卓飛症候群 (Dravet Syndrome) 之治療

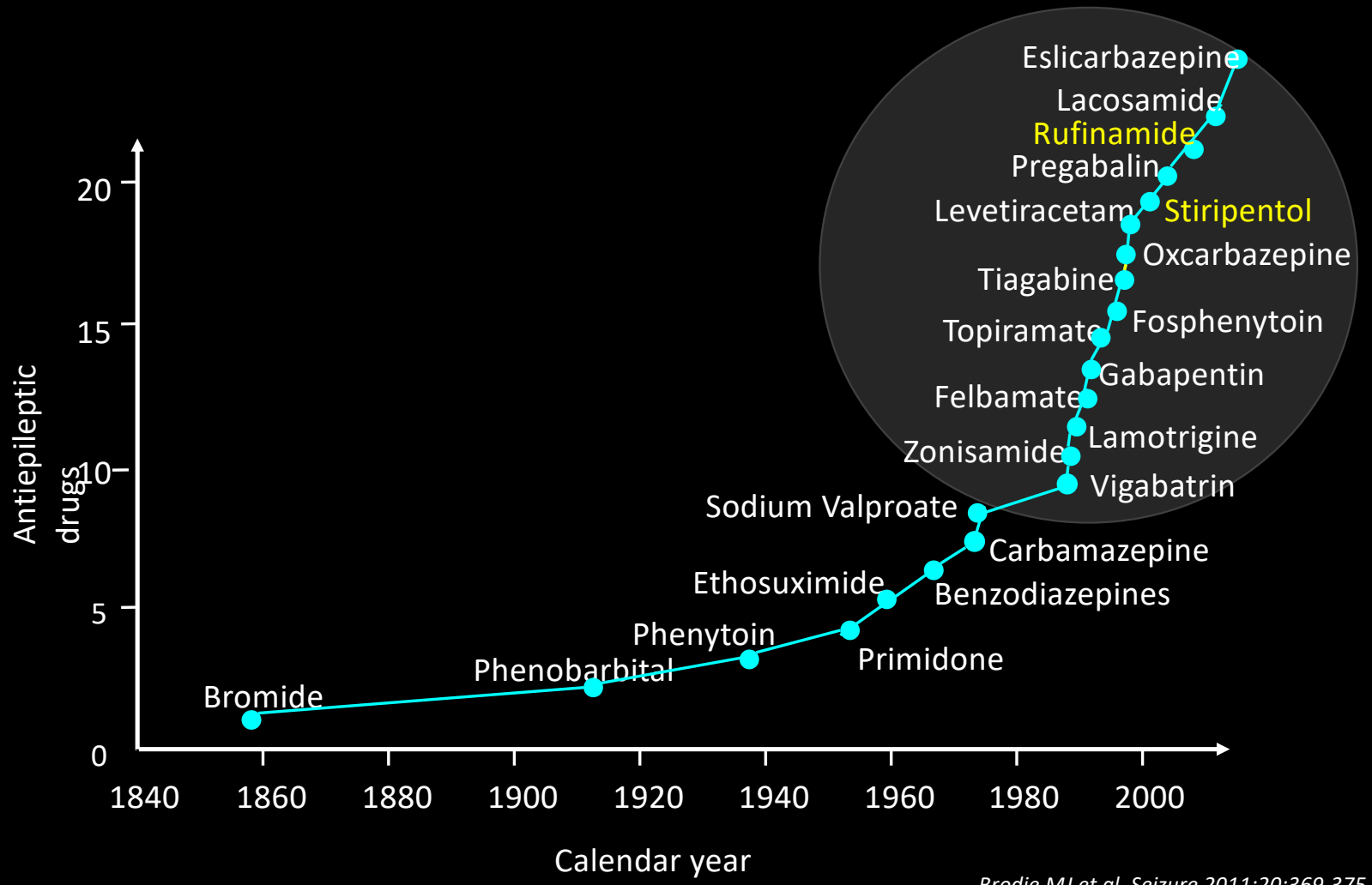
台中榮總兒童醫學部 兒童神經科

李秀芬

治療方式

- 抗癲癇藥物
- 生酮飲食
- 迷走神經刺激術
- 外科治療

抗癲癇藥物過去150年的進展
(Chronology of AED introduction over the past 150 years)



