癫痫药物时讯

ANTIEPILEPTIC DRUGS NEWS

2022年 7 月（第六期）

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中国抗癫痫协会药物治疗专业委员会
卫材（中国）药业有限公司协助排版

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临床研究

1. 血浆左乙拉西坦浓度、MGMT 甲基化和性别与放化疗治疗成胶质细胞瘤患者生存率的关系

Association of plasma levetiracetam concentration, MGMT methylation and sex with survival of chemoradiotherapy-treated glioblastoma patients. *Pharmacol Res. 2022 Jul;181:106290. doi: 10.1016/j.phrs.2022.106290.*

Cucchiara F, Luci G, Giannini N, Giorgi FS, Orlandi P, Banchi M, Di Paolo A, Pasqualetti F, Danesi R, Bocci G.

Glioblastoma multiforme (GBM) is an aggressive brain tumor, often occurring with seizures managed with antiepileptic drugs, such as levetiracetam (LEV). This study is aimed at associating progression-free survival (PFS) and overall survival (OS) of GBM patients with LEV plasma concentration, MGMT promoter methylation, and sex. In this retrospective, non-interventional, and explorative clinical study, GBM patients underwent surgery and/or radiotherapy and received LEV during adjuvant temozolomide (TMZ) treatment. A high-performance liquid chromatography with UV-detection was used for therapeutic drug monitoring of LEV plasma concentrations. Follow-up average drug concentration was related to patients' clinical characteristics and outcomes. Forty patients (42.5 % female; mean age=54.73 ± 11.70 years) were included, and GBM MGMT methylation status was assessed. All were treated with adjuvant TMZ, and LEV for seizure control. Patients harboring methylated MGMT promoter showed a longer median PFS (460 vs. 275 days, log-rank $p < 0.001$). The beneficial effect of MGMT promoter methylation was more evident for females ($p < 0.001$) and in patients with LEV concentration ≤ 20.6 μg/mL (562 days vs. 274.5 days, $p = 0.032$). Female patients also showed longer OS (1220 vs. 574 days, $p = 0.03$). Also, higher LEV concentration (>20.6 μg/mL) synergized with MGMT promoter methylation by extending the OS (1014 vs. 406 days of patients with no methylation and low LEV average concentration, $p = 0.021$). Beneficial effect of higher LEV plasma levels was more evident in males ($p = 0.024$). Plasma concentrations of LEV may support better outcomes for chemoradiotherapy when other positive prognostic factors are lacking and may promote overall survival by synergizing with MGMT promoter methylation and male sex.

多形性成胶质细胞瘤（GBM） 是一种侵袭性脑肿瘤，通常发生在使用抗癫痫药物[如左乙拉西坦 （LEV）]治疗癫痫发作时。本研究旨在将 GBM 患者的无进展生存期（PFS）和总生存期（OS）与血浆 LEV 浓度、MGMT 启动子甲基化和性别相关联。在这项回顾性、非干预性和探索性临床研究中，GBM 患者接受了手术和/或放疗，并在替莫唑胺辅助治疗 （TMZ） 期间给予 LEV 治疗。使用具有紫外检测功能的高效液相色谱法对 LEV 血浆浓度进行监测。随访的平均药物浓度与患者的临床特征和预后相关。纳入 40 例患者（女性 42.5%;平均年龄 54.73±11.70 岁），并评估 GBM MGMT 甲基化状态。所有患者均接受 TMZ 辅助治疗，LEV 用于控制癫痫发作。MGMT 启动子甲基化的患者表现出较长的中位 PFS（460 vs. 275 天，$p<0.001$）。MGMT 启动子甲基化的有益作用对女性（$p <0.001$）和 LEV 浓度≤20.6μg/mL 的患者更为明显（562 天 vs.274.5 天，$p = 0.032$）。女性患者也表现出更长的 OS（1220 vs.574 天，$p = 0.03$）。此外，较高的 LEV 浓度（>20.6μg/ mL）通过延长 OS 与 MGMT 启动子甲基化相互协同 [1014 天 vs.406 天（无甲基化和低 LEV 平均浓度患者），$p = 0.021$]。较高 LEV 血浆水平在男性患者中获益更为显著（$p = 0.024$）。当缺乏其他阳性预后因素时，LEV 的血浆浓度可能支持更好的放化疗结局，并且可能通过与 MGMT 启动子甲基化和男性协同作用来延长生存期。

2. 负荷剂量与间歇性低剂量苯巴比妥治疗苯二氮卓类耐药性重度酒精戒断综合征的比较。

Front-Loaded Versus Low-Intermittent Phenobarbital Dosing for Benzodiazepine-Resistant Severe Alcohol Withdrawal Syndrome. *J Med Toxicol. 2022 Jul;18(3):198-204. doi: 10.1007/s13181-022-00900-8.*

Shah P, Stegner-Smith KL, Rachid M, Hanif T, Dodd KW.

Introduction: Phenobarbital is frequently used to manage severe alcohol withdrawal. The purpose of this study was to compare the incidence of mechanical ventilation in patients with benzodiazepine-resistant alcohol withdrawal between front-loaded and low-intermittent phenobarbital dosing strategies.

Methods: In this retrospective before-after study, we analyzed patients that received phenobarbital for severe alcohol withdrawal syndrome in a tertiary medical ICU. Patients received low-intermittent phenobarbital doses (260 mg intravenous push × 1 followed by 130 mg intravenous push every 15 min as needed) from January 2013 to July 2015, and front-loaded phenobarbital doses (10 mg/kg intravenous infusion over 30 min) from July 2015 to January 2017.

Results: In total, 87 patients met inclusion criteria for this study: 41 received low-intermittent phenobarbital and 46 received front-loaded phenobarbital). The incidence of mechanical ventilation was 13 (28%) in the front-loaded dosing group vs. 26 (63%) in the low-intermittent dosing group (odds ratio 4.4 [95% CI 1.8-10.9]). The cumulative dose of phenobarbital administered and serum phenobarbital levels were similar between both groups, although the front-loaded group had significantly lower benzodiazepine requirements than the low-intermittent group (median 86 mg [IQR 24-197] vs. 228 mg [115-298], P < 0.01) and reduced need for any continuous sedative infusion (OR 7.7 [95% CI 1.6-27], P < 0.01). There was no difference in respiratory failure or hypotension.

Conclusions: Front-loaded phenobarbital dosing, when compared to low-intermittent phenobarbital dosing, for benzodiazepine-resistant alcohol withdrawal was associated with significantly lower mechanical ventilation incidence and continuous sedative use.

介绍： 苯巴比妥常被用于治疗严重的酒精戒断。本研究的目的是比较负荷剂量和间歇性低剂量苯巴比妥给药策略之间对于苯二氮卓类耐药性酒精戒断患者机械通气的发生率。

方法： 在这项回顾性对照研究中，我们分析了在三级医疗机构 ICU 中接受苯巴比妥治疗的严重酒精戒断综合征患者。2013 年 1 月至 2015 年 7 月的患者接受间歇性低剂量苯巴比妥（260 mg 静推× 1 次，然后根据需要每 15 分钟静脉推注 130 mg），2015 年 7 月至 2017 年 1 月的患者接受负荷剂量（30 分钟内静脉推注 10 mg/kg）。

结果： 总共有 87 名患者符合本研究的纳入标准：41 例接受间歇性低剂量苯巴比妥，46 名接受负荷剂量苯巴比妥）。负荷剂量给药组机械通气的发生率为 13 例 （28%），而间歇性低剂量给药组为 26 例 （63%）[比值比 4.4 （95% CI 1.8-10.9）]。两组苯巴比妥的累积剂量和血清苯巴比妥浓度水平相似，但负荷剂量组苯二氮卓类药物需求量明显低于间歇性低剂量组[中位数 86 mg （IQR 24-197）vs. 228 mg (115-298)，P <0.01]，并且对其他持续镇静药物输注的需求减少[OR 7.7 （95% CI 1.6-27），P <0.01]。呼吸衰竭或低血压没有差异。

结论：对于苯二氮卓类药物耐药的酒精戒断综合征，与间歇性低剂量苯巴比妥给药相比，负荷剂量苯巴比妥与机械通气发生率和持续镇静药物使用显著降低相关。

3. 复杂热性惊厥急性脑炎及早期癫痫发作复发的危险因素

Risk factors for acute encephalitis and early seizure recurrence in complex febrile seizures *Eur J Pediatr. 2022 Jun 17 doi: 10.1007/s00431-022-04529-1.*

Kajiwara K, Koga H.

The purpose of this study is to elucidate risk factors for central nervous system infection and early seizure recurrence in children with febrile seizures (FSs) and thus facilitate outpatient management of complex FS. This single-center, retrospective cohort study investigated 688 children (6-60 months old) with FSs in Japan during 2011-2021. We investigated the incidence and clinical manifestations of children with acute encephalitis or bacterial meningitis. Logistic regression modeling was used to examine risk factors for seizure recurrence within 24 h. Among children with recurrent FSs, the distribution of intervals between first and second FS was assessed. Among 145 children with complex FSs, 2 patients (1.4%) had acute viral encephalitis and none had bacterial meningitis. Acute encephalitis was found in 2 of 8 patients (25%) with FSs prolonged ≥30 min and 2 of 3 patients (67%) requiring ≥2 intravenous anticonvulsants to stop seizures. Seizure recurrence within 24 h was observed in 16% of participants and was independently associated with preceding use of diazepam and family history of FS. In 82% of patients with FS recurrence within 24 h, early recurrences occurred within 8 h of the first seizure. Conclusion: Patients with prolonged or refractory FSs are still indicated for hospital admission due to the risk of acute encephalitis. FS patients with a family history of FS may be managed safely by 8-h observation or single-dose rectal diazepam as prophylaxis against early recurrent seizure. What is Known: • Hospitalization has been recommended for children with complex febrile seizures due to the increased risk of central nervous infections. • Recent studies showed low incidences of bacterial meningitis (<1%) in children with complex febrile seizures in the presence of routine immunization. What is New: • Acute encephalitis was identified in 1.4% of children with complex febrile seizures, characterized by prolonged seizures ≥30 min and refractory seizures. • Early recurrent seizures may be safely managed by prophylactic diazepam or 8-h expectant observation.

本研究的目的是阐明热性惊厥（FSs）患儿中枢神经系统感染和早期癫痫发作复发的危险因素，从而有助于复杂 FS 的门诊管理。这项单中心回顾性队列研究调查了 2011-2021 年期间日本 688 名患有 FS 的儿童（6-60 个月龄），分析了急性脑炎或细菌性脑膜炎患儿的发病率和临床表现。采用 Logistic 回归分析 24 小时内癫痫发作复发的危险因素。在复发性 FSs 的儿童中，评估了第一次 FS 和第二次 FS 之间的时间间隔分布。在 145 例患有复杂性 FSs 的儿童中，2 例（1.4%）患有急性病毒性脑炎，无细菌性脑膜炎病例。见于 8 例 FSs 超过 30 分钟的患者中有 2 例（25%）为急性脑炎，3 例需要 2 次以上静脉注射抗惊厥药物来终止癫痫发作的患者中有 2 例（67%）为急性脑炎。在 16%的受试者中观察到 24 小时内癫痫发作复发，并且与先前使用地西泮和 FS 家族史独立相关。在 82%的 FS 患者中，FS 在 24 小时内复发，早期复发出现在第一次癫痫发作后 8 小时内。结论：持续性或难治性 FS 患者因急性脑炎风险仍需住院治疗。对于有 FS 家族史的患者，可通过 8 小时观察或单剂量直肠给予地西泮进行安全治疗，以预防早期复发。已知：•由于中枢神经系统感染的风险增加，建议患有复杂热性惊厥的儿童住院治疗。•最近的研究表明，在常规免疫接种的情况下，患有复杂热性惊厥的儿童中细菌性脑膜炎的发病率较低（<1%）。更新内容：•急性脑炎在有复杂发热性癫痫的儿童中占 1.4%，以长时间癫痫发作≥30 分钟和难治性癫痫发作为特征。• 早期复发性癫痫发作可通过预防性给予地西泮或 8 小时的期待观察安全处理。

4. 接受抗癫痫药物的癫痫儿童中非对称二甲基精氨酸和同型半胱氨酸的评估。

Assessment of asymmetric dimethylarginine and homocysteine in epileptic children receiving antiepileptic drugs *Pediatr Res. 2022 Jun 10. doi: 10.1038/s41390-022-02132-6.*

Mahmoud AA, Aboelghar HM, Abdelmageed SM, Abdallah HM, Garib MI, Abd El Hady NMS.

Background: Epilepsy is a neurological disease that requires long-term antiepileptic drugs (AEDs). The old generation of AEDs may affect serum homocysteine and asymmetric dimethylarginine (ADMA) and disturb lipid levels. The aim of the study was to evaluate serum ADMA, homocysteine, lipid profile, and carotid intima-media thickness (CIMT) in epileptic children.

Methods: This study was implemented on 159 epileptic children who were subdivided into 3 subgroups, with 53 receiving sodium valproate, 53 receiving levetiracetam, and 53 receiving polytherapy, for over 6 months and 53 healthy children.

Results: Low-density lipoprotein, triglycerides, and cholesterol levels were increased in epileptic children ($p < 0.001$), which were higher in those receiving multidrug followed by a valproate receiver. While high-density lipoprotein was lower in those receiving multidrug more than those receiving valproate. ADMA and homocysteine levels increased in epileptic patients than in controls ($p < 0.001$). Higher ADMA was also observed in the multidrug receiver (5.78 ± 0.62), followed by the levetiracetam group (5.56 ± 0.61). Homocysteine levels were significantly higher in multidrug and valproate-treated children than those treated with levetiracetam. CIMT was significantly higher in multidrug and valproate-treated patients ($p < 0.001$).

Conclusions: Long-term use of AEDs, especially old-generation polytherapy, can elevate lipid profiles, homocysteine, ADMA levels, and carotid intima-media thickness compared to the minimal effect of new AEDs.

Impact: The long-term use of antiepileptic drugs, especially old-generation polytherapy, can increase lipid profiles, homocysteine levels, ADMA, and carotid intima thickness compared to the minimal effect of new antiepileptic generation. A routine follow-up of these markers and a lifestyle modification are recommended to avoid cerebrovascular events as much as possible.

背景：癫痫是一种神经系统疾病，需要长期应用抗癫痫药物（AED）。传统 AED 可能会影响血清同型半胱氨酸和非对称二甲基精氨酸 （ADMA）并干扰血脂水平。该研究的目的是评估癫痫患儿的血清 ADMA、同型半胱氨酸和血脂水平以及颈动脉内膜中层厚度（CIMT）。

方法：本研究纳入 159 例癫痫患儿以及 53 名健康儿童。患者分为 3 个亚组，其中 53 名接受丙戊酸钠治疗，53 名接受左乙拉西坦治疗，53 名接受多种药物治疗，持续 6 个月以上。

结果：癫痫患儿低密度脂蛋白、甘油三酯和胆固醇水平升高（$P < 0.001$），相较于接受丙戊酸的儿童，接受多种药物治疗儿童的低密度脂蛋白、甘油三酯和胆固醇水平更高。而高密度脂蛋白则更低。癫痫患者的 ADMA 和同型半胱氨酸水平比对照组高（$P < 0.001$）。在多种药物治疗的患儿中也观察到更高的 ADMA（5.78 ±0.62），其次是左乙拉西坦组（5.56±0.61）。在接受多种药物治疗和丙戊酸治疗的儿童，其同型半胱氨酸水平显著高于左乙拉西坦治疗的儿童。多种药物和丙戊酸治疗患者的 CIMT 显著增高（$P < 0.001$）。

结论：长期使用 AED，尤其是多种传统抗癫痫药物治疗与新型抗癫痫药物相比，可升高血脂、同型半胱氨酸、ADMA 水平和颈动脉内膜中层厚度。

影响：与新一代抗癫痫药物的最小影响相比，长期使用抗癫痫药物，特别是传统多药治疗，可增高血脂水平、同型半胱氨酸水平、ADMA 和颈动脉内膜厚度。建议对这些标志物进行常规随访并改变生活方式，以尽可能避免脑血管事件。

5. 一项荟萃分析：抗癫痫药物联合激素治疗儿童睡眠期癫痫性电持续状态的有效性和安全性

The Effectiveness and Safety of Hormonal Combinations of Antiepileptic Drugs in the Treatment of Epileptic Electrical Continuity in Children during Sleep: A Meta-Analysis. *Comput Intell Neurosci. 2022 Jun 8;2022:5395383. doi: 10.1155/2022/5395383.*

Zhang J.

Objective: A systematic evaluation of the efficacy of hormones in combination with antiepileptic drugs (AEDs) compared to AEDs alone in the treatment of children with encephalopathy related to status epilepticus during slow sleep (ESES). This study provides an evidence-based approach to the treatment of children with ESES.

Materials and methods: To find all relevant studies published before March 2022, we searched PubMed, Embase, Web of Science, Clinical Trials, Cochrane Library, CNKI, and Wanfang databases. We explore the difference between AEDs combined with hormones and AEDs alone for ESES treatment. All outcome data, including Wechsler Intelligence Scale for Children, the effective rate, EEG discharges, and adverse effects rate (AER), were compared using Review Manager 5.3.

Results: There were 805 patients in this study's seven investigations, including 403 in the experimental group and 402 in the control group. Meta-analysis showed that after treatment, compared with the AEDs alone group, the hormone combined with AEDs. The difference in clinical improvement rate [RR = 1.25, 95% CI (1.15, 1.36), $p < 0.00001$], electroencephalographic (EEG) discharge improvement rate [RR = 1.31, 95% CI (1.22, 1.41), $p < 0.00001$], and cognitive intelligence score [SMD = 1.02, 95% CI (0.76, 1.28), $p < 0.00001$] was statistically significant. The differences were statistically significant in terms of 0.00001; the incidence of adverse reactions was higher in the hormone combined with AEDs group than in the AEDs group alone, and the differences were statistically significant [RR = 4.13, 95% CI (1.06, 16.13), $p < 0.01$], and all adverse reactions improved or disappeared after discontinuation of the drug.

Conclusions: The combination of hormones with AEDs for the treatment of epileptic electrical continuity in sleep has advantages over AEDs alone in terms of controlling seizures, improving EEG abnormalities, and improving cognition. The combination of hormones with AEDs has advantages over AEDs alone in controlling seizures, improving EEG abnormalities, and improving cognition and is relatively safe.

目的：系统评估激素联合抗癫痫药物 （AED） 与单独使用 AED 相比治疗儿童睡眠期癫痫性电持续状态（ESES）的疗效。本研究为 ESES 儿童的治疗提供了一种循证医学方法。

材料和方法：通过收集 2022 年 3 月之前发表的所有相关研究，我们检索了 PubMed，Embase，Web of Science，Clinical Trials，Cochrane 图书馆，CNKI 和 Wanfang 数据库。我们探讨了 AED 与激素联合和 AED 单独治疗 ESES 的差异。纳入数据，包括韦氏儿童智力量表、治疗有效率、脑电图改善率和不良反应率（AER），均使用 Review Manager 5.3 进行比较。

结果：本研究的七项调查共纳入 805 名患者，其中受试组 403 例，对照组 402 例。Meta 分析显示，激素联合 AED 与单独使用 AED 组相比，临床改善率[RR = 1.25，95% CI （1.15， 1.36），p < 0.00001]，脑电图（EEG）放电改善率[RR = 1.31，95% CI （1.22， 1.41），p <0.00001]和认知智力评分[SMD = 1.02， 95% CI （0.76，1.28），p <0.00001]的差异有统计学意义。激素联合 AED 组的不良反应发生率高于单独使用 AED 组，差异有统计学意义[RR = 4.13，95%CI（1.06，16.13），p <0.01]，停药后所有不良反应均改善或消失。

结论：激素与 AED 联合治疗睡眠期癫痫性电持续状态在控制癫痫发作、改善脑电图异常和改善认知方面比单独使用 AED 具有优势。激素与 AED 联合使用在控制癫痫发作、改善脑电图异常和改善认知方面比单独使用抗癫痫药具有优势，且相对安全。

6. 药物依从性障碍的种族差异:儿科癫痫为例

Racial Disparities in Medication Adherence Barriers: Pediatric Epilepsy as an Exemplar.*J Pediatr Psychol. 2022 Jun 7;47(6):620-630. doi: 10.1093/jpepsy/jsac001.*

Gutierrez-Colina AM, Wetter SE, Mara CA, Guilfoyle S, Modi AC.

