癫痫药物时讯

ANTIEPILEPTIC DRUGS NEWS

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临床研究 5

临床研究

1. 儿童神经病学：新发难治性癫痫持续状态的 PCDH19 相关癫痫的初步介绍和阿那白滞素治疗

Child Neurology: Initial Presentation of PCDH19-Related Epilepsy With New-Onset Refractory Status Epilepticus and Treatment With Anakinra. *Neurology. 2022 Aug 2;99(5):208-211. doi: 10.1212/WNL.0000000000200855. Epub 2022 Jun 3.*

Varughese RT, Karkare S, Poduri A, Kothare SV.

PCDH19-related epilepsy is a developmental and epileptic encephalopathy typically presenting with epilepsy and varying degrees of intellectual disability. Seizures typically present in clusters of focal or generalized seizures, sometimes in the setting of fever. We present the case of a 7-month-old girl presenting with new-onset refractory status epilepticus that followed routine vaccine administration and ensuing cytokine storm. She was diagnosed with a pathogenic variant in PCDH19. The patient required 5 antiseizure medications and pentobarbital-induced burst suppression for control of seizures. She was noted to have elevated serum cytokine levels (interleukin [IL]-2, IL-4, IL-10, IL-13, IL-17, IL-1, IL-1β, and IL-8) and CSF cytokine levels (IL-6 and IL-13). Anakinra was initiated and titrated based on serial cytokine levels, with doses ranging from 5 to 20 mg/kg/d resulting in reduction in cytokine levels and seizure reduction. By age 14 months, she was able to be maintained on 3 active antiseizure medications and ketogenic diet for seizure control.

PCDH19 相关癫痫是一种发育性和癫痫性脑病，通常表现为癫痫和不同程度的智力障碍。癫痫发作通常表现为局灶性或全面性发作，有时还伴有发热。我们在此展示一个 7 个月大的女孩的病例，她在注射常规疫苗和随后的细胞因子风暴之后出现了新发难治性癫痫持续状态。她被诊断出患有 PCDH19 的致病性变异。患者需要服用 5 种抗癫痫药物和戊巴比妥诱导的爆发抑制来控制癫痫发作。她被注意到血清细胞因子水平（白细胞介素[IL]-2、IL-4、IL-10、IL-13、IL-17、IL-1、IL-1β和 IL-8）和 CSF 细胞因子水平（IL-6 和 IL-13）升高。开始使用阿那白滞素，并根据连续的细胞因子水平进行滴定，剂量从 5 到 20mg/kg/d，使细胞因子水平下降和癫痫发作减少。到 14 个月大时，她能够维持使用 3 种有效的抗癫痫发作药物和生酮饮食来控制癫痫发作。

2. 非氨酯附加疗法治疗耐药性局灶性癫痫

Felbamate add-on therapy for drug-resistant focal epilepsy.Cochrane Database Syst Rev. *2022 Aug 1;8(8):CD008295. doi: 10.1002/14651858.CD008295.pub6.*

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BACKGROUND: This is an updated version of the Cochrane Review first published in 2011, and most recently updated in 2019. Epilepsy is a chronic and disabling neurological disorder, affecting approximately 1% of the population. Up to 30% of people with epilepsy have seizures that are resistant to currently available antiepileptic drugs and require treatment with multiple antiepileptic drugs in combination. Felbamate is a second-generation antiepileptic drug that can be used as add-on therapy to standard antiepileptic drugs.

OBJECTIVES: To evaluate the efficacy and tolerability of felbamate versus placebo when used as an add-on treatment for people with drug-resistant focal-onset epilepsy.

SEARCH METHODS: For the latest update, we searched the Cochrane Register of Studies (CRS Web) and MEDLINE (Ovid, 1946 to 13 July 2021) on 15 July 2021. There were no language or time restrictions. We reviewed the reference lists of retrieved studies to search for additional reports of relevant studies. We also contacted the manufacturers of felbamate and experts in the field for information about any unpublished or ongoing studies.

SELECTION CRITERIA: We searched for randomised placebo-controlled add-on studies of people of any age with drug-resistant focal seizures. The studies could be double-blind, single-blind or unblinded and could be of parallel-group or cross-over design.

DATA COLLECTION AND ANALYSIS: Two review authors independently selected studies for inclusion and extracted information. In the case of disagreements, a third review author arbitrated. Review authors assessed the following outcomes: 50% or greater reduction in seizure frequency; absolute or percentage reduction in seizure frequency; treatment withdrawal; adverse effects; quality of life.

MAIN RESULTS: We included four randomised controlled trials, representing a total of 236 participants, in the review. Two trials had parallel-group design, the third had a two-period cross-over design, and the fourth had a three-period cross-over design. We judged all four studies to be at an unclear risk of bias overall. Bias arose from the incomplete reporting of methodological details, the incomplete and selective reporting of outcome data, and from participants having unstable drug regimens during experimental treatment in one trial. Due to significant methodological heterogeneity, clinical heterogeneity and differences in outcome measures, it was not possible to perform a meta-analysis of the extracted data. Only one study reported the outcome of 50% or greater reduction in seizure frequency, whilst three studies reported percentage reduction in seizure frequency compared to placebo. One study claimed an average seizure reduction of 35.8% with add-on felbamate whilst another study claimed a more modest reduction of 4.2%. Both studies reported that seizure frequency increased with add-on placebo and that there was a significant difference in seizure reduction between felbamate and placebo (P = 0.0005 and P = 0.018, respectively). The third study reported a 14% reduction in seizure frequency with add-on felbamate but stated that the difference between treatments was not significant. There were conflicting results regarding treatment withdrawal. One study reported a higher treatment withdrawal for placebo-randomised participants, whereas the other three studies reported higher treatment withdrawal rates for felbamate-randomised participants. Notably, the treatment withdrawal rates for felbamate treatment groups across all four studies remained reasonably low (less than 10%), suggesting that felbamate may be well tolerated. Felbamate-randomised participants most commonly withdrew from treatment due to adverse effects. The adverse effects consistently reported by all four studies were headache, dizziness and nausea. All three adverse effects were reported by 23% to 40% of felbamate-treated participants versus 3% to 15% of placebo-treated participants. We assessed the evidence for all outcomes using GRADE and rated the evidence as very low certainty, meaning that we have little confidence in the findings reported. We mainly downgraded evidence for imprecision due to the narrative synthesis conducted and the low number of events. We stress that the true effect of felbamate could likely be significantly different from that reported in this current review update.

