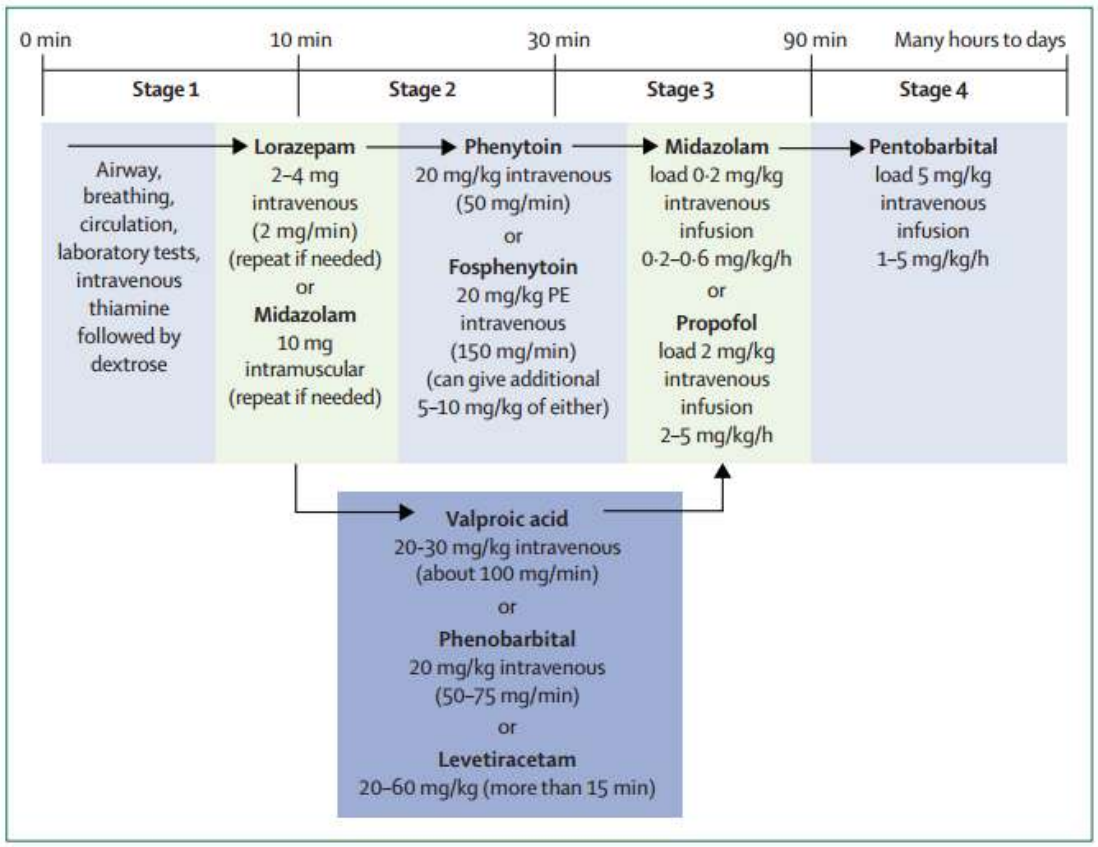
National Essential Medicine List Medication Review Process
Adult Hospital Level
Component: Neurology

Date: 27 Oct 2015

Medicine: Treatment of status epilepticus

Indication: Valproate, intravenous (IV)

There are several systematic reviews, and there has been an application to WHO to include it as a paediatric essential medicine. A 2015 narrative review[1] notes the agent, and lists it as an alternative to phenytoin:

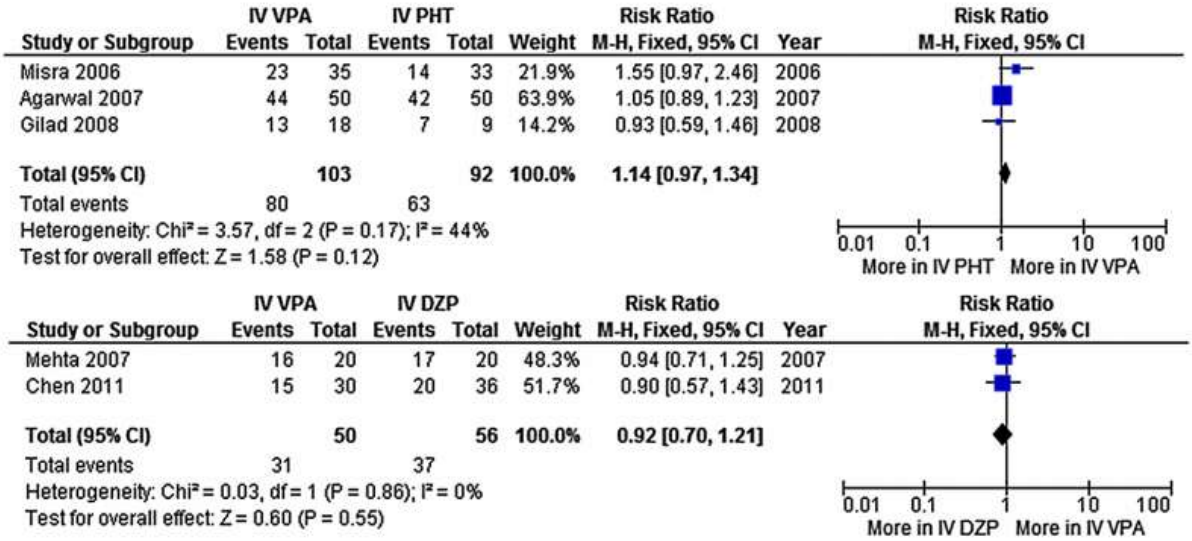


The authors do not discuss the quality of the evidence in detail, and do not list any other evidence than that identified in the earlier systematic reviews. They note that there appears to be a move away from having an intermediate step between phenytoin and induction of anaesthesia, but provide little evidence for this.

It appears that there are three randomised controlled trials comparing valproate to phenytoin, of which none were double blinded, and one left out the step of first administering a benzodiazepine. The patients were mixed – both adults and children.

[1] Betjemann JP, Lowenstein DH. Status epilepticus in adults. Lancet Neurol2015; 14: 615–24.

A forest plot from a 2014 systematic review[2] portrays the totality of the evidence quite well. While the authors contend that this provides evidence for the comparative tolerability and efficacy of IV valproate, they readily acknowledge that better quality evidence is required.



(Data is for the endpoint of seizure cessation; dzp = diazepam; pht = phenytoin.)

Another systematic review from 2011[3] lists two of the same trials showing no difference in efficacy on any endpoint. Regarding safety, there were also only two studies: Misra 4/23 (V) vs 6/14(P), and Gilad 0/18(V) and 2/9(P). It was stated in the discussion that the evidence was insufficient to change practice.

Adverse events

Gilad – in the original paper[4], there were three adverse events in the phenytoin group and none in the valproate group: one each of vertigo, ventricular premature beats, and hyponatraemia (noted during the infusion and thus probably unrelated.)

In the Misra paper[5], the 6 adverse events in the phenytoin group were two each of hypotension, respiratory depression, and liver dysfunction, although the definition and clinical relevance of these was not clear, and more liver dysfunction was actually found in the valproate group (3 episodes versus 2):

[2] Trinker E, Hofler J, Zerbs A, Brigo F. Efficacy and Safety of Intravenous Valproate for Status Epilepticus: A Systematic Review CNS Drugs 2014;28:623–639.
[3] Brigo F, Storti M, Del Felice A, et al. IV valproate in generalised convulsive status epilepticus: a systematic review. European J Neurology 2012;19:1180-91. doi:10.1111/j.1468-1331.2011.03606.x
[4] Gilad R, Izkovitz N, Dabby R, et al. Treatment of status epilepticus and acute repetitive seizures with i.v. valproic acid vs phenytoin. Acta Neurol Scand 2008: 118: 296–300.
[5] Misra UK, Kalita J, Patel R. Sodium valproate versus phenytoin in status epilepticus: a pilot study. Neurology 2006;67:340–342

Side effect	Phenytoin (n = 14)	Valproate (n = 23)	p Value
Cardiac			0.14
Present	2	0	
Absent	12	23	
Respiratory			0.27
Present	2	1	
Absent	12	22	
Liver dysfunction			0.37
Present	2	3	
Absent	12	20	

Agarwal et al[6] found no statistically significant difference in adverse events:

Table 5 Adverse effects of therapy

Adverse effects	Group A (n = 50)	Group B (n = 50)
Hypotension	0	6
Respiratory depression	0	2
Mild elevation of SGPT	4	0
Total adverse events	4*	8*

* p value > 0.05.

No definitions were given for hypotension or respiratory depression. Valproate = Group A.

A further more recent study is sometimes quoted[7], and on first glance appears interventional (the authors talk about patient enrolment) but is actually a retrospective cohort, and thus unhelpful, mainly because patient numbers were still very small (phenytoin 37, valproate 17). There were no statistically significant differences for any efficacy outcome or adverse event.

So from these three small RCTs at some risk of bias a tiny number of adverse events of unclear clinical relevance are available.

Conclusion

In the absence of better quality evidence of either improved tolerability or efficacy, it will be difficult to justify inclusion of this agent on the adult formulary, particularly in light of its registration status.

[6] Agarwal P, Kumar N, Chandra R, et al. Randomized study of intravenous valproate and phenytoin in status epilepticus. Seizure (2007) 16, 527 - 532 doi:10.1016/j.seizure.2007.04.012

[7] Tiamkao et al.: The efficacy of intravenous sodium valproate and phenytoin as the first-line treatment in status epilepticus: a comparison study. BMC Neurology 2013 13:98. doi:10.1186/1471-2377-13-98