Objective: To evaluate how racial disparities in medication adherence barriers relate to key clinical outcomes (i.e., seizure control and adherence) in pediatric epilepsy and to identify the most critical barriers in determining health outcomes in Black youth and White youth.

Methods: This observational study included a sample of youth aged 2-17 years with epilepsy obtained by combining data from four different studies. A total of 226 caregivers and 43 adolescents reported on adherence barriers. An electronic monitor was used to measure adherence to the primary antiepileptic drug. Racial disparities in individual barriers were examined. The relative importance of different types of barriers in determining clinical outcomes was evaluated in both Black and White youth.

Results: Adherence barriers, including running out of medications, access to pharmacies, competing demands, and difficulty swallowing, disproportionally affected Black children with epilepsy compared to White children. System- and community-level barriers emerged as the most important in determining seizure outcomes among Black youth. Both system- and individual-level barriers, on the other hand, were important for adherence outcomes.

Conclusions: System- and community-level barriers, as opposed to individual-level barriers, are more highly endorsed by Black families compared to White families. These barriers are also the most critical in driving seizure outcomes among Black youth. There is a critical need to shift from a primary focus on individual-level barriers to an approach that deliberately targets larger systemic barriers to reduce the existing adherence and health disparities that affect Black children with pediatric conditions.

目的：评估药物依从性障碍中的种族差异与小儿癫痫的关键临床结局（即癫痫发作控制和依从性）之间的关系，并确定黑人青少年和白人青少年健康结局的最关键障碍。

方法：这项观察性研究包括结合四项不同研究的数据获得的 2-17 岁癫痫青年样本。共有 226 名照护者和 43 名青少年报告了依从性障碍。使用电子监视器来监测对主要抗癫痫药物的依从性。研究个体障碍中的种族差异。在黑人和白人青少年中评估不同类型的障碍在决定临床结局方面的相对重要性。

结果：与白人儿童相比，黑人癫痫儿童受到依从性障碍（药物短缺、药物获得、需求竞争和吞咽困难）的影响更大。体制和社区层面的障碍成为决定黑人青年癫痫发作结局的最重要因素。另一方面，体制层面和个人层面的障碍对依从性结局都起到重要作用。

结论：与白人家庭相比，黑人家庭受体制和社区层面的障碍影响更大，而非个人层面的障碍。这些障碍也是导致黑人青年癫痫发作结局的最关键因素。迫切需要将重点从个人层面的障碍转向一种有意针对更大的体制性障碍的方法，以减少现有的依从性和健康差异，这些差异影响着患有儿科疾病的黑人儿童。

7. 生酮饮食治疗癫痫：超过 18 年的 160 例患者治疗经验

Ketogenic dietary therapies for epilepsy: Experience in 160 patients over 18 years. *An Pediatr (Engl Ed). 2022 Jun;96(6):511-522.doi: 10.1016/j.anpede.2022.05.001.*

Ruiz Herrero J, Cañedo Villarroya E, García Peñas JJ, García Alcolea B, Gómez Fernández B, Puerta Macfarland LA, Pedrón-Giner C.

Aim: Ketogenic dietary therapies (KDT) produce anticonvulsant and neuroprotective effects, reduce seizures and improve the cognitive state in patients with epilepsy. Our purpose was to evaluate the effects of KDT in children with refractory epilepsy (effectiveness, side effects, impact on nutritional status and growth).

Methods: A retrospective and prospective observational descriptive study was conducted in a Spanish tertiary hospital (January 2000 to December 2018). One hundred sixty pediatric patients with epilepsy were treated with KDT (82 males; mean age 5 years 9 months). Seizures, anti-epileptic drugs, anthropometric measures, side effects, and laboratory assessment were monitored baseline and at 3, 6, 12 and 24 months after the onset of KDT.

Results: In these time intervals, the seizure-free patients were: 13.7, 12.5, 14.4 and 10.6%, respectively, and a reduction of seizures ≥ 50% was achieved in 41.9, 37.5, 28.7 and 16.2%. Side effects were frequent, especially digestive disorders, hypercalciuria, hypoglycemia, hepatic dysfunction and dyslipidemia. Prealbumin, retinol binding protein, vitamin A and magnesium decreased significantly. Height was affected, especially in children below 2 years.

Conclusions: KDT are effective for refractory epilepsy in children. However, adverse effects are frequent, and it may affect nutritional status and growth.

目的：生酮饮食疗法（KDT）具有抗惊厥和神经保护作用，减少癫痫发作并改善癫痫患者的认知状态。我们的目的是评估 KDT 对难治性癫痫患儿的影响（有效性、副作用、对营养状况和生长的影响）。

方法：采用回顾性和前瞻性观察描述性研究(2000 年 1 月- 2018 年 12 月)，在西班牙某三级医院进行。160 名儿科癫痫患者接受了 KDT 治疗（82 名男性患儿;平均年龄 5 岁 9 个月）。于基线期以及 KDT 治疗后 3、6、12 和 24 个月监测癫痫发作、抗癫痫药物、体格检查、副作用和实验室评估。

结果： 在这些时间间隔内，无癫痫发作的患者分别为：13.7%，12.5%，14.4%和 10.6%，癫痫发作减少≥50%的患者分别为 41.9%，37.5%，28.7%和 16.2%。副作用频繁，特别是消化系统症状、高钙尿症、低血糖、肝功能异常和血脂异常。前白蛋白、视黄醇结合蛋白、维生素 A 和镁显著降低。尤其是在 2 岁以下的儿童中，身高会受到影响。

结论： KDT 对儿童难治性癫痫有效。然而，不良反应经常发生，并可能影响营养状况和生长。

8. 使用硫噻嗪作为肌阵挛-失张力癫痫患儿的添加疗法——一项 35 例患者的研究

Use of sulthiame as add-on therapy in children with myoclonic atonic epilepsy: A study of 35 patients. *Epilepsy Behav. 2022 Jun;131(Pt A):108702. doi: 10.1016/j.yebeh.2022.108702.*

Caraballo RH, Reyes Valenzuela G, Fortini S, Espeche A, Gamboni B, Bautista C, Cachia P, Semprino M, Gallo A, Galicchio S.

Purpose: The aim of this retrospective study was to evaluate efficacy and tolerability of sulthiame (STM) as add-on treatment in 35 patients with myoclonic atonic epilepsy (MAE) resistant to other antiseizure medications (ASMs) and/or non-pharmacological treatment.

Methods: Patients were selected according to the diagnostic definition of MAE and were resistant to at least four previous to ASM, alone or in combination. Neurologic examinations, brain magnetic resonance imaging, and repeated prolonged electroencephalography (EEG) or video-EEG studies as well as neurometabolic studies were performed in all cases. Genetic studies were performed in 15 patients. Data on school achievements and/or neuropsychological evaluations were obtained over a mean follow-up of 30 months. Sulthiame was added in doses ranging from 10 to 30 mg/kg/day. Efficacy was assessed by comparing seizure frequency before and after initiating STM therapy.

Results: Twenty-one of 35 patients (60%) who received STM as add-on therapy had a greater than 50% seizure decrease after a mean follow-up of 30 months. Complete seizure freedom was achieved in two patients (5.8%). The remaining 14 patients (40%) had a 25-50% seizure reduction. Adverse effects, consisting of hyperpnea and dyspnea, decreased appetite, nausea, drowsiness, headache, and irritability, were observed in 11 (31.4%). The adverse effects were mild and transient in all cases. Discontinuation of STM was not necessary.

Conclusion: Add-on STM led to a more than 50% seizure reduction in 21 of 35 patients with MAE with only mild or moderate adverse effects.

目的： 这项回顾性研究旨在评估硫噻嗪（STM）作为添加治疗 35 例对其他抗癫痫发作药物（ASM）和/或非药物治疗耐药的肌阵挛-失张力癫痫（MAE）患者的疗效和耐受性。

方法： 根据 MAE 的诊断定义选择患者，这些患者对至少四种 ASM 单药或联合治疗耐药。所有病例均进行神经系统检查、脑磁共振成像、重复长程脑电图 （EEG） 或视频脑电图检查以及神经代谢产物检查。在 15 名患者中进行了遗传学相关研究。关于学习成绩和/或神经心理学评估的数据是在平均 30 个月的随访中获得的。硫噻嗪的剂量范围为 10-30mg / kg /d。通过比较开始 STM 治疗前后的癫痫发作频率来评估疗效。

结果： 在接受 STM 作为添加治疗的 35 名患者中，有 21 名（60%）在平均随访 30 个月后癫痫发作减少超过 50%。两名患者（5.8%）实现了完全无发作。其余 14 名患者（40%）的癫痫发作减少 25-50%。在 11 人中观

察到不良反应，包括呼吸急促和呼吸困难，食欲下降，恶心，嗜睡，头痛和烦躁，占比 31.4%。在所有病例中，不良反应都是轻微和短暂的。没有必要停止使用 STM。

结论： 添加 STM 使 35 名 MAE 患者中的 21 例癫痫发作减少 50% 以上，只有轻度或中度不良反应。

9. 快速输注左乙拉西坦的安全性:一项系统综述

The safety of rapid infusion levetiracetam: A systematic review. *Pharmacotherapy. 2022 Jun;42(6):495-503. doi: 10.1002/phar.2687.*

Jense A, Douville A, Weiss A.

Epilepsy is a common diagnosis and can quickly progress to status epilepticus which requires rapid treatment. Levetiracetam is a frequent treatment choice in these situations. The approved administration of intravenous levetiracetam is an infusion over 15 min. In recent years, studies have been published on faster infusion rates of levetiracetam. The objective of this review is to discuss the safety of levetiracetam as an intravenous push at a rate quicker than recommended. A literature search using PubMed, Cochrane Library, ClinicalTrials.gov, and Google Scholar resulted in 192 articles. Inclusion criteria consisted of English language, human studies, use of levetiracetam administered intravenously at a rate faster than 15 min, discussion of safety, and full-text availability. After screening, nine articles remained for inclusion. Of the nine articles, one was a prospective, open-label study, six were retrospective studies, and two were open-label, randomized controlled trials. The most common rapid infusion speed was 5 min and doses ranged from 280 to 4500 mg. Some of these trials used undiluted levetiracetam and many reported that peripheral access was used for a portion or all of the administrations. There were few adverse effects, including specific adverse effects relating to medication concentration and speed of infusion, in all the studies. Administration of intravenous levetiracetam at a rate faster than recommended in the labeling information appears to be safe and tolerable and can be given via a peripheral line. Rapid infusion of levetiracetam is a beneficial method of administration in an acute care setting where patients need rapid attainment of therapeutic levels of antiepileptic medications. Additional research is needed to ensure that rapid administration of intravenous levetiracetam is as efficacious as the traditional dosing method.

癫痫是一种常见的诊断，可迅速进展为癫痫持续状态，需要快速治疗。在这些情况下，左乙拉西坦是一种常见的治疗选择。经批准的静脉注射左乙拉西坦是 15 分钟以上的输注。近年来，关于更快左乙拉西坦输注速度的研究已发表。这篇综述的目的是讨论左乙拉西坦以比推荐更快的速度静脉推注的安全性。使用 PubMed，Cochrane Library，ClinicalTrials.gov 和 Google Scholar 进行文献检索，收集 192 篇文章。纳入标准包括英语语言、人体研究、静脉注射左乙拉西坦的使用速度超过 15 分钟、安全性讨论和全文可用性。经过筛选，仍有九篇文章可供纳入。在这九篇文章中，一篇是前瞻性的开放标签研究，六篇是回顾性研究，两篇是开放标签的随机对照试验。最常见的快速输注速度为 5 分钟，剂量范围为 280-4500mg。其中一些试验使用未稀释的左乙拉西坦，有报道称，外周途径用于部分或全部给药。在所有研究中，不良反应很少，包括与药物浓度和输注速度相关的特定不良反应。以比标签信息中建议的更快的速度静脉注射左乙拉西坦似乎是安全和可耐受的，并且可以通过外周血途径给药。快速输注左乙拉西坦是急性期治疗的有益给药方法，患者需要快速达到抗癫痫药物的治疗水平。需要进一步的研究来确保静脉注射左乙拉西坦的快速给药与传统的给药方法一样有效。

10. 新诊断癫痫患者自行终止治疗的危险因素和结局

Risk factors and consequences of self-discontinuation of treatment by patients with newly diagnosed epilepsy. *Epilepsy Behav. 2022 Jun;131(Pt A):108664.doi: 10.1016/j.yebeh.2022.108664.*

Jense A, Douville A, Weiss A.

Objective: Patients with epilepsy not uncommonly self-discontinue treatment with antiseizure medications (ASM). The rate, reasons for this, and consequences have not been well studied.

Methods: We analyzed self-discontinuation of ASM treatment in patients with recently diagnosed epilepsy via review of clinic letters and hospital correspondence in a prospective cohort of first seizure patients.

Results: We studied 489 patients with newly diagnosed and treated epilepsy (median age 41, range 14-88, 62% male), followed up for a median duration of 3.0 years (interquartile range [IQR]: 1.2-6.0). Seventy eight (16.0%) self-discontinued ASM therapy after a median treatment duration of 1.4 years (IQR: 0.4-2.9), and after a median duration of seizure freedom of 11.8 months (IQR: 4.6-31.8). Patients commonly self-discontinued treatment due to adverse effects (41%), perception that treatment was no longer required (35%), and planned or current pregnancy (12%). Patients who self-discontinued were less likely to have epileptogenic lesions on neuroimaging (hazard ratio [HR] = 0.44, 95% confidence interval [CI]: 0.23-0.83), presentation with seizure clusters (HR = 0.32, 95% CI: 0.14-0.69) and presentation with tonic-clonic seizures (HR = 0.36, 95% CI: 0.19-0.70). Patients with shorter interval since the last seizure (HR = 0.76, 95% CI: 0.66-0.86) were more likely to self-discontinue treatment. Sleep deprivation prior to seizures before diagnosis (HR = 1.80, 95% CI: 1.05-3.09) and significant alcohol or illicit drug use (HR = 2.35, 95% CI: 1.20-4.59) were also associated with higher rates of discontinuation. After discontinuation, 51 patients (65%) experienced seizure recurrence, and 43 (84%) restarted treatment. Twenty two patients (28%) experienced a seizure-related injury after treatment discontinuation.

Significance: Self-initiated discontinuation of ASM treatment was not uncommon in patients with newly treated epilepsy. Reasons for discontinuation highlight areas for improved discussion with patients, including the chronicity of epilepsy and management strategies for current or potential adverse effects.

目的： 癫痫患者自行停用抗癫痫发作药物(ASM) 在临床上很常见。其比率、原因和后果尚未得到很好的研究。

方法： 我们通过回顾诊所信件和医院信件，对新近确诊癫痫患者自行停用 ASM 治疗的情况进行了前瞻性队列研究。

结果： 我们研究了 489 名新诊断和治疗的癫痫患者（中位年龄 41 岁，范围 14-88 岁，62%为男性），随访的中位持续时间为 3.0 年[四分位差范围（IQR）： 1.2-6.0]。78 例(16.0%)在中位治疗时间为 1.4 年(IQR: 0.4-2.9)和中位无发作时间为 11.8 个月(IQR: 4.6-31.8)后自行终止 ASM 治疗。患者通常因不良反应（41%）、认为不再需要治疗（35%）以及计划或当前妊娠（12%）而自行终止治疗。自我停药的患者在神经影像学上有致痫灶（风险比 [HR] = 0.44，95% 可信区间 [CI]：0.23-0.83）、出现癫痫丛集发作（HR = 0.32，95% CI：0.14-0.69）和强直阵挛发作（HR = 0.36，95% CI：0.19-0.70）的可能性较低。距离上一次发作间隔较短的患者（HR = 0.76，95% CI：0.66-0.86）更有可能自行停止治疗。诊断癫痫发作前的睡眠剥夺（HR = 1.80，95% CI： 1.05-3.09）和大量饮酒或非法药物使用（HR = 2.35，95% CI： 1.20-4.59）也与较高的停药率相关。停药后，51 名患者

（65%）出现癫痫复发，43 名（84%）患者重新开始治疗。22 名患者（28%）在停止治疗后发生癫痫发作相关的损伤。

意义： 在新治疗的癫痫患者中，自行终止 ASM 治疗并不少见。停药的原因突显出需要与患者做进一步讨论的方向，包括癫痫的长期性和当前或潜在不良影响的管理策略。

11. 青少年遗传性全面性癫痫患者停药后癫痫复发的复发率及危险因素

Recurrence rates and risk factors for seizure recurrence following antiseizure medication withdrawal in adolescent patients with genetic generalized epilepsy. *Epilepsia Open. 2022 Jun;7(2):332-343. doi: 10.1002/epi4.12603.*

Komatsubara T, Kobayashi Y, Hiraiwa A, Magara S, Hojo M, Ono T, Okazaki K, Fukuda M, Tohyama J.

Objective: This study aimed to identify the recurrence rate of genetic generalized epilepsy (GGE) and risk factors for recurrence after antiseizure medication (ASM) withdrawal in adolescent patients.

Methods: We retrospectively reviewed medical records of patients with GGE who were included in the registry at the Department of Child Neurology, National Hospital Organization Nishiniigata Chuo Hospital from 2000 through 2020. The eligibility criteria were as follows: onset of epileptic seizures at <15 years of age, treatment with an ASM, and attempted treatment withdrawal at 10-19 years of age. The rates of seizure recurrence after drug withdrawal were evaluated. Moreover, several variables were evaluated as predictors of recurrence.

Results: In total, 77 patients with GGE (21, 13, and 43 patients with juvenile myoclonic epilepsy [JME], juvenile absence epilepsy [JAE], and epilepsy with generalized tonic-clonic seizures alone [EGTCSA], respectively) were included in this study. Recurrence was detected in 68% of patients with GGE (86%, 31%, and 70% of patients with JME, JAE, and EGTCSA, respectively). Recurrence rates for patients who developed epilepsy at ≥13 years of age, those who started dose reduction at ≥16 years of age, those who exhibited a seizure-free period of <36 months before withdrawal, and those who chose to discontinue treatment at their own discretion were significantly higher than those for their counterparts. Multivariate analysis revealed that initiation of dose reduction at ≥16 years of age was associated with increased recurrence risk. Meanwhile, a diagnosis of JAE was associated with decreased recurrence risk. All patients with JAE were treated with valproic acid.

Significance: Antiseizure medication withdrawal at ≥16 years of age and a diagnosis other than JAE may be independent risk factors for seizure recurrence after drug withdrawal in adolescent patients.