AUTHORS' CONCLUSIONS: In view of the methodological deficiencies, the limited number of included studies and the differences in outcome measures, we have found no reliable evidence to support the use of felbamate as an add-on therapy in people with drug-resistant focal-onset epilepsy. A large-scale, randomised controlled trial conducted over a longer period of time is required to inform clinical practice.

背景：这是 2011 年首次发表的 Cochrane 回顾性的更新版本，最近一次高达 30%的癫痫患者的发作对目前可用的抗癫痫发作药物有抵抗力，需要用多种抗癫痫发作药物联合治疗。非氨酯是第二代抗癫痫发作药物，可作为标准抗癫痫发作药物的附加疗法。

目的：评估非氨酯与安慰剂作为耐药性局灶性发作癫痫患者的附加治疗的疗效和耐受性。.

搜索方法： 对于最新的更新，我们于 2021 年 7 月 15 日搜索了 Cochrane 研究注册库 (CRS Web) 和 MEDLINE（Ovid，1946 年至 2021 年 7 月 13 日），没有语言或时间限制。我们审查了检索到的研究的参考列表，以寻找相关研究的其他报告。我们也联系了非氨酯厂家和该领域的专家，以获取有关任何未发表或正在进行的研究的信息。

选择标准： 我们搜索了任何年龄的耐药性局灶性发作患者的随机安慰剂对照的附加研究。这些研究可以是双盲、单盲或无盲，可以是平行组或交叉设计。

数据收集和分析： 两位综述作者独立选择纳入研究并提取信息。在出现分歧的情况下，由第三位评审作者进行仲裁。评审作者评估了以下结果：癫痫发作频率减少 50% 或更多；癫痫发作频率的绝对值或百分比减少；治疗中止；不良反应；生活质量。

主要结果： 我们在评价中纳入了四项随机对照试验，共 236 名参与者。两项试验采用平行组设计，第三项采用两期交叉设计，第四项采用三期交叉设计。我们判断所有四项研究总体上存在不明确的偏倚风险。偏差源于方法学细节报告不完整、结果数据报告不完整和选择性以及参与者不稳定药品在一项试验中的实验治疗期间的方案。由于显著的方法学异质性、临床异质性和结果测量的差异，无法对提取的数据进行荟萃分析。只有一项研究报告了癫痫发作频率降低 50% 或更多的结果，而三项研究报告了与安慰剂相比癫痫发作频率降低的百分比。一项研究声称，加用非氨酯后，癫痫发作平均减少 35.8%，而另一项研究则声称减少 4.2%，幅度较小。两项研究都报告说，加用安慰剂后，癫痫发作频率增加，而且非氨酯和安慰剂之间的发作减少有显著差异（分别为 P = 0.0005 和 P = 0.018）。第三项研究报告说，加用非氨酯后癫痫发作频率减少 14%，但指出治疗之间的差异并不显著。关于治疗退出有相互矛盾的结果。一项研究报告说，安慰剂随机参与者的治疗退出率较高，而其他三项研究报告说，非氨酯随机参与者的治疗退出率较高。值得注意的是，所有四项研究中，非氨酯治疗组的治疗停药率仍然相当低（低于 10%），这表明非氨酯可能具有良好的耐受性。非氨酯的随机参与者最常因不良反应而退出治疗。所有四项研究一致报告的不良反应是头痛、头晕和恶心。23% 至 40%的非氨酯治疗参与者报告了这三种不良反应，而 3%至 15%的安慰剂治疗参与者报告了这三种不良反应。我们使用 GRADE 评估了所有结果的证据，并将证据评为非常低的确定性，这意味着我们对报告的结果信心不足。由于所进行的叙述性综述和事件的数量较少，我们主要将证据的不精确性降级。我们强调，非氨酯的真实效果可能与本次综述更新中报告的效果有很大不同。

作者的结论：鉴于方法学上的缺陷、纳入研究的数量有限以及结果测量的差异，我们没有发现可靠的证据来支持将非氨酯作为耐药性局灶性癫痫患者的附加疗法。需要在较长时间内进行大规模的随机对照试验，为临床实践提供参考。

3. 生酮饮食对难治性癫痫儿童的影响，脑电图和神经行为的发展

Effects of ketogenic diet on children with refractory epilepsy, electroencephalogram and neurobehavioral development.

Minerva Med. 2022 Aug;113(4):741-742. doi: 10.23736/S0026-4806.20.07106-2. Epub 2020 Dec 18. PMID: 33337122.

Xing Y, Liu S, Lin Q.

The incidence rate of epilepsy is high in children's development. Because of the obstacles in cognition, psychology and sociology, it can cause serious impact on children's healthy growth, and also bring heavy burden to families and society. Studies have shown that the incidence of refractory epilepsy in all children with epilepsy can be as high as 13.7%. Intractable epilepsy refers to the clinical manifestations that it is still difficult to control seizures after more than two conventional antiepileptic drugs, the maximum tolerated dose and the appropriate course of treatment.1

Some studies have pointed out that ketogenic diet is a kind of diet containing high fat, low carbohydrate and appropriate protein. By adjusting the proportion of three nutrients, ketogenic diet can make the body produce ketone body and finally control epilepsy. Most scholars believe that the therapeutic mechanism of ketogenic diet may be related to the change of glutamate metabolism of amino acids, especially the precursor of neurotransmitters, and the mitochondrial decoupling induced by fatty acids, thus affecting the activation of nerve cells. However, there are few reports on the influence of EEG and neurobehavioral development in refractory epilepsy. Therefore, this paper intends to use ketogenic diet to treat refractory epilepsy in children, and to explore its clinical application value in epilepsy, EEG changes and neurobehavioral development.2

The reports are as follows. From April 2016 to October 2019, 120 patients with refractory epilepsy in our hospital were selected as the research objects. According to the random number table method, the children were divided into control group and observation group, 60 cases in each group. The control group was given routine treatment, including clonazepam, sodium valproate, levetiracetam, lamotrigine and prednisone acetate. If the blood glucose value is less than 2.24 mmol/L, take 30 mL orange juice; if the blood ketone value is more than 2.0 mmol/L, start to take ketogenic diet. Ketogenic diet should be given low calorie and limited water intake in order to produce enough ketones quickly.

