(4):346-388.
2. Stahl SM. Stahl's essential psychopharmacology: neuroscientific basis and practical applications: Cambridge: Cambridge University Press; 2013.
3. Ferreira MA, O'Donovan MC, Meng YA, et al. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genet. 2008;40(9):1056-1058.
4. Goldsmith DR, Wagstaff AJ, Ibbotson T, Perry CM. Spotlight on lamotrigine in bipolar disorder. CNS Drugs. 2004;18(1):63-67.
5. Rosenberg G. The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees? Cell Mol Life Sci. 2007;64(16):2090-2103.
6. Yatham LN, Goldstein JM, Vieta E, et al. Atypical antipsychotics in bipolar depression: potential mechanisms of action. J Clin Psychiatry. 2005;66 Suppl 5:40-48.
7. Li X, Ketter TA, Frye MA. Synaptic, intracellular, and neuroprotective mechanisms of anticonvulsants: are they relevant for the treatment and course of bipolar disorders? J Affect Disord. 2002;69(1-3):1-14.
8. Mathew SJ, Manji HK, Charney DS. Novel drugs and therapeutic targets for severe mood disorders. Neuropsychopharmacology. 2008;33(9):2080-2092.
9. Chen G, Zeng WZ, Yuan PX, et al. The mood-stabilizing agents lithium and valproate robustly increase the levels of the neuroprotective protein bcl-2 in the CNS. J Neurochem. 1999;72(2):879-882.
10. Bowden C, Singh V. Valproate in bipolar disorder: 2000 onwards. Acta Psychiatr Scand Suppl. 2005;(426):13-20.
11. Marmol F. Lithium: bipolar disorder and neurodegenerative diseases: possible cellular mechanisms of the therapeutic effects of lithium. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(8):1761-1771.
12. Mühleisen TW, Leber M, Schulze TG, et al. Genome-wide association study reveals two new risk loci for bipolar disorder. Nat Commun. 2014;5:3339.
13. Phiel CJ, Zhang F, Huang EY, et al. Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. J Biol Chem. 2001;276(39):36734-36741.
14. Sarrazin S, Poupon C, Linke J, et al. A multicenter tractography study of deep white matter tracts in bipolar I disorder: psychotic features and interhemispheric disconnectivity. JAMA Psychiatry. 2014;71(4):388-396.
15. Sussmann JE, Lymer GKS, McKirdy J, et al. White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging. Bipolar Disord. 2009;11(1):11-8.
16. Houenou J, Frommberger J, Carde S, et al. Neuroimaging-based markers of bipolar disorder: evidence from two meta-analyses. J Affect Disord. 2011;132(3):344-355.
17. Konradi C, Zimmerman EI, Yang CK, et al. Hippocampal interneurons in bipolar disorder. Arch Gen Psychiatry. 2011;68(4):340-350.
18. Post RM. Role of BDNF in bipolar and unipolar disorder: clinical and theoretical implications. J Psychiatr Res. 2007;41(12):979-990.
19. Emsley R, Colin F, Flisher AJ, et al. The South African Society of Psychiatrists (SASOP) treatment guidelines for psychiatric disorders. South African Journal of Psychiatry. 2013;19(3):128-199.
20. Connolly KR, Thase ME. The clinical management of bipolar disorder: a review of evidence-based guidelines. Primary Care Companion CNS Disord. 2011;13(4). pii: PCC.10r01097