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Bipolar disorder CHAPTER 2 Valproate Mechanism of action¹ Valproate is a simple branched-chain fatty acid. Its mechanism of action is complex and not fully understood. Valproate inhibits the catabolism of gamma-aminobutyric acid (GABA), reduces the turnover of arachidonic acid, activates the extracellular signal- regulated kinase (ERK) pathway and thus alters synaptic plasticity, interferes with intracellular signalling, promotes brain-derived neurotrophic factor (BDNF) expression and reduces levels of protein kinase C. Research has focused on the ability of valproate to alter the expression of various genes that are involved in transcription regulation, cytoskeletal modifications and ion homeostasis. Other mechanisms that have been proposed include depletion of inositol and indirect effects on non-GABA pathways through the inhibition of voltage-gated sodium channels. There is a growing literature relating to the potential use of valproate as an adjunctive treatment in several types of cancer,² a property which may also confer some effects on neuroplasticity.³ Formulations Valproate is available in the UK in three forms: sodium valproate and valproic acid (licensed for the treatment of epilepsy) and semi-sodium valproate (licensed for the treatment of acute mania). Both semi-sodium and sodium valproate are metabolised to valproic acid, which is responsible for the pharmacological activity of all three preparations.⁴ Clinical studies of the treatment of affective disorders variably use sodium valproate, semi-sodium valproate, 'valproate' or valproic acid. The great majority have used semi-sodium valproate. It is unclear if there is any difference in efficacy between valproic acid, valproate semi-sodium and sodium valproate. One large US quasi-experimental study found that in-patients who initially received the semi-sodium preparation had a hospital stay that was a third longer than patients who initially received valproic acid.⁵ One clear difference is that controlled-release sodium valproate (Epilim Chrono⁶) can be administered as a once daily dose whereas other sodium and semi-sodium valproate preparations require at least twice daily administration. Overall, there are probably no important differences between different valproate forms,⁷ except for the small differences in bioavailability related to valproate content. Indications Randomised controlled trials (RCTs) have shown valproate to be effective in the treatment of mania,^{8,9} with a response rate of 50% and a number needed to treat (NNT) of 2–4,¹⁰ although large negative studies do exist.¹¹ One RCT found lithium to be more effective overall than valproate⁹ but a large (n = 300) randomised open trial of 12 weeks' duration found lithium and valproate to be equally effective in the treatment of acute mania.¹² Valproate may be effective in patients who have failed to respond to lithium.¹³ It may be less effective than olanzapine, both as monotherapy¹⁴ and as an adjunctive treatment to lithium¹² in acute mania. One network meta-analysis reported that valproate was