After 6 months of treatment, the epileptic seizure control level of the two groups was observed. Total effective rate = (no attack cases + markedly effective cases)/total cases × 100%. Evaluation of EEG improvement: complete control – the background activity was basically normal, and the peak rhythm disorder disappeared completely; improvement – there was focal high amplitude slow wave or spike slow wave, but the peak rhythm disorder disappeared; no improvement – there was persistent peak rhythm disorder and no improvement in EEG performance. The improvement rate of EEG = (control cases + improved cases)/total cases × 100%. Gesell development scale (Chinese version) was used to evaluate the neurobehavioral development of the two groups before treatment and at 6, 12 and 18 months after treatment. Epilepsy control in the observation group was significantly better than that in the control group ($P<0.05$). After 6 months of treatment, the effect of EEG control level in the observation group was better than that in the control group, and the difference between the two groups was statistically significant ($P<0.05$). Before treatment, there was no significant difference in the levels of development indicators between the two groups ($P>0.05$). After 6, 12, 18 months of treatment, the level of the observation group was higher than that of the control group, and the differences were statistically significant ($P<0.05$). The treatment of epilepsy mainly includes drug treatment, surgical treatment and ketogenic diet treatment. Studies have shown that in the process of conventional drug treatment, about 20% of patients will develop resistance to antiepileptic drugs or have serious adverse reactions after taking drugs. Ketogenic diet is often used to reduce the frequency of attacks, reduce the amount of drug use, and improve the harm of adverse drug reactions.3

Ketogenic diet is a kind of diet with high fat, low carbohydrate and appropriate protein. By changing diet composition, reducing glucose supply, the body can produce ketone body with fat as energy source to control epilepsy. Studies have shown that compared with conventional antiepileptic drugs, ketogenic diet has a significant effect on refractory epileptic spasm caused by different causes, but there is no consensus on the improvement of EEG and neurodevelopment.

In this study, conventional drugs combined with ketogenic diet were used for clinical treatment of children with refractory epilepsy. The results showed that the control of epileptic seizures and EEG in ketogenic diet group were significantly better than those in conventional drug treatment group, indicating that ketogenic diet can effectively control epileptic seizures and improve abnormal EEG performance, which is consistent with previous research results.

Romão et al.4 pointed out that ketogenic diet can not only reduce the frequency of seizures in children with refractory epilepsy, but also improve their neurobehavioral and cognitive functions by changing the metabolic mechanism of the body and affecting the excitability of neurons. The results of this study indicated that the total development quotient (TDQ) scores of children in the observation group were significantly higher than those in the control group at 6, 12 and 18 months of treatment, indicating that ketogenic diet can improve the neurobehavioral development of children with epilepsy, and the longer the treatment time, the more obvious the improvement of neurobehavioral development. Some scholars have pointed out that ketogenic diet metabolites can reduce the production of intracellular reactive oxygen species (ROS), improve cell antioxidant neuroprotective function and anti-apoptosis, but it is easy to lead to insufficient intake of calcium, iron, zinc, vitamin B group, vitamin C, D and other nutrients during the treatment process, so it is necessary to pay attention to supplement when using for a long time. In addition, if the proportion of MCT oil is high, it is necessary to pay attention to whether the necessary fatty acids in the diet are enough.5

In conclusion, ketogenic diet can significantly reduce epileptic seizures in children with epilepsy, improve EEG and neurobehavioral development, and provide an effective clinical treatment for children with refractory epilepsy, which is worthy of promotion and application.

在儿童成长过程中，癫痫的发病率很高。由于其在认知、心理和社会学方面的障碍，会对儿童的健康成长造成严重影响，也给家庭和社会带来沉重负担。研究表明，难治性癫痫在所有儿童癫痫患者中的发病率可高达13.7%。难治性癫痫是指经过两种以上的常规抗癫痫发作药物、最大耐受剂量和适当疗程的治疗，仍难以控制癫痫发作的临床表现。

有研究指出，生酮饮食是一种含有高脂肪、低碳水化合物和适当蛋白质的饮食。通过调整三种营养物质的比例，生酮饮食可以使人体产生酮体，最终控制癫痫。多数学者认为，生酮饮食的治疗机制可能与氨基酸，特别是神经递质的前体谷氨酸代谢的改变，以及脂肪酸诱导的线粒体解耦有关，从而影响神经细胞的激活。然而，关于难治性癫痫的脑电图和神经行为发展的影响，目前还没有什么报道。因此，本文拟采用生酮饮食治疗儿童难治性癫痫，并探讨其在癫痫、脑电图变化和神经行为发育方面的临床应用价值。

报告内容如下。2016 年 4 月至 2019 年 10 月，选择我院 120 例难治性癫痫患者作为研究对象。按照随机数字表法，将患儿分为对照组和观察组，每组 60 例。对照组给予常规治疗，包括氯硝西泮、丙戊酸钠、左乙拉西坦、拉莫三嗪和醋酸泼尼松。如果血糖值低于 2.24mmol/L，服用 30mL 橙汁；如果血酮值超过 2.0mmol/L，开始服用生酮饮食。生酮饮食应给予低热量和有限的水摄入，以便迅速产生足够的酮体。

治疗 6 个月后，观察两组的癫痫发作控制水平。总有效率=（无发作病例+明显有效病例）/总病例×100%。脑电图改善评价：完全控制--背景活动基本正常，峰律紊乱完全消失；改善--有局灶性高波幅慢波或尖峰慢波，但峰律紊乱消失；无改善--有持续的峰律紊乱，脑电图表现无改善。脑电图的改善率=（对照组病例+改善组病例）/总病例×100%。采用 Gesell 发展量表（中文版）评价两组患者治疗前及治疗后 6、12、18 个

月的神经行为发展。观察组的癫痫控制情况明显好于对照组（P<0.05）。治疗 6 个月后，观察组的脑电图控制水平效果优于对照组，两组差异有统计学意义（P<0.05）。治疗前，两组的发育指标水平无明显差异（P>0.05）。治疗 6、12、18 个月后，观察组的水平高于对照组，差异有统计学意义（P<0.05）。癫痫的治疗主要包括药物治疗、手术治疗和生酮饮食治疗。研究表明，在常规药物治疗过程中，约有 20%的患者会对抗癫痫发作药物产生耐药性或服药后出现严重不良反应。生酮饮食常被用来减少发作频率，减少用药量，改善药物不良反应的危害。

生酮饮食是一种高脂肪、低碳水化合物和适当蛋白质的饮食。通过改变饮食成分，减少葡萄糖供应，身体可以产生以脂肪为能量来源的酮体来控制癫痫。研究表明，与常规抗癫痫发作药物相比，生酮饮食对不同原因引起的难治性癫痫痉挛有显著疗效，但对脑电图和神经发育的改善尚无共识。