目的： 本研究旨在探讨青少年遗传性全面性癫痫（GGE）的复发率和抗发作药物（ASM）撤药后复发的危险因素。

方法： 我们回顾了 2000 年至 2020 年被列入国立医院机构西新泻中央病院儿童神经内科登记的 GGE 患者的医疗记录。入选标准如下：在<15 岁时癫痫发作，使用 ASM 治疗，以及在 10-19 岁时尝试停止治疗。评估停药后癫痫发作复发率。此外，还评估了几个变量作为复发的预测因子。

结果： 本研究共纳入 77 例 GGE 患者（分别为 21 例、13 例和 43 例青少年肌阵挛性癫痫[JME]、青少年失神癫痫[JAE]和仅有全面性强直阵挛发作[EGTCSA]患者）。在 68% 的 GGE 患者中检测到复发（分别为 86%、31% 和

70% 的 JME、JAE 和 EGTCSA 患者）。在≥13 岁时发生癫痫的患者，在≥16 岁时开始减少剂量的患者，在撤药前表现出<36 个月无癫痫发作期的患者以及选择自行决定停止治疗的患者的复发率显著高于其同类型患者。多因素分析显示，≥16 岁时开始减少剂量与复发风险增加有关。同时，JAE 的诊断与复发风险降低有关。所有 JAE 患者均接受丙戊酸治疗。

意义： ≥16 岁时停用抗癫痫药物和 JAE 以外的诊断可能是青少年患者停药后癫痫发作复发的独立危险因素。

12. 米诺环素对戊四氮诱发小鼠癫痫发作的抗惊厥作用:5-HT3 受体的参与

Entezari Z, Jahanabadi S. Anticonvulsant Effect of Minocycline on Pentylenetetrazole-Induced Seizure in Mice: Involvement of 5-HT3 Receptor. *Drug Res (Stuttg). 2022 Jun;72(5):268-273. doi: 10.1055/a-1783-7836. Epub 2022 Apr 14. PMID: 35426093.*

摘要:

Minocycline, widely used as an antibiotic, has recently been found to have an anti-inflammatory, neuroprotective and anticonvulsant effects. This study was aimed to investigate the anticonvulsant effect of acute administration of minocycline on pentylenetetrazole (PTZ)-induced seizures considering the possible involvement of 5-HT3 receptor in this effect. For this purpose, seizures were induced by intravenous PTZ infusion. All drugs were administrated by intraperitoneal (i.p.) route before PTZ injection. Also, 1-(m-chlorophenyl)-biguanide (mCPBG, a 5-HT3 receptor agonist) and Tropisetron (a 5-HT3 receptor antagonist) were used 45 minutes before minocycline treatment. Our results demonstrate that acute minocycline treatment (80 and 120 mg/kg) increased the seizure threshold. In addition, the 5-HT3 antagonist, tropisetron, at doses that had no effect on seizure threshold, augmented the anticonvulsant effect of minocycline (40 mg/kg), while mCPBG (0.2 mg/kg) blunted the anticonvulsant effect of minocycline (80 mg/kg). In conclusion, our findings revealed that the anticonvulsant effect of minocycline is mediated, at least in part, by inhibition of 5-HT3 receptor.

米诺环素被广泛用作抗生素，最近发现其具有抗炎、神经保护和抗惊厥作用。本研究旨在探究紧急给予米诺环素对戊四氮（PTZ）诱导的癫痫发作的抗惊厥作用，考虑可能是 5-HT3 受体参与这一作用。为此，通过静脉注射 PTZ 诱发癫痫发作。所有药物在注射 PTZ 前均经腹腔（i.p.）注射给药。用米诺环素治疗前 45 分钟给予 1-（间氯苯基）-双胍（mCPBG，一种 5-HT3 受体激动剂）和托烷司琼（一种 5-HT3 受体拮抗剂）。我们的结果表明，紧急给予米诺环素治疗（80 和 120 mg/kg）可提高癫痫发作阈值。此外，5-HT3 拮抗剂托烷司琼在不影响癫痫发作阈值的剂量下，增强了米诺环素(40 mg/kg)的抗惊厥作用，而 mCPBG（0.2 mg/kg）减弱了米诺环素（80 mg/kg）的抗惊厥作用。总之，我们的研究结果表明，米诺环素的抗惊厥作用至少部分是通过抑制 5-HT3 受体介导的。

13. 长期服用抗癫痫发作药物儿童的维生素 D 缺乏:我们的立场是什么?

Gupta S, Sahu JK. Vitamin D Deficiency in Children on Long-Term Antiseizure Medications: Where Do We Stand?. *Indian J Pediatr. 2022 Jun;89(6):533. doi: 10.1007/s12098-022-04152-w. Epub 2022 Mar 23. PMID: 35320501.*

In this issue of the Journal, Vijayakumar and colleagues tried to answer an essential question of whether long-term use of antiseizure medications in children with epilepsy afects vitamin D levels [1]? The question arises because antiseizure medications aim to improve quality of life by controlling seizures. However, there is concern that long-term use of antiseizure medications can impact vitamin D metabolism and may lead to poor bone health. Children with epilepsy are often at risk of injuries due to seizures and comorbidities. Poor underlying bone health might result in fracture and adversely afect the quality of life [2]. The present study is remarkable in highlighting that vitamin D defciency is common in children with epilepsy, the majority of whom were on valproate or levetiracetam longterm monotherapy, and especially with comorbid cerebral palsy [1]. Having a control group of 295 children, control over the infuence of season, and large sample size (n=269) of children with epilepsy were the strengths of the study. The limitations of the study were the lack of a causality relationship, lack of bone-density assessment, and inclusion of a large number of children with cerebral palsy in the study cohort. Overall, the present study suggests the need of pharmacological vitamin D and calcium supplementation in children with epilepsy, especially with comorbidity of cerebral palsy. Childhood epilepsy is a group of heterogeneous disorders and includes various age-related electroclinical syndromes from infancy to adolescence age, varying from self-limited epilepsies to drug-resistant epilepsies [3]. The therapeutic choice is also guided by underlying epilepsy diagnosis, e.g., a diagnosis of infantile spasms requires peculiar hormonal therapy. Perinatal insults are an important etiological cause of drug-resistant epilepsies and are associated with comorbidity of cerebral palsy [4]. Etiology and comorbidities are important determinants of long-term outcomes. Furthermore, one must carefully diferentiate treatment-emergent adverse effects of antiseizure medications with comorbidities. Now, various new antiseizure medications are increasingly available to treat childhood epilepsies, e.g., ethosuximide, brivaracetam, eslicarbazepine, vigabatrin, etc. [5]. Future studies should be targeted towards assessing the causal effect of new-generation antiseizure medications on bone health. Studies should be targeted towards specific electroclinical syndrome to have a more homogenous study population and wider external applicability.

在这期杂志中，Vijayakumar 和他的同事们试图回答一个基本问题，患有癫痫的儿童长期服用抗癫痫发作药物是否会影响维生素 D 水平？问题的出现是因为抗癫痫发作药物旨在通过控制癫痫发作来提高生活质量。然而，令人担心的是长期服用抗癫痫发作药物会影响维生素 D 代谢，可能导致骨骼健康不佳。癫痫患儿由于癫痫发作和共患病常有受伤的风险。潜在的骨骼健康状况不佳可能会导致骨折，并对生活质量产生不利影响。本研究值得注意的是，维生素 D 缺乏在癫痫儿童中很常见，其中大多数患儿长期接受丙戊酸钠或左乙拉西坦单药治疗，尤其是共病脑瘫的患者。有 295 名儿童作为对照组，控制季节的影响，以及大样本量（n=269）的癫痫儿童是本研究的优势。该研究的局限性在于缺乏因果关系，缺乏骨密度评估，以及在研究队列中纳入了大量脑瘫儿童。总的来说，本研究表明癫痫儿童，尤其是共病脑瘫的患儿需要补充维生素 D 和钙。儿童癫痫是一组异质性疾病，包括从婴儿期到青春期的不同年龄相关的电临床综合征，从自限性癫痫到耐药性癫痫。治疗选择也以潜在的癫痫诊断为指导，例如，诊断婴儿痉挛症需要特殊的激素治疗。围产期损害是耐药性癫痫的一个重要病因，与共病脑瘫有关。病因学和共患病是长期预后的重要决定因素。此外，必须仔细区分抗癫痫发作药物的治疗期不良事件(TEAE)与共患病。现在，各种各样的新型抗癫痫发作药物越来越多地用于治疗儿童癫痫，例如，乙琥胺、布瓦西坦、艾司利卡西平及氨己烯酸等。未来的研究应着眼于评估新一代抗癫痫发

作药物对骨骼健康的因果效应。研究应针对特定的电临床综合征，以获得更多同质的研究人群和更广的外部适用性。

14. 乙酰左旋肉碱对海人酸小鼠颞叶癫痫模型的神经保护和抗惊厥作用

Acetyl-L-Carnitine Exerts Neuroprotective and Anticonvulsant Effect in Kainate Murine Model of Temporal Lobe Epilepsy. *J Mol Neurosci. 2022 Jun;72(6):1224-1233. doi: 10.1007/s12031-022-01999-8. Epub 2022 Mar 23. PMID: 35320462.*

Tashakori-Miyanroudi M, Ramazi S, Hashemi P, Nazari-Serenjeh M, Baluchnejadmojarad T, Roghani M.

摘要：

The most well-known type of focal epilepsy that is resistant to existing treatments is temporal lobe epilepsy (TLE), with seizure foci in various structures including temporal lobe, hippocampus, amygdala, entorhinal cortex, and subcortex. The most significant processes involved in the pathophysiology of temporal lobe epilepsy (TLE) are oxidative stress, inflammation, and pyroptosis. There are evidences indicating that acetyl-l-carnitine (ALC) has anti-oxidative, anti-inflammatory, and anti-pyroptotic effects. In the present study, rat model of TLE was induced by intrahippocampal kainate and animals received ALC (100 mg/kg, p.o.). ALC properly attenuated intensity of seizures and also incidence of kainate-induced status epilepticus (SE). As well, obtained findings showed that ALC can partially reverse hippocampal levels of MDA, ROS, SOD, TNFa, NF-kB, TLR4, GFAP, and caspase 1. Besides, treatment of kainate group with ALC exerted a protective effect against CA1 neuronal loss and abnormal mossy fiber sprouting (MFS). Conclusively, these results suggest that ALC is capable to attenuate kainate-induced SE which is somewhat mediated through its lowering of oxidative stress, neuroinflammation, and pyroptosis that are related to its neuroprotective effect.

最广为人知的对现有治疗耐药的局灶性癫痫类型就是颞叶癫痫（TLE），其致痫灶存在于不同的结构中，包括颞叶、海马、杏仁核、内嗅皮质和皮层下。颞叶癫痫（TLE）最重要的病理生理过程是氧化应激、炎症和细胞焦亡。有证据表明，乙酰左旋肉碱（ALC）具有抗氧化、抗炎和抗细胞焦亡的作用。在本研究中，大鼠 TLE 模型由海马内微量注射海人酸诱导，并给予 ALC（100 mg/kg 口服）。ALC 可适当降低癫痫发作的强度以及海人酸诱导的癫痫持续状态（SE）的发生率。此外，研究结果表明，ALC 可部分逆转海马中 MDA、ROS、SOD、TNFa、NF-kB、TLR4、GFAP 和 caspase 1 的水平。此外，用 ALC 治疗的海人酸组对 CA1 神经元丢失和异常苔藓纤维出芽（MFS）有保护作用。综上所述，这些结果表明 ALC 能够减少海人酸诱导的 SE，这在某种程度上是通过其降低氧化应激、神经炎症和焦亡介导的，与其神经保护作用有关。

15. 老年患者癫痫切除性手术术后效果的预测因素

Predictive factors of postoperative outcome in the elderly after resective epilepsy surgery. *Rev Neurol (Paris). 2022;178(6):609-615. doi:10.1016/j.neurol.2021.08.011*

Thomas B, Aupy J, Penchet G, et al.

摘要：

OBJECTIVE: To evaluate the efficiency of resective epilepsy surgery (RES) in patients over 50 years and determine prognostic factors.

RESULTS: Over the 147 patients over 50 years (54.9±3.8 years [50-69]) coming from 8 specialized French centers for epilepsy surgery, 72.1%, patients were seizure-free and 91.2% had a good outcome 12 months after RES. Seizure freedom was not associated with the age at surgery or duration of epilepsy. In multivariate analysis, seizure freedom was associated with MRI and neuropathological hippocampal sclerosis (HS) (P=0.009 and P=0.028 respectively), PET hypometabolism (P=0.013), temporal epilepsy (P=0.01). On the contrary, the need for intracranial exploration was associated with a poorer prognosis (P=0.001). Postoperative number of antiepileptic drugs was significantly lower in the seizure-free group (P=0.001). Neurological adverse event rate after surgery was 21.1% and 11.7% of patients had neuropsychological adverse effects overall transient.

CONCLUSIONS: RES is effective procedure in the elderly. Even safe it remains at higher risk of complication and population should be carefully selected. Nevertheless, age should not be considered as a limiting factor, especially when good prognostic factors are identified..

目的：评估 50 岁以上患者切除性癫痫手术 (RES) 的疗效并确定预后因素。

结果：来自法国 8 个癫痫外科专科中心的 147 名 50 岁以上（54.9±3.8）的患者，72.1% 的患者在 RES 后 12 个月无癫痫发作，91.2% 的患者预后良好。 无癫痫发作与手术年龄或癫痫持续时间无关。在多因素分析中，无癫痫发作与 MRI 和神经病理性海马硬化（HS）（P=0.009 和 P=0.028）、PET 低代谢（P=0.013）、颞叶癫痫（P=0.01）相关。 相反，需要颅内探查与较差的预后有关（P=0.001）。 无癫痫发作组术后使用抗癫痫发作药物的数量显着降低（P=0.001）。术后神经系统不良事件发生率为 21.1%，11.7%的患者出现整体短暂性的神经心理不良反应。

结论：RES 在老年患者中是有效的治疗方法。 即使是安全的，并发症的风险仍然较高，应谨慎选择人群。然而，年龄不应被视为一个限制因素，尤其是在有明确好的预后时。

16. ABCB1 多态性对中国维吾尔族儿科癫痫患者拉考沙胺血清浓度的影响

Impact of ABCB1 Polymorphisms on Lacosamide Serum Concentrations in Uygur Pediatric Patients With Epilepsy in China.

Ther Drug Monit. 2022 Jun 1;44(3):455-464. doi: 10.1097/FTD.0000000000000927. Epub 2021 Oct 5. PMID: 34610620; PMCID: PMC9083488.

T, Li HJ, Feng J, Zhang HL, Ting-Ting W, Ma L, Yu J, Zhao WB, Sun L, Yu LH, Sun Y.

摘要：

BACKGROUND: P-glycoprotein, encoded by ABCB1 (or MDR1), may contribute to drug resistance in epilepsy by limiting gastrointestinal absorption and brain access to antiseizure medications. The study aimed to evaluate the impact of ABCB1 polymorphisms on lacosamide (LCM) serum concentrations in Uygur pediatric patients with epilepsy.

METHODS: The serum concentrations of LCM were determined by ultrahigh performance liquid chromatography, and the ABCB1 polymorphism was analyzed through polymerase chain reaction-fluorescence staining in situ hybridization. The χ2 test and the Fisher exact test were used to analyze the allelic and genotypic distributions of ABCB1 polymorphisms between the drug-resistant and drug-responsive patient groups. Differences in steady-state and dose-corrected LCM serum concentrations between different genotypes were analyzed using the one-way analysis of variance and the Mann-Whitney test.

RESULTS: A total of 131 Uygur children with epilepsy were analyzed, and of them, 41 demonstrated drug resistance. The frequency of the GT genotype of ABCB1 G2677T/A was significantly higher in the drug-resistant group than that in the drug-responsive group (P < 0.05, OR = 1.966, 95% CI, 1.060-3.647). Patients with the G2677T/A-AT genotype had a statistically significantly lower concentration-to-dose (CD) value than patients with the G2677T/A-GG genotype (mean: 0.6 ± 0.2 versus 0.8 ± 0.5 mcg/mL per mg/kg, P < 0.001). Significantly lower LCM serum concentrations were observed in ABCB1 C3435T CT and TT genotype carriers than those in the CC carriers (P = 0.008 and P = 0.002), and a significantly lower LCM CD value was observed in ABCB1 C3435T CT genotype carriers than that in the CC carriers (P = 0.042).

CONCLUSIONS: ABCB1 G2677T/A and C3435T polymorphisms may affect LCM serum concentrations and treatment efficacy in Uygur pediatric patients with epilepsy, leading to drug resistance in pediatric patients.

背景：由 ABCB1（或 MDR1）编码的 P 糖蛋白可能通过限制抗癫痫发作药物的胃肠道吸收以及进入脑部的通路从而导致癫痫的耐药。本研究旨在评估 ABCB1 多态性对维吾尔族儿童癫痫患者拉考沙胺（LCM）血清浓度的影响。

方法：采用超高效液相色谱法测定血清 LCM 浓度，采用聚合酶链反应荧光染色原位杂交法分析 ABCB1 多态性。采用χ2 检验和 Fisher 精确检验分析 ABCB1 多态性在耐药和药物反应患者组间的等位基因和基因型分布。使用单因素方差分析和 Mann-Whitney 检验分析不同基因型间稳态和剂量校正的 LCM 血清浓度的差异。

结果：共分析 131 例维吾尔族癫痫患儿，其中 41 例表现出耐药性。耐药组 ABCB1 G2677T/A 的 GT 基因型频率显著高于药物反应组（P<0.05，OR=1.966，95%CI，1.060-3.647）。与 G2677T/A-GG 基因型患者相比，G2677T/A-AT 基因型患者的剂量浓度（CD）值在统计学上显著降低（平均值：0.6±0.2 vs 0.8±0.5 mcg/mL/mg/kg，P<0.001）。ABCB1 C3435T CT 和 TT 基因型携带者的 LCM 血清浓度显著低于 CC 携带者（P=0.008 和 P=0.002），ABCB1 C3435T CT 基因型携带者的 LCM CD 值显著低于 CC 携带者（P=0.042）。

结论：ABCB1 G2677T/A 和 C3435T 多态性可能影响维吾尔族小儿癫痫患者 LCM 血药浓度和治疗效果，导致患儿耐药。

17. 1 型神经纤维瘤病中的海马硬化与癫痫外科手术：1 例 3 岁儿童的 SEEG 探查的病例报告及文献复习

Hippocampal sclerosis and epilepsy surgery in neurofibromatosis type 1: case report of a 3-year-old child explored by SEEG and review of the literature. *Childs Nerv Syst. 2022 Jun;38(6):1217-1221. doi: 10.1007/s00381-021-05343-0. Epub 2021 Sep 10. PMID: 34508273.*

Sculier C, Taussig D, Aeby A, Blustajn J, Bekaert O, Fohlen M.

摘要

PURPOSE: Epilepsy associated with neurofibromatosis type 1 (NF1) is infrequent and usually controlled with anti-epileptic drugs. However, in some drug-resistant patients a presurgical evaluation should be considered. Hippocampal sclerosis (HS) is one of the rare causes of epilepsy in neurofibromatosis type 1, which can lead to surgery.

METHODS: We present a three-year-old child with refractory epilepsy associated with several structural brain abnormalities but normal hippocampi on brain MRI and a heterozygous variant in the NF1 gene (c.2542G > A). A complete presurgical evaluation was performed including stereo-electroencephalography (SEEG).

RESULTS: Usual seizures were recorded, and the seizure onset zone was delineated in the anterior hippocampus. Pathological examination performed after a tailored mesio-temporal resection confirmed hippocampal sclerosis, and the child achieved seizure freedom with 2 years of follow-up.