Brodie MJ et al. Seizure 2011;20:369-375

抗癲癇藥物

- 第一線用藥
  - 帝拔癲 (Valproate; Depakine®)
  - 福利寧 (Clonazam; Frisium®)

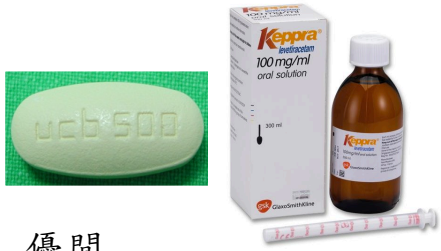
帝拔癲
(Valproate; Depakine)

服利寧
(Clobazam; Frisium)

抗癲癇藥物

- 第二線用藥
  - 利福全 (Clonazepam; Rivotril ®)
  - 妥泰 (Topiramate; Topamax ®)
  - 優閒 (Levetiracetam; Keppra®)
  - Stiripentol (250)

利福全
(Clonazepam; Rivotril)



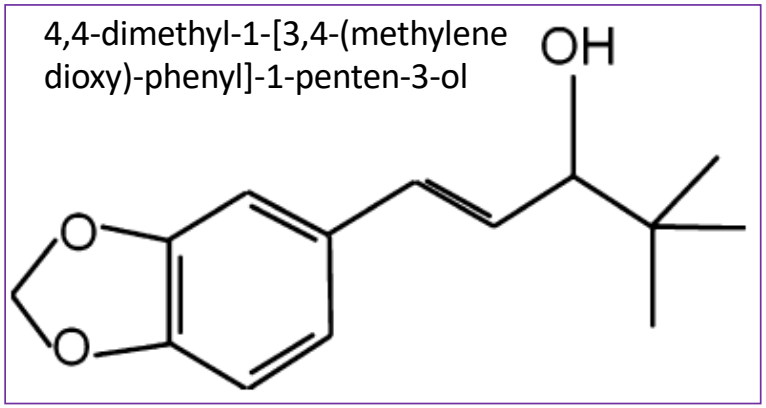
優閒
(Levetiracetam; Keppra)

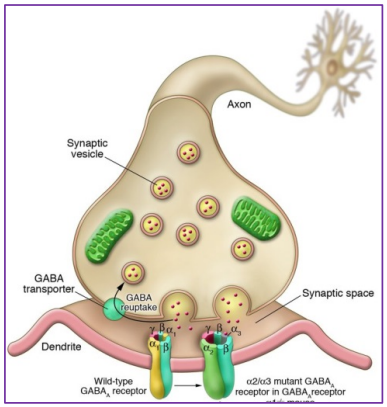
Stiripentol

妥泰
(Topiramate; Topamax)

Stiripentol (Dicomit®)

4,4-dimethyl-1-[3,4-(methylene dioxy)-phenyl]-1-penten-3-ol





• Indication	• European Medicines Agency (EMEA) approval for adjunctive therapy with valproate (VPA) and clobazam (CLB) of Dravet syndrome pts
• Mechanism of action	• Direct effect: Enhances central GABA transmission • Indirect effect: Inhibits the metabolism of concurrent AEDs for various cytochrome P450 isoenzymes (CYP1A2, CYP3A4, CYP2C19, in vivo)
• Dosage and administration	• Initial dose: 50mg/kg/day or 1000mg, increasing by 10mg/kg/day each week • Target dose: 100mg/kg/day or 4000mg • Route of administration: oral • Additional administration information: should be taken with a meal

Fisher JL Epilepsia 2011;52(Suppl 2):76-78
Plosker GL CNS drugs 2012;26:993-1001

Cannabidiol 藥物動力學及藥物交替作用

- 半衰期 (T1/2) 約24小時 (~ 24h)
- 高度蛋白質結合Highly protein bound
- 吸收良好 Well absorbed
- CYP450 metabolism (CYP3a4 and CYP2C9)

  Inhibits CYP2C19, CYP3A4, CYP2D6

  Inhibition of CYP2C19 increases N-desmethylclobazam levels

  (the long-acting active metabolite of clobazam)

Mudigoudar B, et al., Semin Pediatr Neurol 2016;23:167-179

Cannabidiol (20mg/kg/day)

120位Dravet 症候群病人接受第三期臨床試驗

- 39% 的病人抽搐頻率減少 v.s. 13% 安慰劑
- 藥物不良反應: 想睡、腹瀉、食慾降低、疲倦、發熱、嘔吐、昏睡、上呼吸道感染、抽搐。84% 為輕度至中度症狀。
- 10 位病人出現嚴重藥物不良反應 v.s. 3位使用安慰劑
- 8位病人因藥物不良反應中斷治療 v.s. 1位使用安慰劑