本研究将常规药物联合生酮饮食用于儿童难治性癫痫的临床治疗。结果显示，生酮饮食组对癫痫发作和脑电图的控制明显优于常规药物治疗组，说明生酮饮食可以有效控制癫痫发作，改善脑电图异常表现，与以往研究结果一致。

罗芒等人。4 指出生酮饮食不仅可以降低难治性癫痫患儿的癫痫发作频率，还可以通过改变机体的代谢机制，影响神经元的兴奋性来改善其神经行为和认知功能。本研究结果表明，观察组患儿在治疗 6、12 和 18 个月时的总发育商（TDQ）得分明显高于对照组，表明生酮饮食可以改善患儿的神经行为发育。癫痫患儿，治疗时间越长，神经行为发育改善越明显。有学者指出，生酮饮食代谢物可以减少细胞内活性氧（ROS）的产生，提高细胞抗氧化神经保护功能和抗凋亡，但在治疗过程中容易导致钙、铁、锌、维生素 B 群、维生素 C、D 等营养物质摄入不足，因此需要注意长期使用时补充。另外，如果 MCT 油的比例高，就要注意饮食中必需的脂肪酸是否足够。

综上所述，生酮饮食可显著减少癫痫患儿的癫痫发作，改善脑电图和神经行为发育，为难治性癫痫患儿提供有效的临床治疗，值得推广应用。

4. 拉莫三嗪在阿尔茨海默病小鼠模型中防止认知缺陷、突触和神经细胞损伤以及标志性神经病变

Lamotrigine protects against cognitive deficits, synapse and nerve cell damage, and hallmark neuropathologies in a mouse model of Alzheimer's disease.*Epileptic Disord. 2022 Oct 1;24(5):1-9. doi: 10.1684/epd.2022.1460.*

Fu XX, Duan R, Wang SY, Zhang QQ, Wei B, Huang T, Gong PY, E YAN, Jiang T, Zhang YD .

Lamotrigine (LTG) is a widely used drug for the treatment of epilepsy. Emerging clinical evidence suggests that LTG may improve cognitive function in patients with Alzheimer's disease. However, the underlying molecular mechanisms remain unclear. In this study, amyloid precursor protein/presenilin 1 (APP/PS1) double transgenic mice were used as a model of Alzheimer's disease. Five-month-old APP/PS1 mice were intragastrically administered 30 mg/kg LTG or vehicle once per

day for 3 successive months. The cognitive functions of animals were assessed using Morris water maze. Hyperphosphorylated tau and markers of synapse and glial cells were detected by western blot assay. The cell damage in the brain was investigated using hematoxylin and eosin staining. The levels of amyloid-β and the concentrations of interleukin-1β, interleukin-6 and tumor necrosis factor-α in the brain were measured using enzyme-linked immunosorbent assay. Differentially expressed genes in the brain after LTG treatment were analyzed by high-throughput RNA sequencing and real-time polymerase chain reaction. We found that LTG substantially improved spatial cognitive deficits of APP/PS1 mice; alleviated damage to synapses and nerve cells in the brain; and reduced amyloid-β levels, tau protein hyperphosphorylation, and inflammatory responses. High-throughput RNA sequencing revealed that the beneficial effects of LTG on Alzheimer's disease-related neuropathologies may have been mediated by the regulation of Ptgds, Cd74, Map3k1, Fosb, and Spp1 expression in the brain. These findings revealed potential molecular mechanisms by which LTG treatment improved Alzheimer's disease. Furthermore, these data indicate that LTG may be a promising therapeutic drug for Alzheimer's disease.

拉莫三嗪（LTG）是一种广泛用于治疗癫痫发作的药物。新出现的临床证据表明，LTG 可以改善阿尔茨海默病患者的认知功能。然而，潜在的分子机制仍不清楚。在这项研究中，淀粉样前体蛋白/前苏氨酸 1（APP/PS1）双转基因小鼠被用作阿尔茨海默病的模型。5 个月大的 APP/PS1 小鼠连续 3 个月每天胃内服用 30 毫克/千克 LTG 或赋形剂。使用莫里斯水迷宫评估动物的认知功能。通过 Western 印迹法检测高磷酸化 tau 以及突触和胶质细胞的标记。使用血红素和伊红染色研究了大脑中的细胞损伤。使用酶联免疫吸附法测量了大脑中淀粉样蛋白-β水平以及白细胞介素-1β、白细胞介素-6 和肿瘤坏死因子-α的浓度。通过高通量 RNA 测序和实时聚合酶链式反应分析了 LTG 治疗后大脑中差异表达的基因。我们发现，LTG 大大改善了 APP/PS1 小鼠的空间认知缺陷；减轻了对大脑突触和神经细胞的损害；并降低了淀粉样蛋白β水平、tau 蛋白高磷酸化和炎症反应。高通量 RNA 测序显示，LTG 对阿尔茨海默病相关神经病理学的有益影响可能是通过调节大脑中 Ptgds、Cd74、Map3k1、Fosb 和 Spp1 表达的。这些发现揭示了 LTG 治疗改善阿尔茨海默病的潜在分子机制。此外，这些数据表明，LTG 可能是治疗阿尔茨海默氏症的有前途的治疗药物。

5. 血脑屏障靶向输送共轭性拉科酰胺金纳米颗粒：改善癫痫失神发作的结果

Blood-brain barrier targeted delivery of lacosamide-conjugated gold nanoparticles: Improving outcomes in absence seizures.*Epilepsy Res. 2022 Aug;184:106939. doi: 10.1016/j.eplepsyres.2022.106939. Epub 2022 May 6.*

Temizyürek A, Yılmaz CU, Emik S, Akcan U, Atış M, Orhan N, Arıcan N, Ahishali B, Tüzün E, Küçük M, Gürses C, Kaya M.

OBJECTIVE: Most currently available antiepileptics are not fully effective in the prevention of seizures in absence epilepsy owing to the presence of blood-brain barrier (BBB). We aimed to test whether binding an antiepileptic drug, lacosamide (LCM), to glucose-coated gold nanoparticles (GNPs) enables efficient brain drug delivery to suppress the epileptic activity in WAG/Rij rats with absence epilepsy.

METHODS: In these animals, intracranial-EEG recording, behavioral test, in vivo imaging of LCM and LCM-GNP conjugate distribution in the brain, inductively coupled plasma mass spectrometry analysis, immunofluorescence staining of glucose

transporter (Glut)- 1, glial fibrillary acidic protein (GFAP), and p-glycoprotein (P-gp) and electron microscopy were performed.