CONCLUSION: This rare pediatric case illustrates that NF1 may be associated with early-onset refractory epilepsy secondary to MRI-negative HS, supporting the major role of SEEG in the presurgical evaluation of patients with extended cortical malformations.

目的：与 1 型神经纤维瘤病（NF1）相关的癫痫并不常见，通常使用抗癫痫发作药物控制。然而，对于一些耐药患者，应考虑术前评估。海马硬化（HS）是 1 型神经纤维瘤病中罕见的癫痫病因之一，可手术治疗。

方法：我们报告了一例患有难治性癫痫的三岁儿童，脑 MRI 显示多种脑结构异常，但海马结构正常，且 NF1 基因存在杂合突变（c.2542G>A）。对其进行了完整的术前评估，包括立体定向脑电图（SEEG）。

结果：记录了癫痫的惯常发作，并在海马前部划定了发作起源区域。裁剪式颞叶内侧切除术后进行病理检查证实为海马硬化，随访 2 年，患儿无癫痫发作。

结论：这例罕见的儿科病例表明，NF1 可能与继发于 MRI 阴性 HS 的早发难治性癫痫有关，支持 SEEG 在广泛皮质畸形患者术前评估中的重要作用。

18. 抗惊厥治疗儿童的维生素 D 状态

Vitamin D Status in Children on Anticonvulsant Therapy. *Indian J Pediatr. 2022 Jun;89(6):541-545. doi: 10.1007/s12098-021-03853-y. Epub 2021 Jul 28. PMID: 34318406*

Ruiz Herrero J, Cañedo Villarroya E, García Peñas JJ, García Alcolea B, Gómez Fernández B, Puerta Macfarland LA, Pedrón-Giner C.

摘要：

OBJECTIVE: To assess vitamin D status of children on long-term anticonvulsants, including the less studied widely used levetiracetam, and the potential risk factors for deficiency.

METHOD: Children on antiepileptic drugs (cases, n = 269) were compared with controls (n = 295) for serum biochemistry, 25OHD, parathormone (PTH), sun exposure, dietary calcium, and vitamin D intake.

RESULTS: Cases had lower serum 25OHD [median (IQR) 18.4 (11.5-24.1) ng/mL] compared to controls [20.8 (15.4-26.2] ng/mL, p < 0.001), as well as more frequent vitamin D deficiency (25OHD < 12 ng/mL, 27.1%) and insufficiency (25OHD < 20 ng/mL, 57.6%) than did controls (11.2% and 46.1%, respectively). Significantly lower median (IQR) serum calcium [8.8 (8.1-9.4) vs. 9.2 (8.5-10.0) mg/dL], phosphorous [3.8 (3.3-4.2) vs. 4.7 (4.0-5.3) mg/dL), and higher PTH [58.4 (42.9-85.8) vs. 38.9 (24.6-55.5) pg/mL, p < 0.001 for all] and proportion of elevated alkaline phosphatase (11.2% vs. 5.1%, p < 0.01) was seen in cases versus controls. Vitamin D deficiency was present in 53.4% of children with cerebral palsy (CP) versus 19.9% in those without CP (p < 0.001). Serum 25OHD did not differ between patients on cytochrome P450 inducers versus noninducers, neither among the 3 major groups, users of carbamazepine,

valproate, and levetiracetam. Logistic regression analysis showed serum 25OHD < 12 ng/mL to be independently influenced by case or control status, presence of CP, and season of sampling.

CONCLUSION: Vitamin D deficiency is common with anticonvulsant therapy, especially in those having CP. In Kerala, the hot, dry season from March to May is protective.

目的：评估长期服用抗惊厥药物（包括研究较少但广泛使用的左乙拉西坦）儿童的维生素 D 状况，以及维生素 D 缺乏的潜在危险因素。

方法：对服用抗癫痫发作药的儿童（n=269 例）和对照组（n=295 例）的血清生化、25OHD、甲状旁腺激素（PTH）、日光照射、膳食钙和维生素 D 摄入量进行比较。

结果：患者血清 25OHD[中位数（IQR）为 18.4（11.5-24.1）ng/mL]低于对照组[20.8（15.4-26.2）ng/mL，p<0.001]。患者组的维生素 D 缺乏（25OHD<12 ng/mL，27.1%）或不足（25OHD<20 ng/mL，57.6%）更多见，对照组分别为 11.2%和 46.1%。血清钙中位数(IQR)显著降低[8.8 (8.1-9.4)vs. 9.2 (8.5-10.0) mg/dL]，磷[3.8 (3.3-4.2)vs. 4.7 (4.0-5.3) mg/dL)]和 PTH 升高[58.4 (42.9-85.8)vs. 38.9 (24.6-55.5) pg/mL, p <0.01]；与对照组相比较，高碱性磷酸酶的比例更高(11.2% vs. 5.1%， p <0.01)。53.4%伴脑瘫(CP) 的患儿存在维生素 D 缺乏，而不伴 CP 的患儿为 19.9% (p < 0.001)。细胞色素 P450 诱导剂组和非诱导剂组患者的血清 25OHD 没有差异，在服用卡马西平、丙戊酸钠和左乙拉西坦的 3 个主要组中也没有差异。Logistic 回归分析显示血清 25OHD <12 ng/mL 受病例或对照，存在 CP 和取样季节的独立影响。

结论：维生素 D 缺乏症在抗惊厥治疗中很常见，尤其是患有 CP 的患者。在喀拉拉邦（译者注：印度西南部），3 月至 5 月的炎热干燥季节对其具有保护作用。

19. KCNQ2 脑病的成人表型

Adult phenotype of KCNQ2 encephalopathy. *J Med Genet. 2022 Jun;59(6):528-535. doi: 10.1136/jmedgenet-2020-107449. Epub 2021 Apr 2. PMID: 33811133.*

Boets S, Johannesen KM, Destree A, Manti F, Ramantani G, Lesca G, Vercueil L, Koenig MK, Striano P, Møller RS, Cooper E, Weckhuysen S.

摘要：

BACKGROUND: Pathogenic KCNQ2 variants are a frequent cause of developmental and epileptic encephalopathy.

METHODS: We recruited 13 adults (between 18 years and 45 years of age) with KCNQ2 encephalopathy and reviewed their clinical, EEG, neuroimaging and treatment history.

RESULTS: While most patients had daily seizures at seizure onset, seizure frequency declined or remitted during childhood and adulthood. The most common seizure type was tonic seizures (early) infancy, and tonic-clonic and focal impaired awareness seizures later in life. Ten individuals (77%) were seizure-free at last follow-up. In 38% of the individuals, earlier periods of seizure freedom lasting a minimum of 2 years followed by seizure recurrence had occurred. Of the 10 seizure-free patients, 4 were receiving a single antiseizure medication (ASM, carbamazepine,

lamotrigine or levetiracetam), and 2 had stopped taking ASM. Intellectual disability (ID) ranged from mild to profound, with the majority (54%) of individuals in the severe category. At last contact, six individuals (46%) remained unable to walk independently, six (46%) had limb spasticity and four (31%) tetraparesis/tetraplegia. Six (46%) remained non-verbal, 10 (77%) had autistic features/autism, 4 (31%) exhibited aggressive behavior and 4 (31%) destructive behavior with self-injury. Four patients had visual problems, thought to be related to prematurity in one. Sleep problems were seen in six (46%) individuals.

CONCLUSION: Seizure frequency declines over the years and most patients are seizure-free in adulthood. Longer seizure-free periods followed by seizure recurrence are common during childhood and adolescence. Most adult patients have severe ID. Motor, language and behavioral problems are an issue of continuous concern.

背景：致病性 KCNQ2 变异是发育性和癫痫性脑病的常见病因。

方法：我们招募了 13 名患有 KCNQ2 脑病的成年人（18 岁至 45 岁），回顾了他们的临床、脑电图、神经影像学和治疗史。

结果：虽然大多数患者在起病时每天均有癫痫发作，但癫痫发作的频率在儿童和成人期有所下降或缓解。最常见的癫痫发作类型是婴儿早期的强直发作，以及后期的强直-阵挛和局灶性发作伴知觉受损。在末次随访中有 10 人（77%）无癫痫发作。38%的患者早期无发作至少持续 2 年，而后癫痫复发。在 10 例癫痫无发作的患者中，4 例接受单一抗癫痫发作药物（卡马西平、拉莫三嗪或左乙拉西坦），2 例停止服用 ASM。智力障碍（ID）从轻度到重度，大多数（54%）属于重度。末次随访时，有 6 名患者（46%）仍不能独立行走，6 名患者（46%）肢体呈痉挛状态，4 人（31%）有四肢轻瘫/四肢瘫痪。6 人（46%）仍不能言语，10 人（77%）有孤独症表现/孤独症，4 人（31%）表现出攻击性行为，4 人（31%）有自残的破坏性行为。四名患者有视力问题，其中一名患者被认为与早产有关。6 名患者（46%）有睡眠问题。

结论：癫痫发作频率逐年下降，大多数患者在成年后无癫痫发作。较长的癫痫无发作期后的癫痫复发在儿童和青少年期很常见，大多数成年患者有严重的智力障碍。运动、语言和行为问题是一个持续关注的问题。

20. 接受连续脑电图监测的蛛网膜下腔出血患者的抗癫痫药物治疗及预后

Antiseizure Medication Treatment and Outcomes in Patients with Subarachnoid Hemorrhage Undergoing Continuous EEG Monitoring. *Neurocrit Care. DOI: 10.1007/s12028-021-01387-x*

Sahar F Zafar [1], Eric S Rosenthal [2], Eva N Postma [3], Paula Sanches [4].

Abstract

Background: Patients with aneurysmal subarachnoid hemorrhage (aSAH) with electroencephalographic epileptiform activity (seizures, periodic and rhythmic patterns, and sporadic discharges) are frequently treated with antiseizure medications (ASMs). However, the safety and effectiveness of ASM treatment for epileptiform activity has not been established. We used observational data to investigate the effectiveness of ASM treatment in patients with aSAH undergoing continuous electroencephalography (cEEG) to develop a causal hypothesis for testing in prospective trials.

Methods: This was a retrospective single-center cohort study of patients with aSAH admitted between 2011 and 2016. Patients underwent ≥ 24 h of cEEG within 4 days of admission. All patients received primary ASM prophylaxis until aneurysm treatment (typically within 24 h of admission). Treatment exposure was defined as reinitiation of ASMs after aneurysm treatment and cEEG initiation. We excluded patients with non-cEEG indications for ASMs (e.g., epilepsy, acute symptomatic seizures). Outcomes measures were 90-day mortality and good functional outcome (modified Rankin Scale scores 0-3). Propensity scores were used to adjust for baseline covariates and disease severity.

Results: Ninety-four patients were eligible (40 continued ASM treatment; 54 received prophylaxis only). ASM continuation was not significantly associated with higher 90-day mortality (propensity-adjusted hazard ratio [HR] = 2.01 [95% confidence interval (CI) 0.57-7.02]). ASM continuation was associated with lower likelihood for 90-day good functional outcome (propensity-adjusted HR = 0.39 [95% CI 0.18-0.81]). In a secondary analysis, low-intensity treatment (low-dose single ASM) was not significantly associated with mortality (propensity-adjusted HR = 0.60 [95% CI 0.10-3.59]), although it was associated with a lower likelihood of good outcome (propensity-adjusted HR = 0.37 [95% CI 0.15-0.91]), compared with prophylaxis. High-intensity treatment (high-dose single ASM, multiple ASMs, or anesthetics) was associated with higher mortality (propensity-adjusted HR = 6.80 [95% CI 1.67-27.65]) and lower likelihood for good outcomes (propensity-adjusted HR = 0.30 [95% CI 0.10-0.94]) compared with prophylaxis only.

Conclusions: Our findings suggest the testable hypothesis that continuing ASMs in patients with aSAH with cEEG abnormalities does not improve functional outcomes. This hypothesis should be tested in prospective randomized studies.

背景：伴有脑电图癫痫样活动（癫痫发作、周期性和节律性模式以及散发性放电）的动脉瘤性蛛网膜下腔出血 (aSAH) 患者经常接受抗癫痫发作药物(ASM) 治疗。然而，ASM 治疗癫痫样活动的安全性和有效性尚未确定。我们使用观察性数据来研究 ASM 治疗在接受连续脑电图 (cEEG)监测 的 aSAH 患者中的有效性，以建立一个用于前瞻性试验检验的因果假设。

方法：这是一项针对 2011 年至 2016 年间入院的 aSAH 患者的回顾性单中心队列研究。患者在入院 4 天内接受了≥ 24 小时的 cEEG。所有患者在动脉瘤治疗前(通常在入院后 24 小时内)都接受了 ASM 预防治疗。治疗暴露定义为动脉瘤治疗和 cEEG 启动后 ASM 的重新启动。我们排除了无 cEEG 适应症的 服用 ASM 患者（例如，癫痫、急性症状性癫痫发作）。结局指标是 90 天死亡率和良好的功能转归（改良 Rankin 量表评分 0-3）。倾向指数用于调整基线协变量和疾病严重程度。

结果：94 名患者符合条件（40 名继续 ASM 治疗；54 名仅接受预防治疗）。继续服用 ASM 与较高的 90 天死亡率无显著相关性（倾向调整风险比 [HR] = 2.01 [95% 置信区间 (CI) 0.57-7.02]），有较低的可能性与 90 天良好功能预后相关（倾向调整 HR = 0.39 [95% CI 0.18-0.81]）。在二次分析中，低强度治疗（低剂量单次 ASM）与死亡率无显著相关性（倾向调整 HR = 0.60 [95% CI 0.10-3.59]），尽管与预防性治疗相比，有较低的可能性与 90 天良好功能预后相关（倾向调整 HR = 0.37 [95% CI 0.15-0.91]）。与单纯的预防治疗相比，高强度治疗（大剂量单次 ASM、多种 ASM 或麻醉剂）与较高的死亡率（倾向调整的 HR = 6.80 [95% CI 1.67-27.65]）和可能性较低的良好预后（倾向调整的 HR = 0.30 [95% CI 0.10-0.94]）相关。

结论：我们的研究结果提出了一个可验证的假设，即在 cEEG 异常的 aSAH 患者中继续服用 ASM 并不会改善功能预后。这一假设应在前瞻性随机研究中进行验证。

副作用

1. 长期给予吡仑帕奈诱导的雄性小鼠攻击性行为的海马蛋白质组学分析

Hippocampal Proteomic Analysis in Male Mice Following Aggressive Behavior Induced by Long-Term Administration of Perampanel.

ACS Omega. 2022;7(23):19388-19400. Published 2022 Jun 1. doi:10.1021/acsomega.2c01008

Yang W, Ma L, Hai DM, et al.

摘要：

Antiepileptic drugs have been shown to be associated with inducing or exacerbating adverse psychotropic reaction, including aggressive behavior. Perampanel, the first pharmacological compound approved by the FDA in 2012, is an effective antiepileptic drug for intractable epilepsy but induces severe aggression. So far, the underlying molecular mechanisms of aggression induced by perampanel remain incompletely understood. In the present study, a model of aggressive behavior based on the clinical use of perampanel was established and resident-intruder test and open field test were performed. Changes in hippocampal protein profiles were detected by tandem mass tag (TMT) proteomics. The behavioral results indicated that long-term use of perampanel increased the aggressive behavior of C57BL/6J mice. Proteomic analysis revealed that 93 proteins were significantly altered in the hippocampus of the perampanel-treated group (corrected $p < 0.05$), which were divided into multiple functional groups, mainly related to synaptic function, synaptogenesis, postsynaptic density protein, neurite outgrowth, AMPA-type glutamate receptor immobilization, and others. Bioinformatic analysis showed that differentially expressed proteins were involved in synaptic plasticity and the Ras signaling pathway. Furthermore, validation results by western blot demonstrated that glutamate receptor 1 (GluA1) and phosphorylation of mitogen-activated protein kinase (ERK1/2) were notably up-regulated, and synaptophysin (Syn) and postsynaptic density 95 (PSD95) were down-regulated in perampanel-treated mice. Therefore, our results provide valuable insight into the molecular mechanisms of aggressive behavior induced by perampanel, as well as potential options for safety treatment of perampanel in the future.

抗癫痫药物已被证明与诱发或加重包括攻击性行为在内的精神性不良反应有关。吡仑帕奈是 2012 年 FDA 批准的首个药物化合物，是一种治疗难治性癫痫的有效抗癫痫药物，但会引起严重的攻击性。到目前为止，吡仑帕奈诱导攻击性的潜在分子机制仍不完全清楚。本研究建立了一个基于吡仑帕奈临床应用的攻击性行为模型，并进行了居住者-入侵者试验和旷场试验。采用串联质谱标签（TMT）蛋白质组学方法检测海马蛋白谱的变化。行为学结果表明，长期使用吡仑帕奈可增加 C57BL/6J 小鼠的攻击行为。蛋白质组学分析显示，吡仑帕奈治疗组海马中有 93 种蛋白质发生了显著改变（校正后 $p<0.05$），这些蛋白质分为多个功能组，主要与突触功能、突触形成、突触后致密蛋白、树突生长、AMPA 型谷氨酸受体固定化有关。生物信息分析表明，差异表达蛋白参与突触可塑性和 Ras 信号通路。此外，western blot 验证结果显示，吡仑帕奈处理的小鼠谷氨酸受体 1（GluA1）和丝裂原活化蛋白激酶（ERK1/2）的磷酸化显著上调，突触小泡蛋白（Syn）和突触后致密蛋白 95（PSD95）下调。因此，我们的研究结果为研究吡仑帕奈诱导的攻击行为的分子机制提供了有价值的见解，同时也为将来吡仑帕奈的安全治疗提供了可能的选择。

2. 异常诱导 p19Arf 介导的细胞衰老可导致神经发育缺陷

Aberrant induction of p19Arf-mediated cellular senescence contributes to neurodevelopmental defects.

PLoS Biol. 2022;20(6):e3001664. Published 2022 Jun 14. doi:10.1371/journal.pbio.3001664

Matteo Candeloro [1 2], John W Eikelboom [2 3], Noel Chan [2 3], Vinai Bhagirath [2 3], James D Douketis [2], Sam Schulman [2 4]

摘要：

Valproic acid (VPA) is a widely prescribed drug to treat epilepsy, bipolar disorder, and migraine. If taken during pregnancy, however, exposure to the developing embryo can cause birth defects, cognitive impairment, and autism spectrum disorder. How VPA causes these developmental defects remains unknown. We used embryonic mice and human organoids to model key features of VPA drug exposure, including exencephaly, microcephaly, and spinal defects. In the malformed tissues, in which neurogenesis is defective, we find pronounced induction of cellular senescence in the neuroepithelial (NE) cells. Critically, through genetic and functional studies, we identified p19Arf as the instrumental mediator of senescence and microcephaly, but, surprisingly, not exencephaly and spinal defects. Together, these findings demonstrate that misregulated senescence in NE cells can contribute to developmental defects.

丙戊酸（VPA）是一种广泛用于治疗癫痫、双相情感障碍和偏头痛的处方药。然而，如果在怀孕期间服用，暴露于发育中的胚胎可能会导致出生缺陷、认知障碍和孤独症谱系障碍。VPA 是如何导致这些发育缺陷的尚不清楚。我们使用胚胎小鼠和人类类器官来模拟 VPA 药物暴露的关键特征，包括露脑畸形、小头畸形和脊柱缺陷。在神经发生缺陷的畸形组织中，我们发现神经上皮（NE）细胞明显诱导细胞衰老。关键的是，通过遗传学和功能研究，我们确定 p19Arf 是衰老和小头畸形的中介环节，令人惊讶的是，p19Arf 并不是露脑和脊柱缺陷的中间环节。总之，这些发现表明，NE 细胞的衰老失调可导致发育缺陷。

3. 药物相关性高氨血症：WHO 药物安全数据库的贝叶斯分析

Drug-associated hyperammonaemia: a Bayesian analysis of the WHO Pharmacovigilance Database.