Source: GW Pharmaceuticals

32 卓飛症候群(Dravet syndrome)病人每月抽搐頻率減少49.8%

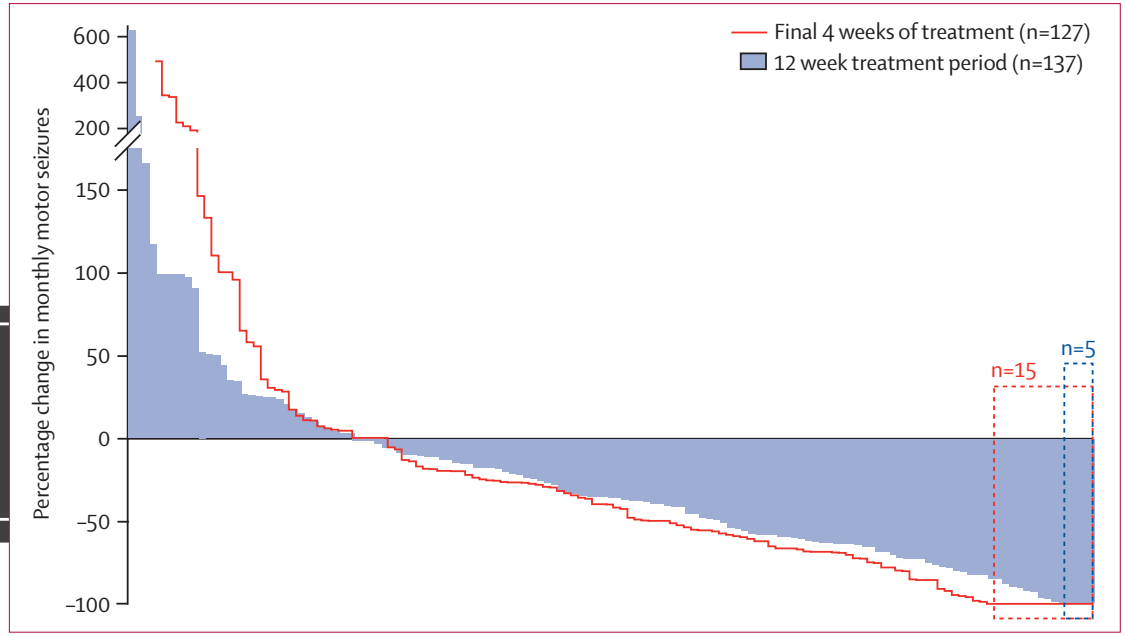


***Figure* 3: Percentage change in monthly frequency of motor seizures in patients in the efficacy analysis group (n=137)**

Percentage changes for each patient are ordered from greatest increase to greatest decrease. The dashed boxes indicate patients who became free of that seizure type during the 12 week treatment period (blue) or the last 4 weeks of treatment (red).

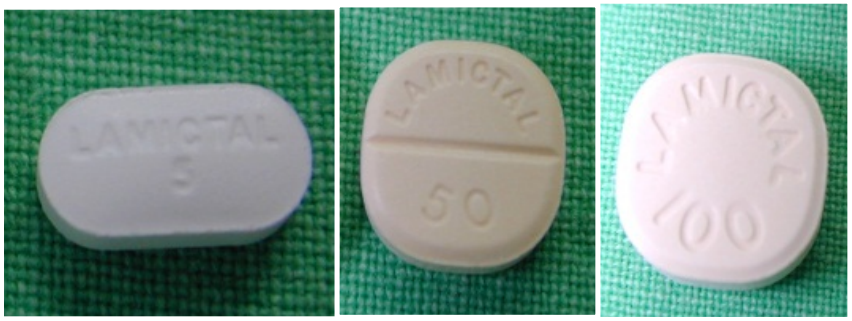
Lancet Neurol 2016;15:270-278

Fenfluramine

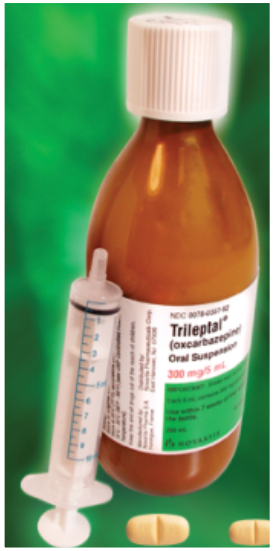
- Fenfluramine (3-triflouromethyl-N-ethylamphetamine)
- FDA approval in 1973 as an anorectic (厭食) agent, withdrawn in 1997 because of cardiovascular side effects
- 於Dravet 症候群的治療效果資料有限， 仍在試驗中