RESULTS: Lacosamide-GNP conjugates decreased the amplitude and frequency of spike-wave-like discharges (SWDs) and alleviated the anxiety-like behavior as assessed by EEG and elevated plus-maze test, respectively ($p < 0.01$). The in vivo imaging system results showed higher levels of fluorescein dye tagged to LCM-GNP in the brain during the 5-day injection period ($p < 0.01$). Immunofluorescence staining displayed decreased P-gp, Glut-1, and GFAP expression by LCM-GNP conjugate treatment predominantly in the cerebral cortex suggesting a potential functionality of this brain region in the modulation of neuronal activity in our experimental setting ($p < 0.01$).

SIGNIFICANCE: We suggest that the conjugation of LCM to GNPs may provide a novel approach for efficient brain drug delivery in light of the effectiveness of our strategy not only in suppressing the seizure activity but also in decreasing the need to use high dosages of the antiepileptics to reduce the frequently encountered side effects in drug-resistant epilepsy.

目的：由于存在血脑屏障（BBB），目前大多数可用的抗癫痫发作药在预防癫痫发作方面并不完全有效。我们旨在测试抗癫痫发作药物拉科酰胺（LCM）与涂有葡萄糖的金纳米颗粒（GNP）结合是否能够有效地提供大脑药物，以抑制没有癫痫的 WAG/Rij 大鼠的癫痫活动。

方法：在这些动物中，进行颅内脑电图记录、行为测试、LCM 和 LCM-GNP 共轭分布的体内成像、电感耦合血浆质谱分析、葡萄糖转运体（Glut）-1、胶质纤维酸蛋白（GFAP）和对糖蛋白（P-gp）的免疫荧光染色。

结果：拉科酰胺-GNP 共轭物降低了尖峰波样放电（SWD）的振幅和频率，并分别缓解了脑电图和高加迷宫测试评估的焦虑样行为（$p < 0.01$）。体内成像系统结果显示，在 5 天注射期间，大脑中标记 LCM-GNP 的荧光素染料水平更高（$p < 0.01$）。LCM-GNP 共轭治疗主要在大脑皮层，免疫荧光染色显示 P-gp、Glut-1 和 GFAP 表达减少，这表明这个大脑区域在我们的实验环境中调节神经元活动方面具有潜在功能（$p < 0.01$）。

意义：鉴于我们的策略不仅在抑制癫痫活动方面，而且在减少使用高剂量抗癫痫药剂的需求方面，减少耐药性癫痫中经常遇到的副作用，我们建议 LCM 与 GNP 的结合可以为高效脑部药物输送提供一种新方法。

6. 年轻人和老年人癫痫的治疗：加拿大抗癫痫发作药物的人口差异和处方模式

The treatment of epilepsy in younger and older adults: Demographic differences and prescribing patterns of anti-seizure medications in Canada.*Epilepsy Res. 2022 Aug;184:106941. doi: 10.1016/j.eplepsyres.2022.106941. Epub 2022 May 13*.

Haris A, Bachour K, Hopkins RB, Tarride JE, Keezer MR

OBJECTIVE: Our study describes adults in Canada between 2009 and 2013 receiving at least one antiseizure medication (ASM) at the end of a hospitalization for newly-diagnosed epilepsy, with a focus on the type of ASM prescribed, changes in drug prescriptions after one year, and how this differs between younger and

older adults.

METHODS: Canada-wide data from the Discharge Abstract Database and the National Prescription Drug Utilization Information System database from 2009 to 2013 were used to identify individuals hospitalized with newly-diagnosed

epilepsy and prescribed an ASM at the end of this hospitalization. We classified ASMs into enzyme inducing (EIASM) and non-enzyme inducing (non-EIASM). Confidence intervals and p-values were generated using an exact binomial distribution.

RESULTS: Our study sample included 10,568 adults. 61.3% (95% CI: 60.3, 62.2) of all prescriptions were for EIASMs. Among EIASMs, phenytoin was the most frequently prescribed drug in both younger (aged 18-59 years) and older subjects. Among older adults prescribed EIASMs, 53.1% (95% CI: 51.5, 54.7) were men; and for non-EIASMs, 45.2% (95% CI: 43.0%, 47.4) were men. Among the 3847 older adults initially prescribed EIASMs, 7.1% (95% CI: 6.4, 8.0) switched to non-EIASMs at one year following their hospital discharge.

CONCLUSION: Non-EIASM have been available to clinicians since the 1990's but suboptimal ASMs such as phenytoin remained frequently prescribed during the period of this study. This is an especially pressing issue among older adults due to the greater risk of drug intolerability, related to metabolic changes that occur with greater age, increasing comorbidity burden, and frailty. Men were disproportionately prescribed EIASM, as compared to women who were more often prescribed non-EIASM.

目的：我们的研究描述了 2009 年至 2013 年间加拿大成年人在新诊断的癫痫住院结束时至少服用一种抗癫痫发作药（ASM），重点是 ASM 处方的类型、一年后药物处方的变化，以及年轻人和老年人之间的差异。

方法：使用 2009 年至 2013 年出院摘要数据库和国家处方药使用信息系统数据库的全加拿大数据来识别新诊断的癫痫住院患者，并在住院结束时开具 ASM 处方。我们将 ASM 分为酶诱导（EIASM）和非酶诱导（非 EIASM）。使用精确的二项分布生成置信区间和 p 值。

结果：我们的研究样本包括 10568 名成年人。61.3%（95%CI：60.3，62.2）的处方是 EIASM。在 EIASM 中，苯妥英是年轻（18-59 岁）和老年受试者最常见的处方药。在开具 EIASM 的老年人中，男性为 53.1%（95%CI：51.5，54.7）；非 ESIASM 为 45.2%（95%CI：43.0%，47.4）为男性。在最初开具 EIASM 的 3847 名老年人中，7.1%（95%CI：6.4，8.0）在出院一年后转向非 EIASM。

结论：自 20 世纪 90 年代以来，临床医生一直可以使用非 EIASM，但在这项研究期间，苯妥英等次优 ASM 仍然经常开处方。在老年人中，这是一个特别紧迫的问题，因为药物不耐受的风险更大，这与随着年龄增长而发生的代谢变化、增加的共病负担和虚弱有关。与女性相比，男性的 EIASM 处方不成比例，而女性则更经常服用非 EIASM。

7. 利拉鲁肽慢性治疗可阻止遗传性癫痫易发大鼠对地西泮抗癫痫作用产生耐受

Liraglutide chronic treatment prevents development of tolerance to antiseizureeffects of diazepam in genetically epilepsy prone rats. *2022 Aug 5;928:175098. doi: 10.1016/j.ejphar.2022.175098. Epub 2022 Jun 11*

De Sarro C, Tallarico M, Pisano M, Gallelli L, Citraro R, DeSarro G, Leo A.

