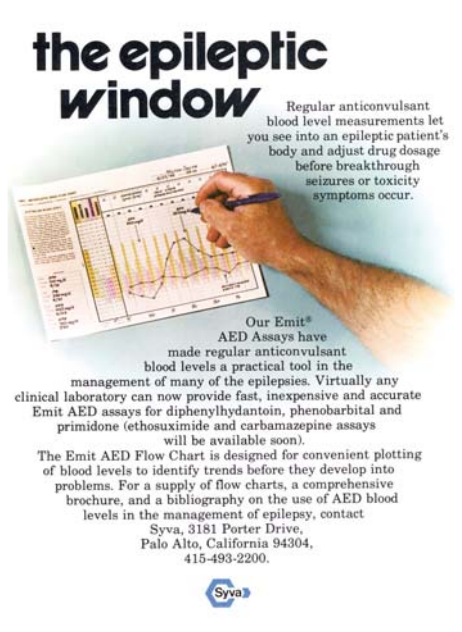
VALPROATE



Dipropylacetic acid (as valproate was then better known) was synthesised in 1881 and had been used for about 80 years as an organic solvent, when in Grenoble in 1962, a small pharmaceutical company, Laboratoire Berthier, chose valproate as the solvent for testing other compounds. When all the investigational materials were found to be effective, it occurred that it was the solvent not the compounds which was the active ingredient. The first experimental epilepsy studies were carried out in 1963 in rabbits given cardiazol to induce seizures. In those days, clinical testing could be started early (the thalidomide tragedy was soon going to put pay to this) and the first 16 patients with largely previously intractable petit mal and grand mal epilepsy were treated in 1963. The results were spectacular, and after further testing and its purchase by Sanofi–Labaz, valproate was licensed first in France in 1967. The license in the US was delayed and Kiffin Penry led a public campaign to the US Senate seeking access to the drug. The battle for the approval of valproate was dramatized in a 1987 ABC television movie, 'Fight for Life,' starring Jerry Lewis, and the drug was eventually licensed in America in 1976. The problems that dogged the prescription of valproate throughout this period were anxieties over its safety, and the slowness in recognising all aspects of valproate toxicity is rather shocking. The rather common cognitive side–effects and effects on hair were early recognised, as was the encephalopathy (two patients in the initial trials were rendered comatose), but the common effect on weight was surprisingly not noticed for many years, and the first report of teratogenicity was in 1980. The first hepatic deaths were reported in 1978, and the reports of pancreatitis in 1979. The possibility that the drug causes polycystic ovarian syndrome and other hormonal problems was first recorded in the 1990s. These problems have limited its use despite its clear efficacy, but valproate remains the drug of choice, especially for many patients with idiopathic generalised epilepsy.