Mudigoudar B, et al., Semin Pediatr Neurol 2016;23:167-179

抗癲癇藥物於卓睇症候群之絕對禁忌：作用於鈉離子孔洞藥物



樂命達
(Lamotrigine; Lamictal)



除癲達
(Oxcarbazepine; Trileptal)

癲通
(Carbazepine; Tegretol)

生酮飲食

早餐

午餐

晚餐

居家生酮飲食

Epilepsia, 52(7):e54–e57, 2011
doi: 10.1111/j.1528-1167.2011.03107.x

BRIEF COMMUNICATION

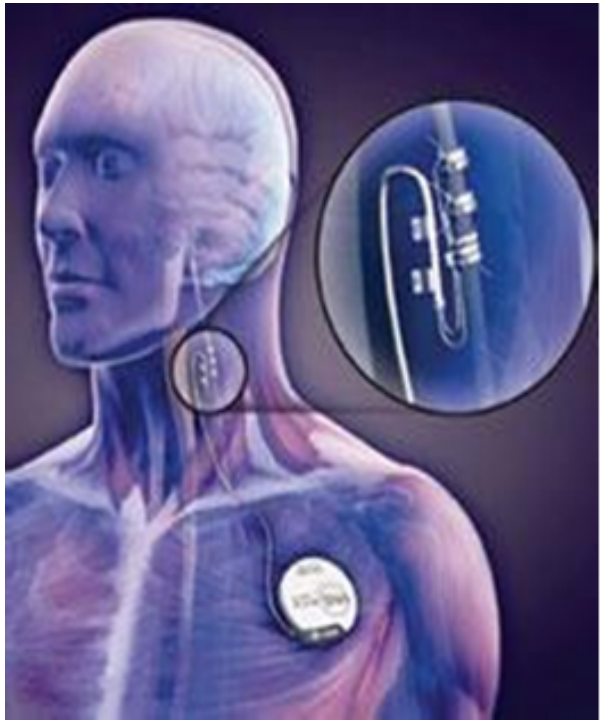
Ketogenic diet also benefits Dravet syndrome patients receiving stiripentol: A prospective pilot study

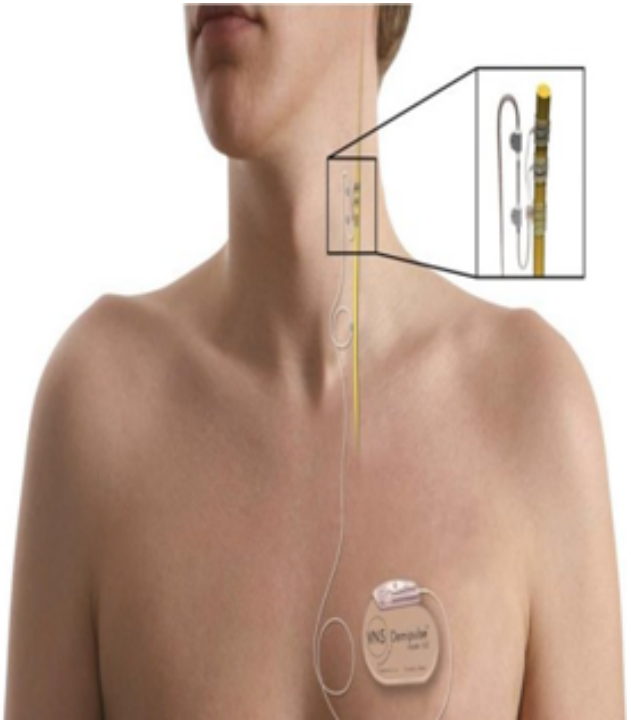
***†‡Rima Nabbout, *Cristiana Copioli, *Mathilde Chipaux, *Nicole Chemaly, *Isabelle Desguerre, *†‡Olivier Dulac, and *†‡Catherine Chiron**