Glucagon-like peptide-1 (GLP-1) is a hormone that can regulate several neuronal functions. The modulation of GLP-1 receptors emerged as a potential target to treat several neurological diseases, such as epilepsy. Here, we studied the effects of acute and chronic treatment with liraglutide (LIRA), in genetically epilepsy prone rats (GEPR-9s). We have also investigated the possible development of tolerance to antiseizure effects of diazepam, and how LIRA could affect this

phenomenon over the same period of treatment. The present data indicate that an acute treatment with LIRA did not diminish the severity score of audiogenic seizures (AGS) in GEPR-9s. By contrast, a chronic treatment with LIRA has shown only a modest antiseizure effect that was maintained until the end of treatment, in GEPR-9s. Not surprisingly, acute administration of diazepam reduced, in a dose dependent manner, the severity of the AGS in GEPR-9s.However, when diazepam was chronically administered, an evident development of tolerance to its antiseizure effects was detected. Interestingly, following an add-on treatment with LIRA, a reduced development of tolerance and an enhanced diazepam antiseizure effect was observed in GEPR-9s. Overall, an add-on therapy with LIRA demonstrate benefits superior to single antiseizure medications and could be utilized to treat epilepsy as well as associated issues. Therefore, the potential use of GLP1 analogs for the treatment of epilepsy in combination with existing antiseizure medications could thus add a new and long-awaited dimension to its management.

胰高血糖素样肽-1 (Glucagon-like peptide-1, GLP-1)是一种调节多种神经元功能的激素。GLP-1 受体的调节成为治疗癫痫等多种神经系统疾病的潜在靶点。在这里，我们研究了利拉鲁肽(liraglutide, LIRA)对遗传性癫痫易感大鼠(GEPR-9s)急性和慢性治疗的影响。我们还研究了地西泮抗癫痫发作作用耐受性的可能发展，以及在相同的治疗期间利拉鲁肽如何影响这一现象。目前的数据表明，LIRA 的急性治疗并没有降低 gepr -9 患者听源性惊厥(AGS)的严重程度评分。相比之下，在 gepr -9 患者中，使用 LIRA 的慢性治疗只显示出适度的抗癫痫作用，直到治疗结束。毫不奇怪，急性给药地西泮以剂量依赖的方式降低了 gepr -9 患者 AGS 的严重程度。

然而，当长期服用安定时，检测到对其抗癫痫作用的耐受性的明显发展。有趣的是，在接受 LIRA 附加治疗后，gepr -9 患者的耐受性降低，而地西泮抗癫痫作用增强。总的来说，LIRA 的附加治疗效果优于单一抗癫痫发作药物，可用于治疗癫痫及其相关问题。因此，GLP1 类似物与现有抗癫痫发作药物联合治疗癫痫的潜在应用可能为其管理增加一个期待已久的新维度。

8. 基于肠道的操作刺激小儿癫痫模型的海马线粒体生物能量学

Gut-based manipulations spur hippocampal mitochondrial bioenergetics in a modelof pediatric epilepsy. *2022 Sep 1;1868(9):166446. doi:10.1016/j.bbadis.2022.166446. Epub 2022 May 17.*

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A growing body of evidence supports a role of the gut microbiota in regulatingdiverse physiological processes, including neural function and metabolism viathe gut-brain axis. Infantile spasms syndrome is an early-onset epileptic encephalopathy associated with perturbed brain mitochondrial bioenergetics. Employing a neonatal rat model of infantile spasms, mitochondria respirometry and biochemical analyses, the present study reveals that gut microbiota manipulation by diet, antibiotics and probiotics have the potential to enhance hippocampal mitochondrial bioenergetics. Although preliminary in nature, our data reveal that microbial manipulation that regulates brain mitochondrial function may be a novel strategy for the treatment of epileptic disorders.

越来越多的证据支持肠道菌群在调节多种生理过程中的作用，包括通过肠道-大脑轴的神经功能和代谢。婴儿痉挛综合征是一种与脑线粒体生物能紊乱相关的早发癫痫性脑病。本研究利用婴儿痉挛症的新生大鼠模型、

线粒体呼吸测量和生化分析，揭示了饮食、抗生素和益生菌对肠道菌群的操纵有可能增强海马线粒体生物能量学。虽然这只是初步研究，但我们的数据显示，微生物操纵大脑线粒体功能可能是治疗癫痫疾病的一种新策略。

9. biotics 靶向 MGBA 治疗癫痫:来自临床前和临床研究的新见解

Targeting the MGBA with -biotics in epilepsy: New insights from preclinical and clinical studies. *Neurobiol Dis. 2022 Aug;170:105758. doi: 10.1016/j.nbd.2022.105758. Epub 2022 May 17.*

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BACKGROUND: Data accumulation reveals that the bidirectional communication between the gut microbiota and the brain, called the microbiota-gut-brain axis (MGBA), can be modulated by differentcompounds including prebiotics, probiotics, symbiotic (a fair combination of both), and diet, thus exerting a beneficial impact on brain activity and behaviors. This review aims to give an overview of the possible beneficial effects of the supplementation of -biotics in epilepsy treatment.

METHODS: A search on PubMed and ClinicalTrials.gov databases using the terms "probiotics", OR "prebiotics", AND "gut microbiota", AND "epilepsy" was performed. The search covered the period of the last eleven years (2010-2021).CONCLUSIONS: Nowadays, studies analyzing the clinical impact of gut microbiota-modulating intervention strategies on epilepsy are limited and heterogenous due either to the different experimental populations studied (i.e., genetic vs lesional mouse models) or the various primary outcomes measure evaluated. However, positive effects have invariably been noticed; particularly, there have been improvements in behavioral comorbidities and associated gastrointestinal (GI) symptoms. More studies will be needed in the next few years to strictly evaluate the feasibility to introduce these new therapeutic strategies in the clinical treatment of highly refractory epilepsies.