Ann Intensive Care. 2022;12(1):55. Published 2022 Jun 18. doi:10.1186/s13613-022-01026-4

Balcerac A, Bihan K, Lebrun-Vignes B, Thabut D, Salem JE, Weiss N.

摘要：

BACKGROUND: Hyperammonaemia is frequent in Intensive Care Unit patients. Some drugs have been described as associated with this condition, but there are no large-scale studies investigating this topic and most descriptions only consist of case-reports.

METHODS: We performed a disproportionality analysis using VigiBase, the World Health Organization Pharmacovigilance Database, using the information component (IC). The IC compares observed and expected values to find associations between drugs and hyperammonaemia using disproportionate Bayesian reporting. An IC0.25 (lower end of the IC 95%

credibility interval) > 0 is considered statistically significant. The main demographic and clinical features, confounding factors, and severity of cases have been recorded.

RESULTS: We identified 71 drugs with a disproportionate reporting in 2924 cases of hyperammonaemia. Most of the suspected drugs could be categorized into 4 main therapeutic classes: oncologic drugs, anti-epileptic drugs, immunosuppressants and psychiatric drugs. The drugs most frequently involved were valproic acid, fluorouracil, topiramate, oxaliplatin and asparaginase. In addition to these molecules known to be responsible for hyperammonaemia, our study reported 60 drugs not previously identified as responsible for hyperammonaemia. These include recently marketed molecules including anti-epileptics such as cannabidiol, immunosuppressants such as basiliximab, and anti-angiogenics agents such as tyrosine kinase inhibitors (sunitinib, sorafenib, regorafenib, lenvatinib) and monoclonal antibodies (bevacizumab, ramucirumab). The severity of cases varies depending on the drug class involved and high mortality rates are present when hyperammonaemia occurs in patients receiving immunosuppressant and oncologic drugs.

CONCLUSIONS: This study constitutes the first large-scale study on drug-associated hyperammonaemia. This description may prove useful for clinicians in patients' care as well as for trial design.

背景：高氨血症在重症监护室的患者中很常见。一些药物被认为与这种情况有关，但没有大规模的研究调查这一主题，大多数描述仅包括病例报告。

方法：我们应用 WHO 药物安全数据库 VigiBase 中的信息组件（IC）进行了歧化分析。IC 比较观察值和预期值，使用歧化贝叶斯报告以发现药物与高氨血症之间的关系。IC0.25（IC 95%可信区间的下限）>0 被认为具有统计学意义。记录了主要的人口学和临床特征、混杂因素和病例的严重程度。

结果：我们在 2924 例高氨血症病例中发现了 71 种歧化报告的药物。大部分可疑药物可分为 4 类：肿瘤药物、抗癫痫药物、免疫抑制剂和精神类药物。最常涉及的药物是丙戊酸、氟尿嘧啶、托吡酯、奥沙利铂和利血生。除了这些已知的可引起高氨血症的药物外，我们的研究还报告了 60 种以前未被确定为可导致高氨血症的药物。这些药物包括最近上市的药物，包括抗癫痫药物如大麻二酚、免疫抑制剂如巴利昔单抗，和抗血管生成药物如酪氨酸激酶抑制剂（舒尼替尼、索拉菲尼、瑞格拉非尼、乐伐替尼）和单克隆抗体（贝伐单抗、雷莫芦单抗）。病例的严重程度取决于所涉及的药物类别，当接受免疫抑制剂和肿瘤药物的患者出现高氨血症时，就会出现高死亡率。

结论：本研究是首个对药物相关性高氨血症进行的大规模研究。这一描述可能被证明对临床医生在病人护理和试验设计中是有用的。

4. 药物与 T 细胞相互作用的认识进展：严重皮肤药物反应中发现生物标志物的意义

Advances in Our Understanding of the Interaction of Drugs with T-cells: Implications for the Discovery of Biomarkers in Severe Cutaneous Drug Reactions.

Chem Res Toxicolhttps://pubmed.ncbi.nlm.nih.gov/35704769/ DOI: 10.1021/acs.chemrestox.1c00434

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Abstract

Drugs can activate different cells of the immune system and initiate an immune response that can lead to life-threatening diseases collectively known as severe cutaneous adverse reactions (SCARs). Antibiotics, anticonvulsants, and antiretrovirals are involved in the development of SCARs by the activation of αβ naïve T-cells. However, other subsets of lymphocytes known as nonconventional T-cells with a limited T-cell receptor repertoire and innate and adaptative functions also recognize drugs and drug-like molecules, but their role in the pathogenesis of SCARs has only just begun to be explored. Despite 30 years of advances in our understanding of the mechanisms in which drugs interact with T-cells and the pathways for tissue injury seen during T-cell activation, at present, the development of useful clinical biomarkers for SCARs or predictive preclinical in vitro assays that could identify immunogenic moieties during drug discovery is an unmet goal. Therefore, the present review focuses on (i) advances in the understanding of the pathogenesis of SCARs reactions, (ii) a description of the interaction of drugs with conventional and nonconventional T-cells, and (iii) the current state of soluble blood circulating biomarker candidates for SCARs.

药物可以激活免疫系统的不同细胞并引发免疫反应，从而导致危及生命的疾病，统称为严重皮肤不良反应(SCARs)。 抗生素、抗惊厥药和抗逆转录病毒药物通过激活 αβ初始 T 细胞参与 SCARs 的发展。 然而，被称为非常规 T 细胞的其他淋巴细胞亚群，具有有限的 T 细胞受体库和先天适应性功能，也会识别药物和药物样分子，但人们对它们在 SCARs 发病机制中的作用才刚刚开始探索。 尽管近 30 年，我们对药物与 T 细胞相互作用的机制以及在 T 细胞激活过程中组织损伤通路的认识取得一些进展，但目前开发用于 SCARs 的有用临床生物标志物或能够在药物发现过程中识别免疫原性部分的预测性临床前体外试验仍是一个未达到的目标。因此，本综述的重点是 (i) 对 SCARs 反应发病机制的认识进展，(ii) 药物与常规和非常规 T 细胞相互作用的描述，以及(iii)SCARs 可溶性血液循环生物标志物候选物的现状。

5. 丙戊酸包裹的稳定核壳脂质体-壳聚糖纳米载体对 PC12 细胞系向神经元分化的影响

Differentiation of PC12 cell line into neuron by Valproic acid encapsulated in the stabilized core-shell liposome-chitosan Nano carriers. Int J Biol Macromol DOI: 10.1016/j.ijbiomac.2022.05.021 https://pubmed.ncbi.nlm.nih.gov/35723537/

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Abstract

Valproic acid (VPA) usage in high dose is teratogenic low bioavailability. Hence to improve its efficacy and reduce its side effect it was encapsulated by the Nano liposomes and stabilized by the chitosan at different concentrations. The cellular uptake, biocompatibility, loading and encapsulation efficiency of the six-different formulations (1:1, 2:1, and 4:1 of chitosan-phospholipids: VPA), PC12 differentiation to neuron cells assays (gene-expression level by qRT-PCR) were conducted for the efficacy assessment of the Nano carriers. The encapsulation efficiency (EE) results revealed that the encapsulation of the VPA corresponds to the phospholipids dose, where 2:1 formulations showed higher encapsulating rate (64.5% for non-coated and 80% for coated by chitosan). The time monitored released of VPA also showed that the chitosan could enhance its controlled release too. The cellular uptake exhibited similar uptake behavior for both the coated and the non-coated Nano carriers and cytoplasmic distribution. We witnessed no toxicity effects, at different concentrations, for both formulations. Moreover, the results indicated that the gene expression level of SOX2, NeuroD1, and Neurofilament 200 increased from 1 to 5 folds for different genes. The qRT-PCR data were confirmed by the immunofluorescence antibodies staining, where Neurofilament 68 and SOX2 cell markers were modulated during differentiation of PC12 cells. Finally, our findings suggest promising potential for the Lip-VPA-Chit Nano carrier in inducing the differentiation of PC12 into neuron for treating neurodegenerative disorders.

高剂量丙戊酸 (VPA) 可致畸，且生物利用度低。 因此，为提高其疗效并减少副作用，我们将其包裹在纳米脂质体中，并用不同浓度的壳聚糖来稳定。通过对六种不同配方（壳聚糖-磷脂：VPA 的 1:1、2:1 和 4:1）的细胞摄取、生物相容性、负载和包封率，PC12 向神经元细胞的分化实验（qRT-PCR 的基因表达水平) 评估纳米载体的有效性。结果表明，VPA 的包封率与磷脂剂量有关，其中 2:1 制剂的包封率更高（未包衣的为 64.5%，壳聚糖包衣的为 80%）。时间监测表明，壳聚糖对 VPA 的控释也有一定的促进作用。包被和未包被纳米载体的细胞摄取行为和细胞质分布相似。我们发现两种配方在不同浓度下均无毒性作用。结果表明， SOX2、NeuroD1 和 Neurofilament 200 的基因表达水平增加了 1- 5 倍。免疫荧光抗体染色证实了 qRT-PCR 数据，其中神经丝 68 和 SOX2 细胞标记物在 PC12 细胞分化过程中被调控。最后，我们的研究结果表明 Lip-VPA-Chit 纳米载体在诱导 PC12 分化为神经元以治疗神经退行性疾病方面具有广阔的潜力。

6. 地西泮的氯消毒副产物影响斑马鱼神经系统功能并具有性别差异

Chlorine disinfection byproduct of diazepam affects nervous system function and possesses gender-related difference in zebrafish.

Ecotoxicol Environ Saf DOI: 10.1016/j.ecoenv.2022.113568

Xiaole Zhao [1] ,Xiaoyong Huang [2] ,Wenjing Peng [3]

Abstract

Chlorinated disinfection byproducts in water posed potential health threat to humans. Nowadays, chlorinated derivatives of diazepam were ubiquitously detected in drinking water. Among these derivatives, 2-methylamino-5-chlorobenzophenone (MACB) was capable of penetrating the blood-brain barrier (BBB) and induced microglial phagocytosis of neurons in zebrafish. However, little is known about the MACB metabolism in vivo. Here, we determined the metabolism of MACB in zebrafish and microglia cell model. We found that MACB mainly disrupted the metabolism of branched-chain amino acids (Leu, Ile and Val) in zebrafish model and gamma-aminobutyric acid (GABA) pathway-related amino acids in microglia model. Additionally, we demonstrated that MACB can be metabolized by the mixed-function oxidase CYP1A2 enzyme which could be inhibited by estrogen causing the gender-difference in the accumulation of MACB in vivo. These results indicated that MACB perturbed metabolism and induced neurological disorders, particularly in the female zebrafish.

水中含氯消毒副产物对人类健康构成潜在威胁。 如今，地西泮的氯化衍生物在饮用水中无处不在。 在这些衍生物中，2-甲氨基-5-氯二苯甲酮（MACB）能够穿透血脑屏障（BBB）并诱导斑马鱼神经元的小胶质细胞吞噬作用。 然而，人们对体内 MACB 代谢知之甚少。 在此，我们测定了斑马鱼和小胶质细胞模型中 MACB 的代谢。我们发现 MACB 主要破坏斑马鱼模型中支链氨基酸（Leu、Ile 和 Val）的代谢，以及小胶质细胞模型中与 γ-氨基丁酸 (GABA) 通路相关的氨基酸的代谢。此外，我们证明 MACB 可以被多功能氧化酶 CYP1A2 代谢，该酶可以被雌激素抑制，导致 MACB 在体内积累的性别差异。 这些结果表明 MACB 干扰新陈代谢并诱发神经系统疾病，特别是在雌性斑马鱼中。

7. 唑尼沙胺、舒噻嗪、拉考沙胺、氯巴占和卢非酰胺抗癫痫药物对青春期前非癫痫大鼠卵巢卵泡发生影响的研究

An Investigation of the Effects of Chronic Zonisamide, Sultiam, Lacosamide, Clobazam, and Rufinamide Antiseizure Drugs on Foliculogenesis in Ovarian Tissue in Prepubertal Non-Epileptic Rats.

DOI: 10.1002/jdn.10200

Pınar Özkan Kart [1], Seren Gülşen Gürgen [2], Gülnur Esenülkü [1], Beril Dilber [1], Nihal Yıldız [1]

Abstract

We aimed to determine the morphological and histological effects of zonisamide, sultiam, lacosamide, clobazam, and rufinamide on ovarian folliculogenesis in rats. Sixty female Wistar rats were equally divided into 6 experimental groups, including control group, zonisamide, sultiam, lacosamide, clobazam, and rufinamide were administered by gavage for 90 days. According to the daily vaginal smears of the rats in the proestrus and diester phases of the estrus cycle, their ovaries were removed and placed in the fixation solution. Immunohistochemical and apoptosis staining protocols were applied. The number of healthy follicles in the control group was found to be statistically significantly higher when compared to the antiseizure drug groups ($p<0.001$). The number of corpus luteum was found to be statistically significantly lower in the control group when compared with the anti-seizure drug groups ($p<0.001$). There was a significant difference in the number of TUNEL positive apoptotic follicles between the control and drug groups ($p<0.001$). HSCORE, immunohistochemical EGF, IGF-1 and GDF-9 staining, a very strong immunoreaction was observed in the ovarian multilaminar primary follicle granulosa cells and oocytes in the control group ($p<0.001$), and an immunoreaction ranging from weak to medium was observed in the antiseizure drug groups. Long-term anti-seizure drug therapy with zonisamide, sultiam, lacosamide, clobazam, and rufinamide from prepubertal to adulthood causes apoptosis and disruption of folliculogenesis in the ovarian follicles of nonepileptic rats.

我们旨在确定唑尼沙胺、舒噻嗪、拉考沙胺、氯巴占和卢非酰胺对大鼠卵泡发生的形态学和组织学影响。60 只雌性 Wistar 大鼠均分为 6 个实验组，包括对照组、唑尼沙胺组、舒噻嗪组、拉考沙胺组、氯巴占组及卢非胺组，灌胃 90 天。 根据发情前期和发情周期二酯期大鼠每日阴道涂片，取出卵巢置于固定液中。 应用免疫组织化学和细胞凋亡染色法。 与抗癫痫药物组相比，对照组中健康卵泡的数量在统计学上显著增加（$p<0.001$）。 与抗癫痫药物组相比，对照组的黄体数量在统计学上显著降低（$p<0.001$）。 对照组和药物组之间 TUNEL 阳性凋亡卵泡的数量存在显著差异（$p<0.001$）。 HSCORE、免疫组化 EGF、IGF-1 和 GDF-9 染色显示，对照组卵巢多层原代卵泡颗粒细胞和卵母细胞有很强的免疫反应（$p<0.001$），抗癫痫药物组的免疫反应从弱到中等。从青春期前到成年期，长期使用唑尼沙胺、舒噻嗪、拉考沙胺、氯巴占和卢非酰胺等抗癫痫药物治疗会导致非癫痫大鼠卵巢卵泡凋亡和卵泡发育中断。

机制研究

1. 自闭症小鼠丙戊酸模型小脑的大小异常及 GABA 能酶表达的改变

Size anomaly and alteration of GABAergic enzymes expressions in cerebellum of a valproic acid mouse model of autism

Behav Brain Res https://pubmed.ncbi.nlm.nih.gov/35429883/ DOI: 10.1016/j.bbr.2022.113896

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Abstract

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by social communication deficit and repetitive behavior. In the past few years, increasing clinical evidence has shown that the cerebellum may contribute to the neuropathology of ASD. However, studies in the mechanism for the involvement of the cerebellum in autism remained speculative. Although some have suggested the possibility of a change of glutamate decarboxylases in the cerebellum of autistic patients, this remains controversial and is limited to the alteration in transcriptional level. This study aimed to investigate the cerebellar structure and determine the expression of rate-limiting GABAergic enzymes in GABA signaling of the autism cerebellum. Pregnant C57BL/6 J mice were intraperitoneally injected with a dosage of 500 mg/kg valproic acid (VPA) on embryonic day 10.5 for autistic behavioral induction. This study found that early prenatal exposure to VPA led to tail deformation and decreased cerebellar weight and size. Early adult mouse models with autistic behavior showed reduced expression of both isoforms of glutamate decarboxylases (GAD) 65 and 67 in the cerebellum. Also, protein expressions of cerebellar type 1 GABA transporter (GAT-1) and GABA transaminase (GABAT) were reduced in VPA mice. It indicated that abnormal GABA production, recycling, and metabolism could alter the excitatory-inhibitory balance in the autistic cerebellum. Thus, our findings provide supporting evidence that cerebellum impairment could be an etiology of environmentally induced autism. Changes in cerebellar structure and the altered GABAergic enzymes in the cerebellum provide targets for future therapeutic studies in idiopathic autism

自闭症谱系障碍（ASD）是一种以社交障碍和重复行为为特征的神经发育障碍。 在过去的几年中，越来越多的临床证据表明小脑可能参与 ASD 的神经病理学改变。然而，关于小脑参与自闭症的机制的研究仍然是推测性的。尽管有些人提出了自闭症患者小脑中谷氨酸脱羧酶可能发生变化，但这仍然存在争议并且仅限于转录水平的改变。本研究旨在研究自闭症小脑 GABA 信号通路的小脑结构，并确定 GABA 限速酶的表达。妊娠 C57BL/6 J 小鼠在胚胎第 10.5 天腹腔注射 500 MG/KG 丙戊酸 (VPA) 以诱导自闭症行为。本研究发现，产前早期暴露于 VPA 会导致尾部变形及小脑的重量和大小下降。 具有自闭症行为的早期成年小鼠模型显示小脑中谷氨酸脱羧酶 (GAD) 65 和 67 两种亚型的表达降低。 此外，VPA 小鼠中，小脑 1 型 GABA 转运蛋白 (GAT-1) 和 GABA 转氨酶 (GABAT) 的蛋白质表达也降低。这表明异常的 GABA 产生、循环和代谢可改变自闭症小脑的兴奋-抑制平衡。因此，我们的研究结果为小脑损伤可能是环境诱发自闭症的病因提供了支持证据。小脑结构的变化和小脑中改变的 GABA 能酶为未来特发性自闭症的治疗研究提供了靶点。

2. 毛喉素诱导分化的 BeWo 细胞中抗癫痫药物的摄取：加巴喷丁转运的改变

Uptake of antiepileptic drugs in forskolin-induced differentiated BeWo cells: alteration of gabapentin transport

Xenobiotica DOI: 10.1080/00498254.2022.2085635

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Abstract

Previous studies have indicated that the expression levels of several transporters are altered during placental trophoblast differentiation. However, changes in the transport activities of therapeutic agents during differentiation must be comprehensively characterized. Antiepileptic drugs, including gabapentin (GBP), lamotrigine (LTG), topiramate, and levetiracetam, are increasingly prescribed during pregnancy. The objective of this study was to elucidate differences in the uptake of antiepileptic drugs during the differentiation process. Human placental choriocarcinoma BeWo cells were used as trophoblast models. For differentiation into syncytiotrophoblast-like cells, cells were treated with forskolin. The uptake of GBP and LTG was lower in differentiated BeWo cells than in undifferentiated cells. In particular, the maximum uptake rate of GBP transport was decreased in differentiated BeWo cells. Furthermore, GBP transport was trans-stimulated by the amino acids His and Met. We investigated the profiles of amino acids in undifferentiated and differentiated BeWo cells. Supplementation with His and Met, which demonstrated trans-stimulatory effects on GBP uptake, restored GBP uptake in differentiated cells. The findings of this study suggest that drug transport in BeWo cells can be altered before and after differentiation, and that the altered GBP uptake could be mediated by the intracellular amino acid status.