***APHP, Department of Neuropediatrics, National Referral Center for Rare Epilepsies, Necker-Enfants Malades Hospital, Paris, France; †Inserm, U663, Paris, France; and ‡Paris Descartes University, Paris, France**

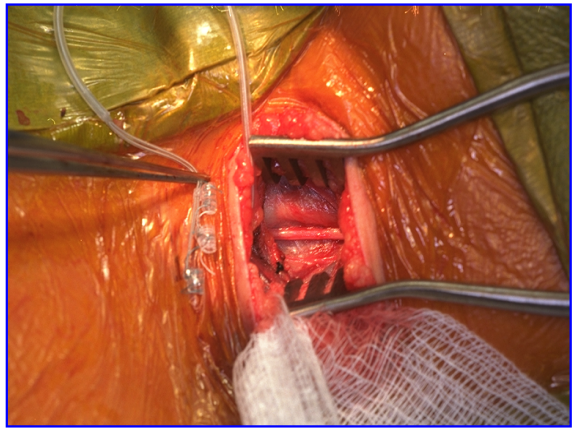
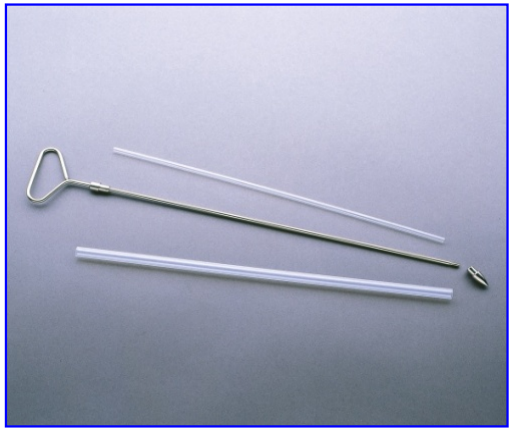
生酮飲食在接受Stiripentol 治療的卓飛症候群病人仍然有效
可控制抽搐、行爲及注意力不集中過動症狀

迷走神經刺激術



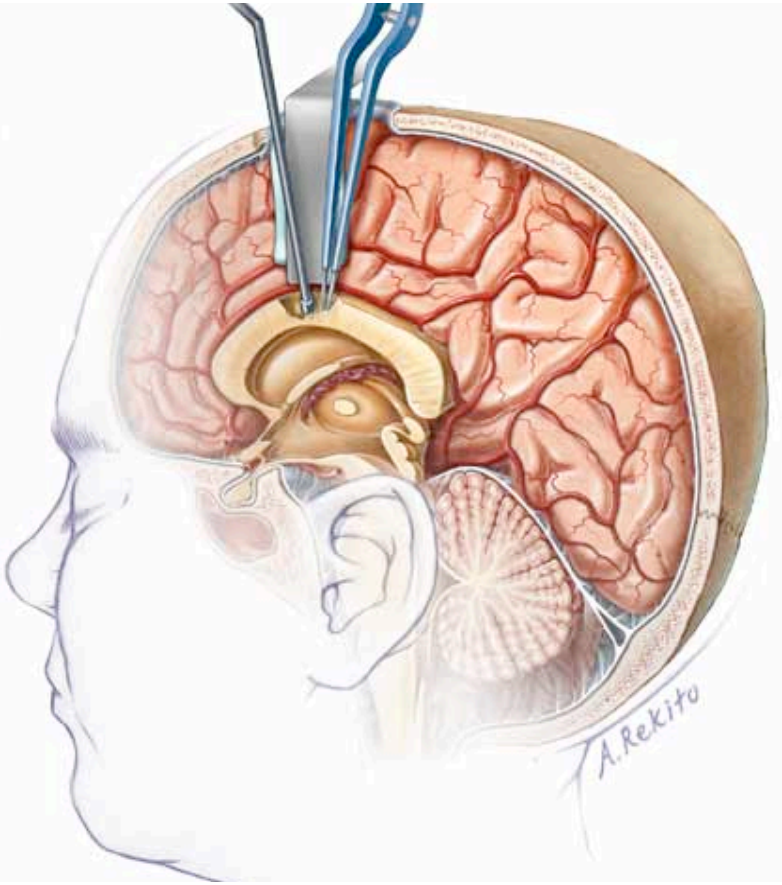


迷走神經刺激器 - 零組件



癲癇手術：胼胝體切開術




DRAVET®
SYNDROME
FOUNDATION