背景:数据积累表明，肠道菌群和大脑之间的双向交流被称为微生物-肠道-大脑轴(MGBA)，可以被不同的化合物调节，包括益生元、益生菌、共生(两者的合理组合)和饮食，从而对大脑活动和行为产生有益的影响。这篇综述旨在综述补充-生物制剂在癫痫治疗中可能的有益作用。

方法:在 PubMed 和 ClinicalTrials.gov 数据库中使用“益生菌”或“益生元”、“肠道菌群”和“癫痫”等术语进行搜索。搜索活动覆盖了过去 11 年(2010-2021 年)。

结论:目前，分析肠道微生物调节干预策略对癫痫的临床影响的研究是有限的，而且由于研究的实验人群不同(即遗传 vs 损伤性小鼠模型)或评估的不同的主要结果衡量标准而存在异质性。然而，积极的影响总是被注意到;特别是行为共病和相关胃肠道(GI)症状方面有所改善。未来几年还需要更多的研究来严格评估将这些新的治疗策略引入高度难治性癫痫的临床治疗的可行性。

10. 胰高血糖素样肽-1 (GLP-1)类似物在癫痫和相关共病中的神经保护作用

Neuroprotective effects of glucagon-like peptide-1 (GLP-1) analogues in epilepsy and associated comorbidities.*Neuropeptides. 2022 Aug;94:102250. doi: 10.1016/j.npep.2022.102250. Epub 2022.*.

Manavi MA

Epilepsy is a common neurological condition induced by losing equilibrium ofdifferent pathway as well as neurotransmitters that affects over 50 millionpeople globally. Furthermore, long-term administration of anti-seizuremedications has been associated with psychological adverse effects. Also,epilepsy has been related to an increased prevalence of obesity and called type2 diabetes mellitus. On the other hand, GLP-1 receptors are located throughout the brain, including the hippocampus, which have been associated to majority ofneurological conditions, such as epilepsy and psychiatric disorders. Moreover,the impact of different GLP-1 analogues on diverse neurotransmitter systems and associated cellular and molecular pathways as a potential therapeutic target for epilepsy and associated comorbidities has piqued curiosity. In this regard, the anticonvulsant effects of GLP-1 analogues have been investigated in various animal models and promising results such as anticonvulsants as well as cognitive improvements have been observed. For instance, GLP-1 analogues like liraglutide in addition to their possible anticonvulsant benefits, could be utilized to alleviate mental cognitive problems caused by both epilepsy and anti-seizure medication side effects. In this review and growing protective function of GLP-1 in epilepsy induced by disturbed neurotransmitter pathways and the probable mechanisms of action of GLP-1 analogues as well as the GLP-1 receptor in these effects have been discussed.

癫痫是一种常见的神经系统疾病，由不同通路和神经递质失去平衡引起，影响全球 5000 多万人。此外，长期服用抗癫痫发作药物与心理不良反应有关。此外，癫痫还与肥胖和 2 型糖尿病的患病率增加有关。另一方面，GLP-1 受体分布在整个大脑，包括海马体，与大多数神经系统疾病，如癫痫和精神疾病相关。此外，不同的 GLP-1 类似物对不同的神经递质系统和相关的细胞和分子通路的影响，作为癫痫和相关共病的潜在治疗靶点，已经引起了人们的好奇。在这方面，GLP-1 类似物的抗惊厥作用已在各种动物模型中进行了研究，并观察到抗惊厥药物和改善认知功能等有前景的结果。例如，GLP-1 类似物，如利拉鲁肽，除了可能的抗惊厥作用外，还可以用来缓解癫痫和抗癫痫发作药物副作用引起的精神认知问题。本文综述了 GLP-1 对神经递质通路紊乱所致癫痫的保护作用，以及 GLP-1 类似物和 GLP-1 受体在其中的可能作用机制。

11. 海马内癫痫样 GluN2B 驱动的兴奋作为抗颞叶癫痫的治疗靶点

Epileptiform GluN2B-driven excitation in hippocampus as a therapeutic target against temporal lobe epilepsy. *Exp Neurol. 2022 Aug;354:114087. doi: 10.1016/j.expneurol.2022.114087. Epub 2022 Apr 22.*.

Gorlewicz , Pijet B, Orlova K, Kaczmarek L, Knapska E.

GluN2B is an NMDAR subunit that displays restricted expression in the mature hippocampus - a structure playing a major role in temporal lobe epilepsy. However, the contribution of GluN2B to the pathophysiology of the condition has not been fully explored. Here we combined status epilepticus models of temporal lobe epilepsy, protein expression studies, and patch-clamp experiments to demonstrate the profound change in the nature of glutamatergic transmission mediated in the epileptiform hippocampus by a subpopulation of GluN2B-containing NMDAR receptors. Satisfactory control of chronic seizures in temporal lobe epilepsy is still impossible for about 40% of patients. Therefore, new therapeutic approaches against the condition are desired. Using video-EEG recordings in animals and ex vivo extracellular recordings in brain sections, we present here the potential of ifenprodil (GluN2B selective NMDAR antagonist) for altering the course of

epileptogenesis and ictogenesis in temporal lobe epilepsy. In sum, we identify GluN2B as one of the factors in the pathogenesis of recurrent seizures and provide a rationale for clinical studies on ifenprodil as a new candidate therapeutic against temporal lobe epilepsy.

GluN2B 是 NMDAR 的一个亚基，在成熟海马区表达受限，在颞叶癫痫中发挥重要作用。然而，GluN2B 在该病的病理生理学中的作用还没有得到充分的研究。在这里，我们结合了颞叶癫痫持续状态模型、蛋白质表达研究和膜片钳实验，展示了含有 GluN2B 的 NMDAR 受体亚群在癫痫样海马区介导的谷氨酸能传递性质的巨大改变。约 40%的患者仍无法满意地控制颞叶癫痫的慢性发作。因此，需要新的治疗方法来对付这种情况。通过动物视频脑电图记录和脑片的离体细胞外记录，我们在这里展示了艾芬地尔(GluN2B 选择性 NMDAR 拮抗剂)改变颞叶癫痫的癫痫发生和发作过程的潜力。综上所述，我们认为 GluN2B 是癫痫反复发作的发病机制中的因素之一，并为临床研究艾芬地尔作为新的候选药物治疗颞叶癫痫提供了理论基础。

12. 癫痫患者和抗癫痫发作药物使用者院外心脏骤停的风险

Risk of out-of-hospital cardiac arrest in patients with epilepsy and users of antiepileptic drugs.*Br J Clin Pharmacol. 2022 Aug;88(8):3709-3715. doi: 10.1111/bcp.15313. Epub 2022 Mar 26.*

Eroglu TE, Folke F, Tan HL, Torp-Pedersen C, Gislason GH.

AIMS: A few studies suggested that epilepsy and antiepileptic drugs with sodium channel-blocking properties were independently associated with out-of-hospital cardiac arrest (OHCA). However, these findings have not yet been replicated.