既往研究表明，胎盘滋养层分化过程中，几种转运蛋白的表达水平发生了变化。然而，在分化过程中，治疗药物转运活性的变化必须得到全面的描述。抗癫痫药物，包括加巴喷丁 (GBP)、拉莫三嗪 (LTG)、托吡酯和左乙拉西坦，在怀孕期间越来越多地被使用。本研究的目的是阐明分化过程中抗癫痫药物摄取的差异。以人胎盘绒癌 BeWo 细胞作为滋养细胞模型。 为了分化成合胞滋养层样细胞，用毛喉素处理细胞。GBP 和 LTG 在分化的 BeWo 细胞中的摄取低于未分化细胞。特别是，在分化的 BeWo 细胞中，GBP 转运的最大摄取率降低。此外，氨基酸 His 和 Met 对 GBP 转运有反式刺激作用。我们研究了未分化和分化的 BeWo 细胞中的氨基酸谱。补充 His 和 Met 证明了对 GBP 摄取的反式刺激作用，可恢复分化细胞中 GBP 的摄取。本研究的结果表明，BeWo 细胞中的药物转运可以在分化前后发生改变，而 GBP 摄取的改变可能与细胞内氨基酸状态有关。

3. 临床推理：不明原因的小儿癫痫发作

Clinical Reasoning: Pediatric Seizures of Unknown Cause

Neurology https://pubmed.ncbi.nlm.nih.gov/35470136/ DOI: 10.1212/WNL.0000000000200711

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Abstract

We describe a neonate and a 14-month-old child presenting with seizures that were not (completely) controlled with antiepileptic medications. There were no signs of infection, and electrolytes and neuroimaging were normal. In the neonate, pyridoxine was administered followed by cessation of seizures, and a diagnosis of pyridoxine-dependent epilepsy (PDE-ALDH7A1, a neurometabolic disorder of lysine metabolism) was genetically confirmed. The 14-month-old child received a genetic diagnosis of PDE-ALDH7A1 after abnormalities in the metabolic investigations. Both children were treated with pyridoxine and adjunct lysine reduction therapy (LRT). Seizures were controlled completely, but both children are developmentally delayed. During her second pregnancy, the mother of the neonate was started on pyridoxine treatment because of the risk of PDE-ALDH7A1. After delivery, pyridoxine treatment was continued in the neonate, who

did not show any clinical symptoms. Molecular analysis identified the familial variants consistent with the diagnosis of PDE-ALDH7A1. Adjunct LRT was initiated. This child has never experienced seizures, and development has been completely normal thus far (age 2.9 years), despite the shared genotype with their sibling with developmental delays (DDs). In conclusion, in neonates, infants, and children presenting with seizures of unknown origin with partial or no response to common antiepileptic medications, the diagnosis of PDE-ALDH7A1 or other pyridoxine-responsive genetic epilepsies should be considered, prompting a trial of pyridoxine as "diagnostic therapeuticum." The digital application Treatable-ID (treatable-id.org) can support clinicians in the early diagnosis of treatable conditions in patients presenting with DD/intellectual disability of unknown cause.

我们描述了一名新生儿和一名 14 个月大的儿童，他们的癫痫发作没有（完全）用抗癫痫药物控制。 没有感染迹象，电解质和神经影像学检查正常。 在新生儿中，给予吡哆醇后癫痫发作停止，并在基因上证实了吡哆醇依赖性癫痫（PDE-ALDH7A1，一种赖氨酸代谢的神经代谢紊乱）的诊断。 这名 14 个月大的孩子在代谢检查异常后被给予 PDE-ALDH7A1 基因诊断。 两名儿童都接受了吡哆醇和辅助性赖氨酸限制疗法 (LRT) 的治疗。 癫痫发作得到完全控制，但两个孩子都发育迟缓。在第二次怀孕期间，由于存在 PDE-ALDH7A1 的风险，新生儿的母亲开始接受吡哆醇治疗。分娩后，新生儿继续接受吡哆醇治疗，未出现任何临床症状。通过分子分析确定了与 PDE-ALDH7A1 诊断一致的家族性变异。 启动辅助性赖氨酸限制疗法 (LRT)。 这个孩子从未经历过癫痫发作，到目前为止发育完全正常（2.9 岁），尽管与发育迟缓 (DDs) 的兄弟姐妹有共同的基因型。 总之，对于出现不明原因的癫痫发作，且对常用抗癫痫药物有部分反应或无反应的新生儿、婴儿和儿童，应考虑诊断为 PDE-ALDH7A1 或其他对吡哆醇有反应的遗传性癫痫，促使吡哆醇作为“诊断治疗”的试验。数字应用程序 Treatable-ID (treatable-id.org) 可以支持临床医生对出现不明原因的 DD/智力残疾的患者进行可治疗疾病的早期诊断。

4. 在阿尔茨海默病模型中，一种阻断 ADORA1-neurabin 相互作用的肽具有抗惊厥和抑制癫痫发作的作用

A peptide blocking the ADORA1-neurabin interaction is anticonvulsant and inhibits epilepsy in an Alzheimer's model

JCI Insight https://pubmed.ncbi.nlm.nih.gov/35674133/ DOI: 10.1172/jci.insight.155002

Shalini Saggu [1], Yunjia Chen [1], Liping Chen [1], Diana Pizarro [2]

Abstract

Epileptic seizures are common sequelae of stroke, acute brain injury, and chronic neurodegenerative diseases, including Alzheimer's disease (AD), and cannot be effectively controlled in approximately 40% of patients, necessitating the development of novel therapeutic agents. Activation of the A1 receptor (A1R) by endogenous adenosine is an intrinsic mechanism to self-terminate seizures and protect neurons from excitotoxicity. However, targeting A1R for neurological disorders has been hindered by side effects associated with its broad expression outside the nervous system. Here we aim to target the neural-specific A1R/neurabin/regulator of G protein signaling 4 (A1R/neurabin/RGS4) complex that dictates A1R signaling strength and response outcome in the brain. We developed a peptide that blocks the A1R-neurabin interaction to enhance A1R activity. Intracerebroventricular or i.n. administration of this peptide shows marked protection against kainate-induced seizures and neuronal death. Furthermore, in an AD mouse model with spontaneous seizures, nasal delivery of this blocking peptide reduces epileptic spike frequency. Significantly, the anticonvulsant and

neuroprotective effects of this peptide are achieved through enhanced A1R function in response to endogenous adenosine in the brain, thus, avoiding side effects associated with A1R activation in peripheral tissues and organs. Our study informs potentially new anti-seizure therapy applicable to epilepsy and other neurological illness with comorbid seizures.

癫痫发作是中风、急性脑损伤和包括阿尔茨海默病 (AD) 在内的慢性神经退行性疾病的常见后遗症，大约 40% 的患者无法有效控制，因此需要开发新的治疗药物。 内源性腺苷激活 A1 受体 (A1R) 是自我终止癫痫发作和保护神经元免受兴奋性毒性的内在机制。然而，由于 A1R 在神经系统外广泛表达，其副作用阻碍了对神经系统疾病的靶向治疗。我们的目标是针对神经特异性的 A1R/ F 肌动蛋白结合蛋白/ G 蛋白信号 4 调节因子 (A1R/neurabin/RGS4)复合体，它决定了大脑中 A1R 信号强度和反应结果。 我们开发了一种肽，可阻断 A1R- F 肌动蛋白结合蛋白相互作用以增强 A1R 活性。 脑室内或静脉注射该肽对海人酸诱导的癫痫发作和神经元死亡有显著保护作用。 此外，在自发性癫痫发作的 AD 小鼠模型中，这种阻断肽的鼻腔给药可降低癫痫放电频率。重要的是，这种肽的抗惊厥和神经保护作用是通过增强 A1R 功能来响应大脑中的内源性腺苷来实现的，从而避免与外周组织和器官中 A1R 激活相关的副作用。我们的研究提示了潜在的新的抗癫痫疗法，适用于癫痫和其他神经系统疾病的共病癫痫。

5. ATP 门控 P2X7 受体的表达增加会降低小鼠癫痫持续状态期间对抗惊厥药的反应性

Increased expression of the ATP-gated P2X7 receptor reduces responsiveness to anti-convulsants during status epilepticus in mice

Br J Pharmacol DOI: 10.1111/bph.15785

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Abstract

Background and purpose: Refractory status epilepticus is a clinical emergency associated with high mortality and morbidity. Increasing evidence suggests neuroinflammation contributes to the development of drug-refractoriness during status epilepticus. Here, we have determined the contribution of the ATP-gated P2X7 receptor, previously linked to inflammation and increased hyperexcitability, to drug-refractory status epilepticus and its therapeutic potential.

Experimental approach: Status epilepticus was induced via a unilateral microinjection of kainic acid into the amygdala in adult mice. Severity of status epilepticus was compared in animals with overexpressing or knock-out of the P2X7 receptor, after inflammatory priming by pre-injection of bacterial lipopolysaccharide (LPS) and in mice treated with P2X7 receptor-targeting and anti-inflammatory drugs.

Key results: Mice overexpressing P2X7 receptors were unresponsive to several anticonvulsants (lorazepam, midazolam, phenytoin and carbamazepine) during status epilepticus. P2X7 receptor expression increased in microglia during status epilepticus, at times when responses to anticonvulsants were reduced. Overexpression of P2X7 receptors induced a pro-inflammatory phenotype in microglia during status epilepticus and the anti-inflammatory drug minocycline restored normal responses to anticonvulsants in mice overexpressing P2X7 receptors. Pretreatment of wild-type mice with LPS increased P2X7 receptor levels in the brain and reduced responsiveness to anticonvulsants during status epilepticus, which was overcome by either genetic deletion of P2X7 receptors or treatment with the P2X7 receptor antagonists, AFC-5128 or ITH15004.

Conclusion and implications: Our results demonstrate that P2X7 receptor-induced pro-inflammatory effects contribute to resistance to pharmacotherapy during status epilepticus. Therapies targeting P2X7 receptors could be novel adjunctive treatments for drug-refractory status epilepticus.

背景和目的：难治性癫痫持续状态是一种与高死亡率和高发病率的临床急症。越来越多的证据表明，神经炎症有助于癫痫持续状态期间药物难治性的发展。在这里，我们已经确定了 ATP 门控 P2X7 受体对药物难治性癫痫持续状态的作用及其治疗潜力，该受体以前与炎症和高兴奋性有关。

实验方法：将海人酸单侧显微注射到成年小鼠杏仁核诱导癫痫持续状态。在 P2X7 受体过表达或敲除的动物中，通过预注射细菌脂多糖(LPS)引发炎症后，在 P2X7 受体靶向药物和抗炎药物治疗的小鼠中，比较癫痫持续状态的严重程度。

主要结果：过表达 P2X7 受体小鼠在癫痫持续状态期间对几种抗惊厥药物(劳拉西泮、咪达唑仑、苯妥英和卡马西平)无反应。癫痫持续状态时，小胶质细胞 P2X7 受体表达增加，抗惊厥药物反应降低。 P2X7 受体的过表达在癫痫持续状态期间诱导小胶质细胞中的促炎表型，抗炎药物米诺环素恢复了过表达 P2X7 受体小鼠对抗惊厥药物的正常反应。用 LPS 预处理野生型小鼠会增加大脑中 P2X7 受体水平并降低癫痫持续状态期间对抗惊厥药的反应，通过 P2X7 受体基因敲除或应用 P2X7 受体拮抗剂 AFC-5128 或 ITH15004 治疗可克服这一问题。

结论和启示：我们的研究结果表明，P2X7 受体诱导的促炎作用有助于癫痫持续状态下药物治疗的耐药性。以 P2X7 受体为靶点的治疗可作为药物难治性癫痫持续状态的新的辅助治疗手段。

其他药物

1. 组胺 H3 受体反向激动剂替洛利生在电点燃癫痫模型中的抗惊厥活性

Anticonvulsant activity of the histamine H3 receptor inverse agonist pitolisant in an electrical kindling model of epilepsy.

Neurosci Lett DOI: 10.1016/j.neulet.2022.136685

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Abstract

Studies have shown that brain histamine has a role in seizure pathophysiology. Histamine acts by four distinct receptor subtypes (H1R-H4R). Previous reports signified the anticonvulsant activity of histamine H3R antagonists. We evaluated the effect of intra-amygdala injection of pitolisant the H3R inverse agonist on seizures induced by the electrical kindling model of epilepsy. Eighteen adult male rats with an approximate weight of 300 g were used. A tri-polar electrode twisted with the guide cannula, and two monopolar electrodes were implanted into the basolateral amygdala or the surface of the skull using stereotaxic surgery. One week after surgery, the threshold was determined in the animals. Twenty-four hours afterward, the animals received six stimuli daily with the threshold intensity until the generation of three consecutive stages five seizures. Then, saline, and 24 h later, pitolisant at three doses (1, 10, and 100 μg) were injected into the amygdala in distinct rats. Thirty minutes after injection of the drug or its solvent, seizure parameters including after-discharge duration (ADD), seizure stage (SS), and stage five duration (S5D) were recorded. Data analysis indicated that pitolisant reduced S5D at all doses, significantly. Pitolisant at the dose of 100 μg also decreased ADD and SS, significantly. However, pitolisant at the doses of 1 and 10 μg did not change ADD and SS. The dose-response curves showed that the anticonvulsant activity of pitolisant changed in a dose-dependent manner. In conclusion, the results confirmed the powerful anticonvulsant effects of pitolisant in the electrical kindling model of epilepsy.

研究表明，脑组胺在癫痫发作的病理生理学中起作用。 组胺通过四种不同的受体亚型 (H1R-H4R) 起作用。 以前的报告表明组胺 H3R 拮抗剂具有抗惊厥活性。 我们评估了杏仁核内注射 H3R 反向激动剂对电点燃癫痫模型诱发的癫痫发作的影响。使用 18 只成年雄性大鼠，体重约为 300 克。 采用立体定向手术将三极电极及弯曲导管和两个单极电极植入杏仁核基底外侧或颅骨表面。术后一周测定动物的阈值。 24 小时后，实验动物每天接受 6 次阈值强度的刺激，直到产生三次连续五阶段的癫痫发作。在 24 小时后，将生理盐水或三种剂量（1MG、10MG 和 100 MG）的替洛利生注射到不同大鼠的杏仁核中。 注射药物或溶剂 30 分钟后，记录癫痫发作参数，包括后放电持续时间 (ADD)、癫痫发作阶段 (SS) 和第五阶段持续时间 (S5D)。 数据分析表明，替洛利生在所有剂量下都显着降低了 S5D。 100 MG 剂量的替洛利生也显着降低了 ADD 和 SS。 然而，1 MG 和 10 MG 剂量的替洛利生没有改变 ADD 和 SS。 剂量-反应曲线显示，替洛利生的抗惊厥活性呈剂量依赖性变化。总之，本实验结果证实了替洛利生在电点燃癫痫模型中具有较强的抗惊厥作用。

2. 拉莫三嗪致噬血细胞性淋巴组织细胞增多症的临床特点分析

Analysis of the clinical characteristics of lamotrigine-induced haemophagocytic lymphohistiocytosis

J Clin Pharm Ther. DOI:10.1111/jcpt.13602

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Abstract

What is known and objective: Lamotrigine is currently known to be related to haemophagocytic lymphohistiocytosis (HLH). Knowledge regarding the association between HLH and lamotrigine is mainly based on case reports. The purpose of this study was to evaluate the clinical characteristics of lamotrigine-induced HLH.

Methods: We collected literature from 1994 to 31 August 2020 in Chinese and English on HLH induced by lamotrigine for retrospective analysis.

Results and discussion: A total of 17 patients (12 men and 5 women) from 15 studies were included, with a median age of 29 years old (range 4-47). Symptoms of lamotrigine-induced HLH were reported to have occurred within 6-24 days following treatment initiation. Six cases reported doses that ranged from 25 mg every other day to 800 mg once daily. The major clinical features of lamotrigine-induced HLH are fever, cytopenia, rash and hyperferritinaemia. Bone marrow showed haemophagocytosis. Fifteen patients improved with drug discontinuation, and 2 patients eventually died.

What is new and conclusion: Hemophagocytic lymphohistiocytosis is a potentially serious adverse reaction to lamotrigine (LTG). Patients should be informed that if they experience any symptoms of HLH while taking lamotrigine, they should immediately seek medical attention.

已知情况与目的：目前已知拉莫三嗪与噬血细胞性淋巴组织细胞增多症（HLH）有关。关于 HLH 和拉莫三嗪之间关联的知识主要基于病例报告。本研究的目的是评估拉莫三嗪诱导的 HLH 的临床特征。

方法：收集 1994 年至 2020 年 8 月 31 日拉莫三嗪致 HLH 的中英文文献进行回顾性分析。

结果与讨论：共纳入来自 15 项研究的 17 名患者（12 名男性和 5 名女性），中位年龄为 29 岁（范围 4-47 岁）。据报道，拉莫三嗪引起的 HLH 症状在治疗开始后 6-24 天内出现。6 例报告的剂量范围从每隔一天 25 毫克到每天一次 800 毫克不等。拉莫三嗪诱导的 HLH 的主要临床特征是发热、血细胞减少、皮疹和高铁蛋白血症。骨髓显示噬血细胞增多。15 名患者因停药而好转，2 名患者最终死亡。

什么是新的和结论：噬血细胞性淋巴组织细胞增多症是拉莫三嗪 (LTG) 潜在的严重不良反应。应告知患者，如果在服用拉莫三嗪期间出现任何 HLH 症状，应立即就医。

3. 拉莫三嗪和强化辩证行为疗法治疗重度多重冲动神经性贪食症后认知和行为控制的变化：fMRI 案例研究

Changes in cognitive and behavioral control after lamotrigine and intensive dialectical behavioral therapy for severe, multi-impulsive bulimia nervosa: an fMRI case study

Eat Weight Disord DOI:10.1007/s40519-021-01308-z

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Abstract

Purpose: Adults with bulimia nervosa (BN) and co-occurring emotional dysregulation and multiple impulsive behaviors are less responsive to existing interventions. Initial data suggest that the combination of Dialectical Behavior Therapy (DBT)

and a mood stabilizer, lamotrigine, significantly reduces symptoms of affective and behavioral dysregulation in these patients. Identifying candidate neurobiological mechanisms of change for this novel treatment combination may help guide future randomized controlled trials and inform new and targeted treatment development. Here, we examined neurocognitive and symptom changes in a female patient with BN and severe affective and behavioral dysregulation who received DBT and lamotrigine.

Methods: Go/no-go task performance data and resting-state functional MRI scans were acquired before the initiation of lamotrigine (after 6 weeks in an intensive DBT program), and again after reaching and maintaining a stable dose of lamotrigine. The patient completed a battery of symptom measures biweekly for 18 weeks over the course of treatment.

Results: After lamotrigine initiation, the patient made fewer errors on a response inhibition task and showed increased and new connectivity within frontoparietal and frontolimbic networks involved in behavioral and affective control. Accompanying this symptom improvement, the patient reported marked reductions in bulimic symptoms, behavioral dysregulation, and reactivity to negative affect, along with increases in DBT skills use.

Conclusion: Improved response inhibition and cognitive control network connectivity should be further investigated as neurocognitive mechanisms of change with combined DBT and lamotrigine for eating disorders. Longitudinal, controlled trials integrating neuroimaging and symptom measures are needed to fully evaluate the effects of this treatment.

