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REVIEW

Evidence that changes the way you practice Bipolar Disorder: Mania and depression explained

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Abstract

Bipolar Disorder (BD) 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 BD has boosted awareness of how anti-bipolar drugs work, and vice versa.[2] This bidirectional relationship has amplified knowledge in both disciplines.

BD is highly heritable and genome-wide association studies (GWAS) 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 stabilizers such as lithium, valproate and lamotrigine stabilize neuronal conduction by modulating these channels.[4] In addition, valproate has been shown to enhance neuro-inhibitory GABA effects[5] while possibly attenuating neuro-excitatory glutamate's effects by up-regulating calcium chaperone protein, GRP 78.[6]

Intracellular actions of lithium and valproate that may also be relevant to their actions in BD include stimulating cell survival pathways and increasing levels of neurotrophic factors to improve cellular resiliency.[7-9] Both agents inhibit pro-apoptotic glycogen synthase kinase (GSK-3ß) and increase anti-apoptotic protein Bcl-2 levels in the frontal cortex, ultimately resulting in downstream regulation of gene expression and neuroprotection.[10,11]Recent GWAS results have implicated a risk locus which encodes ADCY2, a protein that is involved in cAMP signal transmission within neurons, and a locus containing MIR2113 and POU3F2, which are thought to play a role in neuro-developmental processes, lending further support to the importance of neuronal integrity in BD.[12] Interestingly, valproate has effects on DNA histone acetylation and may thereby regulate epigenetic phenomena as well.[13]

The pathophysiology and treatment model of mood disorders has thus 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 amongst others, heritable changes in cortical and corpus callosum volumes, abnormal myelination in several brain regions implicated in BD as well as hippocampal cell damage and loss.[14-17] The hypothesis supports the clinical observation that the more episodes 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 the second generation antipsychotics (SGA) 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 anti-manic 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 stabilizing 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 serotonin $5HT_{2A}$ receptors while stimulating $5HT_{1A}$ receptors and this is

Table 1: 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	
Valproate	Valproate	Valproate	
Lamotrigine		Lamotrigine	
Olanzapine	Olanzapine	Olanzapine	
Quetiapine	Quetiapine	Quetiapine	Quetiapine
Aripiprazole	Aripiprazole		
Risperidone LAI	Risperidone		
	Paliperiodone		
	Ziprasidone		
	Drugs that may trigger mania	**Drugs that may trigger depression**	**Drugs that may trigger depression**
	Antidepressants such as SSRIs and SNRIs alone/with mood stabilisers	Antipsychotics such as chlorpromazine antihypertensive agents and corticosteroids	Antipsychotics such as chlorpromazine antihypertensive agents and corticosteroids

*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.

thought to contribute to their antidepressant effects. In addition, 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 BD.[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]

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