22 - Discontinuation

Discontinuation

Bipolar disorder CHAPTER 2 Adverse effects Valproate can cause both gastric irritation and hyperammonaemia,41 both of which can lead to nausea. Lethargy and confusion can occasionally occur with starting doses above 750mg/day. Weight gain can be significant,42 particularly when valproate is used in combination with clozapine. Valproate causes dose-related tremor in up to a quarter of patients.43 In most of these patients, it is intention/postural tremor that is problematic, but a very small proportion develop parkinsonism associated with cognitive decline; these symptoms are reversible when valproate is discontinued.44 Hair loss (with curly regrowth)45 and peripheral oedema can occur, as can thrombocytopenia, leucopenia, red cell hypoplasia and pancreatitis.46 Valproate can cause hyperandrogenism in women47 and has been linked with the development of polycystic ovaries although the evidence supporting this association is conflicting. Valproate is a major human teratogen (see Chapter 7). Valproate may also affect male fertility48 but its teratogenic effect in men is disputed.49–51 Valproate may very rarely cause fulminant hepatic failure. Young children receiving multiple anticonvulsants are most at risk. Any patient with raised liver function tests (LFTs; common in early treatment52) should be evaluated clinically and other markers of hepatic function such as albumin and clotting time should be checked. Many adverse effects of valproate are dose-related (and often peak plasma level related) and increase sharply in frequency and severity when the plasma concentration is >100mg/L. The once daily modified-release form of sodium valproate does not produce as high peak plasma levels as the conventional formulation, and so may be better tolerated. Valproate and other antiseizure medications have been associated with an increased risk of suicidal behaviour53 but this finding is not consistent across studies.54 Patients with depression55 or who take another antiseizure medication that increases the risk of developing depression may be a subgroup at greater risk.56 Pre-treatment tests Baseline full blood count (FBC), LFTs and weight or BMI are recommended by NICE in the UK. On-treatment monitoring In the UK, NICE recommends that an FBC and LFTs should be repeated after 6 months, and that BMI should be monitored. Valproate summary of product characteristics (SPCs) recommends more frequent LFTs during the first 6 months with albumin and clotting measured if enzyme levels are abnormal. Where there is clear hypalbuminaemia, free valproate levels should be measured. Discontinuation It is unknown if abrupt discontinuation of valproate worsens the natural course of bipolar illness in the same manner as lithium. One small naturalistic retrospective study suggested that it might.57 Until further data are available, if valproate is to be discontinued, it should be done slowly over at least a month, preferably longer. In people with epilepsy, valproate withdrawal is associated with depression, falls and hospital admissions.58

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