目的：患有神经性贪食症 (BN) 并伴有情绪失调和多重冲动行为的成年人对现有干预措施的反应较差。 初步数据表明，辩证行为疗法 (DBT) 和情绪稳定剂拉莫三嗪的联合治疗可显著减轻这些患者的情感和行为失调症状。 确定这种新型治疗组合的候选神经生物学变化机制可能有助于指导未来的随机对照试验，并为新的靶向治疗开发提供信息。 在这里，我们检查了一名接受 DBT 和拉莫三嗪治疗并伴有严重情感和行为失调的女性 BN 患者的神经认知和症状变化。

方法：在拉莫三嗪治疗开始之前（在强化 DBT 计划中 6 周后）以及达到并维持稳定剂量之后，分别获取 GO/NO-GO 任务数据并进行静息态功能 MRI 扫描。 在 18 周的治疗过程中，患者每两周完成一系列症状测评。

结果：开始使用拉莫三嗪后，患者在反应抑制任务上的错误更少，并且在涉及行为和情感控制的额顶叶和额叶边缘网络中表现出连接增加和新的连接。 随着这种症状的改善，患者报告贪食症状、行为失调和对负面影响的反应显著减少，同时 DBT 技能的使用有所增加。

结论： 应进一步研究改善的反应抑制和认知控制网络连接，作为联合 DBT 和拉莫三嗪治疗进食异常的神经认知变化机制。 需要整合神经影像学和症状评测的纵向对照试验来全面评估这种治疗的效果。

药物检测

1. Taguchi 法优化绿色定量核磁共振氢谱在左乙拉西坦和布瓦西坦药物鉴定中的应用

Taguchi Approach for Optimization of a Green Quantitative 1H-NMR Practice for Characterization of Levetiracetam and Brivaracetam in Pharmaceuticals.

Journal of AOAC International. DOI:10.1093/jaoacint/qsac077

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Background: Recently, quantitative nuclear magnetic resonance (qNMR) competes with separation techniques like HPLC and capillary electrophoresis for quantification purposes when dealing with molecules that lack a chromophore.

Objective: The advantages of the proton nuclear magnetic resonance spectroscopy as a revolutionary quantitative analysis method were exploited aimed at simple and green assessment of two racetams namely, levetiracetam (LEV) and brivaracetam (BRV) as a new family of antiepileptic medications with unique mechanism of action. The developed technique was effectively utilized to determine LEV in Keppra tablets and BRV in laboratory prepared tablets without interfering with the ordinarily suspected excipients.

Method: Taguchi approach was applied as a powerful and user-friendly statistical technique for optimization of the qH1NMR experimental design for both drugs. The optimum acquisition conditions were number of scans 32, pulse angel 20° and relaxation delay of 40 sec for LEV and number of scans 128, pulse angle 90° and relaxation delay 1 sec for BRV. NMR Spectra were obtained by means of phloroglucinol as an internal standard and dimethyl sulfoxide-d6 as a solvent.

Results: The diagnostic doublet of doublet quantitative signals at 4.3 and at 4.2 ppm were chosen to estimate LEV and BRV respectively. The recovery of both drugs was quantified through the range of 0.1-12 mg/mL. The limits of detection were 0.013, 0.0013 and the limits of quantitation were 0.04, 0.0039 mg/mL for LEV and BRV correspondingly.

Conclusions: The suggested technique was fully validated according to ICH guidelines and proved to be an eco-friendly practice by means of three different assessment tools including; green analytical procedures index, national environmental methods index and analytical eco-scale. qH1NMR should be considered as a green alternative for quantification and quality control assessment of pharmaceuticals.

背景:最近，在处理无发色团分子时，定量核磁共振(qNMR)可与高效液相色谱(HPLC)和毛细血管电泳等分离方法相媲美。

目的:利用质子核磁共振波谱技术作为一种革命性的定量分析方法的优势，对左乙拉西坦(LEV)和布瓦西坦(BRV)这两种具有独特作用机制的新型抗癫痫药物家族进行简单、绿色的评价。该方法可在不干扰正常辅料的情况下，有效测定实验室制剂中 Keppra 片和 BRV 中的 LEV 含量。

方法:Taguchi 法是一种强大的、用户友好的统计技术，用于优化两种药物的定量核磁共振氢谱(qH1NMR)实验设计。LEV 的最佳采集条件为扫描次数 32 次，脉冲角度 20°，弛豫延迟 40 秒;BRV 的最佳采集条件为扫描次数 128 次，脉冲角度 90°，弛豫延迟 1 秒。以间苯三酚为内标，二甲亚砜-d6 为溶剂，获得核磁共振波谱。

结果:分别选择 4.3 ppm 和 4.2 ppm 的双定量诊断信号来评估 LEV 和 BRV。两种药物的回收率均在 0.1 ~ 12 mg/mL 范围内进行定量。LEV 和 BRV 的检出限分别为 0.013、0.0013，定量限分别为 0.04、0.0039 mg/mL。

结论:根据 ICH 指南对该技术进行了充分验证，并通过以下三种不同的评估工具证明其是一种生态友好的方法:绿色分析程序指数、国家环境方法指数和分析生态量表。qH1NMR 可作为药物定量和质量控制评价的绿色选择。

2. 在氨基甲酸酯（肉桂酸盐）滴定期出现的疗效和不良事件

Onset of efficacy and adverse events during Cenobamate titration period

Acta Neurologica Scandinavica. DOI:10.1111/ane.13659

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Objectives: Cenobamate is an antiseizure medication (ASM) approved in Europe as adjunctive therapy for adults with inadequately controlled focal seizures. This post hoc analysis reports onset of efficacy and characterizes time to onset, duration, and severity of the most common treatment-emergent adverse events (TEAEs) during cenobamate titration.

Materials & methods: Adult patients with uncontrolled focal seizures taking 1 to 3 concomitant ASMs were randomized to receive adjunctive cenobamate or placebo (double-blind studies C013 and C017) or cenobamate (open-label study C021). Outcome assessments included efficacy (median percentage change in seizure frequency and onset [studies C013 and C017]) and safety (onset, duration, and severity of TEAEs [all studies]).

Results: Onset of efficacy was observed by Weeks 1 to 4 of titration in studies C013 and C017 which used a faster titration schedule than study CO21. In study C013, the median percentage seizure frequency reduction was 36.7% in patients receiving cenobamate versus 16.3% in those taking placebo ($p = .002$); in study C017, significant differences in seizure frequency emerged in Week 1 and continued throughout titration between all cenobamate groups and placebo ($p < .001$). The most commonly reported TEAEs were somnolence, dizziness, fatigue, and headache, with first onset of each reported as early as Week 1; however, the majority resolved.

Conclusions: Reductions in seizure frequency occurred during titration with initial efficacy observed prior to reaching the target dose. These reductions were regarded as clinically meaningful because they may indicate early efficacy at lower doses than previously expected and had a considerable impact on patient quality of life. Long-term treatment with adjunctive cenobamate was generally safe and well-tolerated.

目的:氨基甲酸酯（肉桂酸盐）是一种抗癫痫发作药物(ASM)，已获欧洲批准用于成人局灶性癫痫控制不佳的添加治疗。这项事后分析报告了氨基甲酸酯滴定过程中疗效出现的时间，并描述了最常见的治疗期不良事件(TEAEs)的出现时间、持续时间和严重程度。

材料和方法:将同时服用 1 ~ 3 种 ASM 的未控制的成年人局灶性癫痫患者随机分为两组，分别接受添加氨基甲酸酯或安慰剂(双盲研究 C013 和 C017)或氨基甲酸酯(开放标签研究 C021)。评估终点包括疗效(癫痫发作

频率的中位数百分比变化以及疗效的出现时间[研究 C013 和 C017])和安全性(TEAEs 的出现时间、持续时间和严重程度[所有研究])。

结果:研究 C013 和 C017 使用比研究 CO21 更快的滴定计划，通过第 1 至 4 周的滴定观察疗效的开始时间。在研究 C013 中，接受氨基甲酸酯的患者癫痫发作频率降低的中位百分比为 36.7%，而服用安慰剂的患者为 16.3% (P = .002);在研究 C017 中，在第 1 周和整个滴定过程中，所有氨基甲酸酯组和安慰剂组之间，癫痫发作频率存在显著差异(P < .001)。最常报道的 TEAEs 为嗜睡、头晕、疲劳和头痛，各种症状最早出现于第 1 周，然而，大多数人都能缓解。

结论:在滴定期癫痫发作频率即出现下降，达到目标剂量之前即已观察到初始疗效。这样的下降被认为具有临床意义，因为它们可能表明在低于预期剂量下的早期疗效，并对患者的生活质量有相当大的影响。添加氨基甲酸酯的长期治疗通常是安全的且耐受性良好。

3. 2014 - 2019 年爱尔兰有生育潜力女性的丙戊酸钠使用趋势:利用间断时间序列分析的药物使用研究

Valproate utilization trends among women of childbearing potential in Ireland between 2014 and 2019: A drug utilization study using interrupted time series.

Pharmacoepidemiol Drug Saf. doi:10.1002/pds.5427

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Purpose: This study aimed to examine trends in valproate use among women of childbearing potential (WCBP) aged 16-44 years in Ireland following two European-directed regulatory interventions in December 2014 and April 2018.

Methods: This was a repeated cross-sectional study using monthly national pharmacy claims data, to examine trend changes in the prevalence of valproate use among WCBP pre and post two separate regulatory events in December 2014 and April 2018. Annual population estimates from the Central Statistics Office were used to calculate the prevalence rate per 1000 eligible women. Segmented regression analysis of interrupted time series with negative binomial regression was used to examine rates for WCBP aged 16-44 years, and by 10-year age groups. Prevalence ratios (PR) are presented with 95% confidence intervals (CIs).

Results: Among WCBP aged 16-44 years, there was no statistically significant change in the month-to-month prevalence ratio in the post- compared to pre-December 2014 intervention period. A significant decline was, however, observed in the post-, compared to pre-April 2018 intervention period (PR = 0.998, [95% CIs: 0.996, 1.000]; p = 0.029). Among those aged 16-24 years, a significant decreasing trend in the month-to-month prevalence ratio was found in the post- compared to pre-December 2014 intervention period (PR = 0.991, [95% CIs: 0.984, 0.998];p<0.01). A marginal effect was observed in the post- compared to pre-April 2018 intervention period for those aged 25-34 years (PR = 0.996, [95% CIs: 0.992, 1.000]; p = 0.048).

Conclusion: Although no evidence of change was observed following the December 2014 intervention period, a significant decline in the prevalence ratio of valproate use was observed after the 2018 intervention, which may reflect the introduction of the most recent contraindication measures.

目的:本研究旨在研究在 2014 年 12 月和 2018 年 4 月两次欧洲指导的监管干预后，爱尔兰 16-44 岁有生育潜力女性(WCBP)丙戊酸钠的使用趋势。

方法:这是一项重复性横断面研究，使用每月的国家药物索赔数据，检查 WCBP 在 2014 年 12 月和 2018 年 4 月两次单独监管事件前后丙戊酸钠使用率的趋势变化。来自中央统计办公室的年人口估计数字用于计算每 1000 名符合条件女性的使用率。采用间断时间序列的分段回归分析和负二项回归分析 16-44 岁 WCBP 的使用率，以 10 岁间隔进行分组。使用率(PR)取 95%可信区间。

结果:在 16-44 岁的 WCBP 中，与 2014 年 12 月干预期之前相比，干预后的使用率环比无显著变化。然而，与 2018 年 4 月干预期之前相比，干预后的数据显著下降(PR = 0.998， [95% ci: 0.996, 1.000];p = 0.029)。在 16-24 岁的患者中，与 2014 年 12 月干预前相比，干预后的使用率有显著下降趋势(PR = 0.991， [95% ci: 0.984, 0.998];p <0.01)。与 2018 年 4 月前相比，25-34 岁患者在干预后观察到了边际效应(PR = 0.996， [95% ci: 0.992, 1.000];p = 0.048)。

结论:尽管在 2014 年 12 月干预期后没有观察到变化的证据，但在 2018 年干预期后，丙戊酸钠使用率显著下降，这可能反映了最新的禁忌症的引入。

环境毒理

1. 来自二酮的过氧自由基增强了卡马西平的间接光化学转化：动力学、机制及产物

Peroxyl radicals from diketones enhanced the indirect photochemical transformation of carbamazepine: Kinetics, mechanisms, and products

Water Res Actions Search in PubMed Search in NLM Catalog Add to Search .

doi: 10.1016/j.watres.2022.118424. Epub 2022 Apr 6.

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In surface waters, photogenerated transients (e.g., hydroxyl radicals, carbonate radicals, singlet oxygen and the triplet states of dissolved organic matter) are known to play a role in the transformation of biorecalcitrant carbamazepine (CBZ). Small diketones, such as acetylacetone (AcAc) and butanedione (BD), are naturally abundant and have been proven to be effective precursors of carbon and oxygen centered radicals. However, the photochemical kinetics and mechanisms of coexisting diketones and CBZ are barely known. Herein, the effects of AcAc and BD on the photochemical conversion of CBZ were investigated compared with H2O2 which was the main ·OH precursor in the environment. An enhancing effect was observed for the degradation of CBZ by the addition of diketones. The enhancing effect of diketones was pH-dependent and much more significant than H2O2 under simulated solar irradiation. On the basis of the identification of transient species and the competition kinetic model, organic peroxyl radicals were found to play a dominant role in CBZ photodegradation, and the second-order rate constants of the reaction between CBZ and peroxyl radicals were determined to be approximately 107-108 M-1s-1. Furthermore, mutagenic acridine was found to be the major cumulative intermediate with a yield of > 30% in the presence of diketones, which might be an environmental concern. This work indicates that the coexistence of diketones and persistent organic pollutants might lead to some detrimental effects on aquatic environments if the water is exposed to sunlight.

在地表水中，光生瞬态物(例如，羟自由基、碳酸根，单重态氧和可溶性有机质的三重态)在生物难降解卡马西平(CBZ)的转化中发挥作用。小分子二酮，如乙酰丙酮(AcAc)和丁二酮(BD)，天然含量丰富，已被证明是以碳和氧为中心的自由基的有效前体。然而，二酮与 CBZ 共存的光化学动力学和机理尚不清楚。本文研究了 AcAc 和 BD 对 CBZ 光化学转化的影响，并与环境中主要的·OH 前驱体 H2O2 进行了比较。添加二酮对 CBZ 的降解有促进作用。在模拟太阳辐照条件下，二酮的增强作用与 pH 有关，且显著高于 H2O2。通过对 CBZ 光降解过程中瞬态物质的鉴定和竞争动力学模型的分析，发现有机过氧自由基在 CBZ 光降解过程中起主导作用，CBZ 与过氧自由基反应的二级速率常数约为 107 ~ 108 M-1s-1。此外，在存在二酮的情况下，诱变吖啶被发现是主要的累积中间体，其产量> 30%，这可能是一个环境问题。这表明，如果水体暴露在阳光下，二酮类与持久性有机污染物的共存可能会对水环境造成一些不利影响。

2. 使用新型碘酸盐辅助光化学和光催化系统在水介质中卡马西平降解的动力学和机制

Kinetics and mechanisms of the carbamazepine degradation in aqueous media using novel iodate-assisted photochemical and photocatalytic systems

Science of the Total Environment doi: 10.1016/j.scitotenv.2022.153871. Epub 2022 Feb 14.

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The present study investigates the kinetics and mechanisms of carbamazepine (CBZ) degradation using a novel UV/iodate (IO3-) system for the first time and explores the influence of process conditions on its degradation. UV/IO3- showed high degradation efficiencies in a wide range of pHs, especially under neutral and acidic conditions, indicating that the system can be considered as a promising method to deal with effluents under various pH conditions. Radical scavenging experiments show that both iodine radicals (IO, IO2 and IO3) and hydroxyl radicals play an important role in CBZ degradation. Furthermore, the combination of UV/IO3- with TiO2 was studied to explore the potential of the addition of IO3- to improve the efficiency of the conventional TiO2 photocatalytic system. Scavenging experiments indicated that iodine radicals (IO, IO2 and IO3) were mainly involved in the degradation of CBZ in the UV/IO3-/TiO2 system, and the reaction mechanism equations were proposed for the first time for the studied UV/IO3-/TiO2 system. Several degradation products and four possible pathways of CBZ degradation were also elucidated using ultra-high-performance liquid chromatography in combination with a quadrupole time-of-flight mass spectrometer (Q-TOF MS). Respirometric tests indicated that the treatment has a positive impact on biomass behavior during subsequent biological purification, highlighting that the developed IO3--assisted AOPs are eco-friendly.

本研究首次采用新型紫外线/碘化物(IO3-)体系研究卡马西平(CBZ)降解的动力学和机理，并探讨工艺条件对其降解的影响。UV/IO3-在大范围的 pH 条件下表现出了很高的降解效率，特别是在中性和酸性条件下，表明该体系可以被认为是一种很有前途的处理各种 pH 条件下废水的方法。自由基清除实验表明，碘自由基(IO、IO2、IO3)和羟自由基在 CBZ 降解中起重要作用。此外，研究了 UV/IO3-与 TiO2 的结合，探索了添加 IO3-提高传统 TiO2 光催化体系效率的潜力。清除实验表明，在 UV/IO3-/TiO2 体系中，碘自由基(IO、IO2 和 IO3)主要参与降解 CBZ，并首次针对所研究的 UV/IO3-/TiO2 体系提出了降解 CBZ 的反应机理方程。利用高效液相色谱结合四极飞行时间质谱仪(Q-TOF MS)分析了几种降解产物和四种降解 CBZ 的可能途径。呼吸测试表明，在随后的生物净化过程中，该处理方法对生物的行为有积极的影响，强调了开发的 IO3 辅助的 AOPs 是生态友好的。

大麻二酚

1. 巴西东南部医用大麻品种的化学分析

Chemical profiling of Cannabis varieties cultivated for medical purposes in southeastern Brazil.

Forensic Sci Int. doi: 10.1016/j.forsciint.2022.111309. Epub 2022

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Cannabis cultivation for medical purposes in Brazil has been increased in the last years. While cannabis crops are prohibited, hundreds patients have been granted with judicial authorizations and there is little information about the cultivation conditions, yields and chemical profiles of the plants. Cannabis plants contain hundreds of compounds, with cannabinoids and terpenes the main drivers of their toxicological and pharmacological properties. Besides the cannabinoids, terpene contents are useful for the chemotaxonomic classification of different varieties, and their role in forensic analyses should be further delineated. The present study monitored cannabis crops of fifteen participants who were granted special licenses by the Brazilian Courts in Rio de Janeiro and São Paulo. The cultivation conditions were monitored and five cannabinoids (tetrahydrocannabinol acid-THCA, tetrahydrocannabinol-THC, cannabidiolic acid-CBDA, cannabidiol-CBD and cannabinol-CBN) and nineteen terpenes were quantified in cannabis flowers. The total grow cycle of thirty-five cannabis plants ranged from 10 to 24 weeks. The dry flower yields ranged 22-90 g per plant. Most cannabis specimens were CBD-rich varieties (CBD levels from 1.6% to 16.7%, and THC levels from 0.0% to 2.6%, n = 22) used to treat epileptic patients. The THC-rich varieties contained CBD levels ranging from 0.03% to 0.8%, and THC levels from 0.7% to 20.1%, n = 11. Fewer of the samples contained THC:CBD ratios of approximately 1:1 (CBD levels of 3.3-3.8% and THC levels of 2.2-3.7%, n = 2). The most abundant terpenes in the cannabis flowers were beta-caryophyllene, alpha-humulene, guaiol and alpha-bisabolol. CBD-rich varieties showed significant higher levels of beta-caryophyllene and alpha-humulene in comparison with THC-rich varieties. Overall, the study herein provides data concerning medical cannabis crops grown in a region of Brazil that not only guide individual medical cannabis cultivation methods but also aid forensic analyses.

•巴西医用大麻的种植在过去几年有所增加。虽然大麻作物是被禁止的，但已有数百名病人获得了司法许可。关于种植条件、产量和这种植物化学成分的资料很少。大麻植物含有数百种化合物，大麻素和萜烯是其毒理学和药理学特性的主要驱动因素。除大麻素外，萜烯的含量对不同品种的化学分类也有帮助，其在法医学分析中的作用有待进一步阐明。本研究对 15 名参与者的大麻作物进行了监测，这些参与者都获得了巴西里

约热内卢和圣保罗法院颁发的特殊许可证。对培养条件进行了监测，并在大麻花中定量检测了五种大麻素(四氢大麻酚酸- THCA、四氢大麻酚- THC、大麻二酚酸- CBDA、大麻二酚- CBD 和大麻二酚-CBN)和 19 种萜烯。35 种大麻的总生长周期为 10 ~ 24 周。干花产量为每株 22-90 克。大多数富含 CBD 的大麻制品(CBD 水平从 1.6%到 16.7%，THC 水平从 0.0%到 2.6%，N = 22)用于治疗癫痫患者。富含 THC 的品种 CBD 含量为 0.03% ~ 0.8%，THC 含量为 0.7% ~ 20.1%，N = 11。THC 含量较少的品种，CBD 含量约为 1:1 (CBD 含量为 3.3-3.8%，THC 含量为 2.2-3.7%，N = 2)。大麻花中萜烯含量最多的是B-石竹烯、A-草烯、愈创酚和A-没药醇。富 CBD 品种B-石竹烯和A-草烯的含量显著高于富 THC 品种。总的来说，这项研究提供了有关巴西地区医用大麻种植的数据，不仅指导个人医用大麻种植方法，而且有助于法医学分析。

2. 单剂和多剂口服给药 1 和 3 mg/kg 大麻二酚在马体内的药代动力学、安全性和滑膜液浓度

Pharmacokinetics, Safety, and Synovial Fluid Concentrations of Single- and Multiple-Dose Oral Administration of 1 and 3 mg/kg Cannabidiol in Horses.

J Equine Vet Sci. doi:10.1016/j.jevs.2022.103933

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Cannabidiol (CBD) products are widely marketed to horse owners, trainers, and veterinarians and are readily available to the consumer despite minimal pharmacokinetic or safety data being available. The objectives of this study were to determine the plasma pharmacokinetics, short-term safety, and synovial fluid levels of CBD following oral administration in horses. A prospective, randomized, controlled study design was used. Twelve horses were administered sunflower lecithin oil-based CBD at either 1 mg/kg (Group 1) or 3 mg/kg (Group 2) for a 24-hour pharmacokinetic study. Horses then received 0.5 mg/kg (Group 1) or 1.5 mg/kg (Group 2) CBD q12 PO for 6 weeks, with steady state and elimination sampling performed up to 96 hours post-final dose. Synovial fluid CBD concentrations were evaluated at 12 and 24 hours, and 5 weeks. Horses were monitored daily and clinicopathologic parameters were evaluated. Mean ± SD Cmax and tmax were 4.3 ± 2.1 ng/ml and 4.1 ± 4.1 hours, and 19.9 ± 15.6 ng/ml and 5.0 ± 3.7 hours for Groups 1 and 2, respectively. CBD was detectable in synovial fluid in 8/12 horses during steady state. Mild hypocalcemia was seen in all horses and elevated liver enzymes were observed in 8/12 horses, but these changes improved or normalized within 10 days after the final CBD dose. CBD had dose-dependent, but variable, oral bioavailability at 1 mg/kg and 3 mg/kg daily dosing and was consistently detectable at steady state in synovial fluid at the higher dose. Further investigation is needed to establish clinically effective doses.

大麻二酚(CBD)产品广泛销售给马主、驯马师和兽医，消费者可以随时获得，尽管只有很少的药代动力学或安全数据。这项研究的目的是确定马口服给药后的血浆药代动力学、短期安全性和滑膜液中 CBD 的水平。采用前瞻性、随机、对照研究设计。12 匹马分别以 1 MG/KG(组 1)或 3 MG/KG(组 2)给药进行 24 小时的药代动力学研究。然后马接受 0.5 MG/KG(组 1)或 1.5 MG/KG(组 2)CBD Q12 PO，持续 6 周，稳态和清除采样持续至最终剂量后 96 小时。滑膜液 CBD 浓度在 12、24 小时和 5 周进行评估。每天监测马匹并评估临床病理参数。CMAX 和 TMAX 的均值分别为 4.3±2.1 NG/ML 和 4.1±4.1 H，分别为 19.9±15.6 NG/ML 和 5.0±3.7 H。8/12 匹马在稳态下滑

膜液中检测到 CBD。所有马均出现轻度低钙血症，8/12 匹马出现肝酶升高，但这些变化在最后一次使用 CBD 剂量后 10 天内得到改善或恢复正常。每日给药 1 MG/KG 和 3 MG/KG 时，CBD 的口服生物利用度有剂量依赖性，但有变量，在较高剂量时，于稳态下在滑膜液中持续可检测到。需要进一步调查以确定临床有效剂量。

吡仑帕奈

1. 吡仑帕奈添加治疗癫痫患者难治性局灶性癫痫发作的疗效和安全性：荟萃分析

The efficacy and safety of adjunctive perampanel for the treatment of refractory focal-onset seizures in patients with epilepsy: A meta-analysis.

Epilepsia Open. doi:10.1002/epi4.12574

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OBJECTIVE: The last decade has seen an increase in the use of anti-seizure medications (ASMs); however, the burden of treating drug-resistant epilepsy has not fallen. We performed this meta-analysis to evaluate the optimal dose of Perampanel (PER) as a new adjunctive treatment for drug-resistant seizures.

METHODS: We searched for studies published from inception to February 1, 2021 from PubMed, Central Register of Controlled Trials (CENTRAL), and ScienceDirect. Research characteristics, patients' characteristics, and treatment regimen, concomitant ASMs, clinical outcomes were extracted. The practical outcome included a reduction in seizures frequency ≥ 50%, ≥75%, and ≥100% from baseline convulsive seizure frequency, and the safety outcome included the proportion of drug withdrawal and adverse reactions. Odds ratios (OR) for 95% confidence intervals (95% CI) were estimated by the inverse variance method.

RESULTS: Four trials which enrolled 2187 participants (1569 in the PER group and 618 in the placebo group) were included. Results showed that 8 or 12 mg per day had the best effect on all three outcomes, with no significant difference between 8 and 12 mg per day (≥50% reduction, 35.5% vs 36.1%, P = .84; ≥75% reduction, 17.8% vs 19.1%, P = .64; seizure-free, 3.5% vs 3.7%, P = .85). In addition, 12-mg PER compared to 8 mg had a higher proportion of trial withdrawal (8.7% vs 17.0%; P < .00001) and treatment-emergent adverse event (TEAE) resulting in dose reduction/discontinuation (18.5% vs 32.0%; P < .00001). The adverse events (AEs) significantly associated with adjunctive PER were dizziness, somnolence, fatigue, and irritability.

SIGNIFICANCE: Adjunctive treatment of PER was associated with a more significant reduction in the frequency of seizures in patients with refractory epilepsy than placebo, but with a higher frequency of AEs. PER at a daily dose of 8 mg appears to have the best ratio between efficacy and tolerance in most study participants.

目的:在过去的十年中，抗癫痫发作药物(ASMs)的使用有所增加;然而，治疗耐药癫痫的负担并没有减轻。我们进行了这项荟萃分析，以评估吡仑帕奈(PER)作为一种新的添加治疗耐药癫痫的最佳剂量。

方法:检索 PubMed、Central Register of Controlled Trials (Central)和 ScienceDirect 从创立到 2021 年 2 月 1 日发表的研究。提取研究特点、患者特点、治疗方案、伴随 ASMs、临床结局。疗效终点包括癫痫发作频率较基线发作频率降低≥50%、≥75%、≥100%，安全终点包括停药和不良反应的比例。采用逆方差法估计 95%可信区间(95% CI)的比值比(OR)。

结果:四项试验共纳入 2187 名受试者(PER 组 1569 人，安慰剂组 618 人)。结果显示，8 或 12 mg / d 对所有三种结果的效果最好，8 和 12 mg / d 之间无显著差异(减少≥50%， 35.5% vs 36.1%， P = .84; 减少≥75%，

17.8% VS 19.1%， P = .64;无发作，3.5% VS 3.7%， P = .85)。此外，与 8 MG 相比，12 MG PER 有更高的试验退出比例(8.7% VS 17.0%;P < .00001)和治疗期不良事件(TEAE)导致剂量减少/停药(18.5% VS 32.0%;P < .00001)。与添加 PER 显著相关的不良事件(AES)为头晕、嗜睡、疲劳和易怒。

意义:与安慰剂相比，PER 治疗添加可显著降低难治性癫痫患者的癫痫发作频率，但 AES 的发生率更高。在大多数研究受试者中，每日剂量为 8MG 的 PER 在疗效和耐受性之间的比例最佳。

2. 基于脂质的纳米系统的鼻内递送作为新一代抗癫痫药物吡仑帕奈脑靶向治疗的有前景的方法

Intranasal delivery of lipid-based nanosystems as a promising approach for brain targeting of the new-generation antiepileptic drug perampanel

Int J Pharm. DOI: 10.1016/j.ijpharm.2022.121853

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Abstract

Perampanel (PER), a new-generation antiepileptic drug effective against different types of seizures, has already demonstrated a potential in status epilepticus therapy. Considering the growing interest of intranasal (IN) administration for nose-to-brain delivery, PER could be envisioned as a good candidate for this route, especially if formulated in a lipid-based nanosystem. With that purpose, a hydrophobic formulation (FO1.2) and a self-microemulsifying drug delivery system (SMEDDS) (FH5) loaded with PER were developed and characterized. Following PER IN administration (1 mg/kg) to mice, its pharmacokinetics was characterized and compared with intravenous and oral routes. Histopathological toxicity was also examined after a 7-day repeated dose study. FH5 homogeneously formed nanodroplets upon dispersion (20.07 ± 0.03 nm), showing a sustained in vitro PER release profile up to 4 h. By IN route, PER brain delivery was more extensive with FH5 (Cmax and AUC of 52.32 ng/g and 190.35 ng.h/g for FO1.2; 93.87 ng/g and 257.75 ng.h/g for FH5). Maximum brain concentration and total brain exposure were higher than those obtained after oral dosage, with maximum PER concentrations reached significantly faster than post-oral administration (15 min vs 2 h). An improvement in PER plasmatic concentration was also obtained, demonstrated by high relative bioavailability values (134.1% for FH5 and 107.8% for FO1.2). PER absolute plasma bioavailability after IN delivery was 55.5% for FH5 and 44.6% for FO1.2, ensuring a somewhat improved targeting of PER to the brain by the IN route compared to the IV route. No signs of toxicity were found by histopathologic evaluation. Results suggest that IN administration of PER might be a feasible and safe approach for acute and chronic epilepsy management, especially using delivery systems as SMEDDS.

吡仑帕奈 (PER) 是一种新一代抗癫痫药物，对不同类型的癫痫发作均有疗效，在癫痫持续状态的治疗中已显示出潜力。考虑到鼻内 (IN) 给药对鼻-脑传输的兴趣日益增长，PER 有望成为这种途径的良好候选者，特别是在基于脂质纳米系统中配制时。为此而开发并表征了负载 PER 的疏水性制剂 (FO1.2) 和自微乳化药物递送系统 (SMEDDS) (FH5)。在对小鼠进行 PER IN (1 MG/KG) 给药后，对其药代动力学进行了表征，并与静脉和口服途径进行了比较。在 7 天重复给药研究后，检测其组织病理学毒性。 FH5 形成均匀分散的纳米液滴 (20.07 ± 0.03 NM)，显示出体外持续释放达 4 小时。通过 IN 途径，FH5 的 PER 脑递送更广泛（FO1.2 的 C MAX 和 AUC 为 52.32 NG/G 和 190.35 NG.H/G；FH5 为 93.87 NG/G 和 257.75 NG.H/G）。最大脑浓度和总脑暴露均高于口服给药后，达到

最大 PER 浓度的速度明显快于口服给药后（15 分钟 vs 2 小时）。PER 血浆浓度也有改善，其相对生物利用度值较高（FH5 为 134.1%，FO1.2 为 107.8%）。 IN 给药后，FH5 和 FO1.2 的 PER 绝对血浆生物利用度分别为 55.5%和 44.6%，与静脉给药相比，确保了 IN 途径在一定程度上提高了 PER 对大脑的靶向性。组织病理学评估未发现毒性迹象。结果表明，在急性和慢性癫痫的治疗中，特别是使用 SMEDDS 等给药系统，PER 的 IN 给药可能是一种可行和安全的方法。

拉考沙胺

1. 拉考沙胺单药治疗伴有中央颞区棘波的儿童癫痫

Lacosamide monotherapy for the treatment of childhood epilepsy with centrotemporal spikes.

Brain Dev. doi:10.1016/j.braindev.2022.02.005

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Objective: Childhood epilepsy with centrotemporal spikes (CECTS) is known as age-limited focal epilepsy syndrome in childhood. Lacosamide is a third-generation antiepileptic drug. This study aimed to evaluate the efficacy of lacosamide monotherapy for the treatment of CECTS.

Methods: We enrolled 18 patients (6 girls and 12 boys) who met the following criteria: 1) the age of onset of the seizures was between 3 and 13 years of age; 2) showing at least hemifacial and/or oropharyngeal seizures; 3) interictal discharges in central and/or middle temporal electrodes; 4) no intellectual disability; 5) treatment duration of lacosamide monotherapy over 6 months. We retrospectively collected and analyzed clinical data and treatment information. We evaluated the seizure occurrences during 0-3, 4-6, and 7-12 months from the treatment initiation and the last 6 months of the follow-up. We also evaluated the outcomes as seizure-free if the patients developed no seizures both over 6 months and 3 times of pretreatment mean seizure interval at the last follow-up.

Results: Of the patients, 39%, 67% and 72% were seizure-free during 0-3, 4-6, and 7-12 months from treatment initiation, respectively. Finally, 83% of the patients achieved seizure freedom. Seizure freedom was achieved in 72% during the first 4 months of treatment. All patients continued lacosamide monotherapy during the study, although four patients showed transient fatigue or somnolence.

Conclusions: Lacosamide showed good efficacy for controlling seizures with fewer adverse effects, and therefore may be a good candidate as a first-line medication for the treatment of new-onset CECTS.

目的: 伴有中央颞区棘波的儿童癫痫 (CECTS)被称为年龄自限性儿童局灶性癫痫综合征。拉考沙胺是第三代抗癫痫药物。本研究旨在评价拉考沙胺单药治疗 CECTS 的疗效。

方法:收集 18 例癫痫发作患者，女孩 6 例，男孩 12 例，符合以下标准:1)癫痫发作年龄在 3 ~ 13 岁之间;2)至少出现偏侧面部和/或口咽部发作;3)中央和/或中颞电极间歇期放电;4)无智力缺陷;5) 拉考沙胺单药治疗时间 6 个月以上。回顾性收集和分析临床资料和治疗信息。我们评估了治疗开始后 0-3 个月、4-6 个月和 7-12 个月以及随访最后 6 个月的癫痫发作情况。如果患者在末次随访时，6 个月以上和 3 倍治疗前平均发作间隔中均未出现发作，我们也评估其预后为无发作。

结果:在治疗开始后的 0-3 个月、4-6 个月和 7-12 个月，分别有 39%、67%和 72%的患者无癫痫发作。最终，83%的患者实现了癫痫无发作。治疗前 4 个月，72%的患者无癫痫发作。所有患者在研究期间继续使用拉考沙胺单药治疗，尽管 4 例患者表现出短暂的疲劳或嗜睡。

结论:拉考沙胺控制癫痫发作效果好，不良反应少，可能是治疗新发 CECTS 的一线药物。

药物相关基因研究

1. 左乙拉西坦精神性药物不良反应的药物基因组学评估

A pharmacogenomic assessment of psychiatric adverse drug reactions to levetiracetam

Epilepsia, doi:10.1111/epi.17228

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Objective: Levetiracetam (LEV) is an effective antiseizure medicine, but 10%-20% of people treated with LEV report psychiatric side-effects, and up to 1% may have psychotic episodes. Pharmacogenomic predictors of these adverse drug reactions (ADRs) have yet to be identified. We sought to determine the contribution of both common and rare genetic variation to psychiatric and behavioral ADRs associated with LEV.

Methods: This case-control study compared cases of LEV-associated behavioral disorder (n = 149) or psychotic reaction (n = 37) to LEV-exposed people with no history of psychiatric ADRs (n = 920). All samples were of European ancestry. We performed genome-wide association study (GWAS) analysis comparing those with LEV ADRs to controls. We estimated the polygenic risk scores (PRS) for schizophrenia and compared cases with LEV-associated psychotic reaction to controls. Rare variant burden analysis was performed using exome sequence data of cases with psychotic reactions (n = 18) and controls (n = 122).

Results: Univariate GWAS found no significant associations with either LEV-associated behavioural disorder or LEV-psychotic reaction. PRS analysis showed that cases of LEV-associated psychotic reaction had an increased PRS for schizophrenia relative to controls (p = .0097, estimate = .4886). The rare-variant analysis found no evidence of an increased burden of rare genetic variants in people who had experienced LEV-associated psychotic reaction relative to controls.

Significance: The polygenic burden for schizophrenia is a risk factor for LEV-associated psychotic reaction. To assess the clinical utility of PRS as a predictor, it should be tested in an independent and ideally prospective cohort. Larger sample sizes are required for the identification of significant univariate common genetic signals or rare genetic signals associated with psychiatric LEV ADRs.

目的:左乙拉西坦(LEV)是一种有效的抗癫痫发作药物，但在左乙拉西坦治疗的患者中，有 10%-20%的人报告有精神类副作用，高达 1%的人可能有精神病性发作。这些药物不良反应(ADRs)的药物基因组预测因子尚未确定。我们试图确定常见和罕见的遗传变异对 LEV 相关的精神和行为 ADRs 的影响。

方法:此项病例对照研究将 LEV 相关行为障碍(n = 149)或精神病性反应(n = 37)与 LEV 暴露者而无精神性 ADRs(n = 920)者进行比较。所有样本均为欧洲血统。我们进行了全基因组关联研究(GWAS)分析，比较 LEV 组和对照组的不良反应。我们进行了精神分裂症的多基因风险评分(PRS)，并将具有 LEV 相关精神病性反应的病例与对照组进行比较。利用精神病性反应患者(n = 18)和对照组(n = 122)的外显子序列数据进行罕见变异负担分析

结果:单因素 GWAS 发现与 LEV 相关的行为障碍或 LEV 精神病性反应均无显著关联。PRS 分析显示，与对照组相比，LEV 相关的精神病性反应病例的精神分裂症 PRS 增加(p = 0.0097，估计= .4886)。罕见变异分析发现，与对照组相比，经历 LEV 相关精神病性反应的人没有发现罕见遗传变异负担增加的证据。

意义:精神分裂症的多基因负担是 LEV 相关精神病性反应的危险因素。为了评估 PRS 作为一个预测指标的临床效用，它应该在一个独立和理想的前瞻性队列中进行测试。需要更大的样本量来识别与精神病性 LEV 不良反应相关的显著单变量常见遗传信号或罕见遗传信号。