METHODS: Using Danish registries, we conducted a nested case-control study in a cohort of individuals between 1 June 2001 and 31 December 2015. Cases were defined as OHCA from presumed cardiac causes, and were matched with non-OHCA-controls based on sex, and age on the date of OHCA. Exposure of interest was epilepsy or antiepileptic drug use. To study the association between individual antiepileptic drug use and the rate of OHCA, we compared each antiepileptic drug with valproic acid. Cox regression with time-dependent covariates was conducted to calculate hazard ratio (HR) and 95% confidence interval (CI).

RESULTS: We identified 35 195 OHCA-cases and 351 950 matched non-OHCA controls. Epilepsy (cases: 3.58%, controls: 1.60%) was associated with increased rate of OHCA compared with the general population (HR: 1.76, 95%CI: 1.64-1.88) when common OHCA risk factors were taken into account. ".CONCLUSION: Epilepsy is associated with increased rate of OHCA. Our findings do not support a possible association between antiepileptic drugs with sodium channel-blocking properties and OHCA.

目的：一些研究表明癫痫和具有钠通道阻滞性的抗癫痫发作药物与院外心脏骤停(OHCA)独立相关。然而，这些发现尚未被重复。

方法：利用丹麦的登记处，我们在 2001 年 6 月 1 日至 2015 年 12 月 31 日期间对一群个体进行了嵌套式病例对照研究。根据推测的心脏病原因将病例定义为 OHCA，并根据 OHCA 发生的日期、性别和年龄与非 OHCA 进行对照配对。感兴趣的暴露是癫痫或抗癫痫发作药物的使用。为了研究个体抗癫痫发作药物使用与

OHCA 发生率之间的关系，我们将每种抗癫痫发作药物与丙戊酸进行比较。采用时间相关的 Cox 回归方法计算风险比(HR)和 95%置信区间(CI)。

结果：我们确定了 35195 例 OHCA 病例和 351950 例非 OHCA 病例进行配对对照。当考虑常见 OHCA 危险因素时，与一般人群(HR：1.76，95%CI：1.64 - 1.88)相比，癫痫(病例：3.58 % ,对照组：1.60%)与 OHCA 发生率增加有关。在研究抗癫痫发作药物的用药时，我们发现两种非钠通道阻滞剂的抗癫痫发作药物氯硝西泮(HR：1.88，95%CI：1.45-2.44)和普瑞巴林(HR：1.33，95%CI：1.05-1.69)与 OHCA 有关，而有钠通道阻断的抗癫痫发作药物均与 OHCA 无关。

结论：癫痫与 OHCA 发生率增高有关。我们的发现不支持抗癫痫发作药物与钠通道阻断特性和 OHCA 之间可能的联系。

13. 耐药性癫痫的研究中未考虑的因素：耐药性癫痫：神经炎症的评估

Factors not considered in the study of drug-resistant epilepsy: Drug-resistant epilepsy: Assessment of neuroinflammation.

Epilepsia Open. 2022 Aug;7 Suppl 1(Suppl 1):S68-S80. doi: 10.1002/epi4.12590. Epub 2022 Mar 16..

Campos-Bedolla P, Feria-Romero I, Orozco-Suárez S.

More than one-third of people with epilepsy develop drug-resistant epilepsy (DRE). Different hypotheses have been proposed to explain the origin of DRE. Accumulating evidence suggests the contribution of neuroinflammation, modifications in the integrity of the blood-brain barrier (BBB), and altered immune responses in the pathophysiology of DRE. The inflammatory response is mainly due to the increase of cytokines and related molecules; these molecules have neuromodulatory effects that contribute to hyperexcitability in neural networks that cause seizure generation. Some patients with DRE display the presence of autoantibodies in the serum and mainly cerebrospinal fluid. These

patients are refractory to the different treatments with standard antiseizure medications (ASMs), and they could be responding well to immunomodulatory therapies. This observation emphasizes that the etiopathogenesis of DRE is involved with immunology responses and associated long-term events and chronic inflammation processes. Furthermore, multiple studies have shown that functional polymorphisms as risk factors are involved in inflammation processes. Several relevant polymorphisms could be considered risk factors involved in inflammation-related DRE such as receptor for advanced glycation end products (RAGE) and interleukin 1β (IL-1β). All these evidences sustained the hypothesis that the chronic inflammation process is associated with the DRE. However, the effect of the chronic inflammation process should be investigated in further clinical studies to promote the development of novel therapeutics useful in treatment of DRE.

超过三分之一的癫痫患者会患上耐药性癫痫(DRE)。人们提出了不同的假说来解释耐药性癫痫的起源。越来越多的证据表明，神经炎症、血脑屏障(BBB)完整性的改变以及免疫反应的改变在耐药性癫痫的病理生理学中起着重要作用。炎症反应主要是由于细胞因子和相关分子的增加；这些分子具有神经调节作用，促使神经网络的过度兴奋，从而导致癫痫的产生。一些耐药性癫痫患者的血清和主要是脑脊液中存在自身抗体。这些患者对标准抗癫痫发作药物(ASMs)的不同治疗都是难治性的，而他们对免疫调节疗法的反应可能会很好。这一

观察强调，耐药性癫痫的发病机制与免疫学反应和相关的长期事件和慢性炎症过程有关。此外，多项研究表明，作为危险因素的功能多样性参与了炎症过程。几个相关的基因多样性可被认为是参与炎症相关耐药性癫痫的危险因素，如晚期糖基化终产物受体(RAGE)和白细胞介素 1β(IL-1β)。所有这些证据支持慢性炎症过程与 DRE 有关的假说。然而，慢性炎症过程的影响还需要进一步的临床研究，以促进治疗 DRE 的新疗法的发展。

14. 樱花素在荷包牡丹碱诱发的癫痫发作中发挥抗惊厥作用

Sakuranetin exerts anticonvulsant effect in bicuculline-induced seizures. *Fundam Clin Pharmacol. 2022 Aug;36(4):663-673. doi: 10.1111/fcp.12768. Epub 2022 Feb 21.*

Vicente-Silva W, Silva-Freitas FR, Beserra-Filho JIA, Cardoso GN, Silva-Martins S, Sarno TA, Silva SP, Soares-Silva B, Dos Santos JR, da Silva RH, Prado CM, Ueno AK, Lago JHG, Ribeiro AM.

Epilepsy is a chronic neurological disorder characterized by an abnormal, spontaneous, and synchronized neuronal hyperactivity. Therapeutic approaches for controlling epileptic seizures are associated with pharmacoresistance and side effects burden. Previous studies reported that different natural products may have neuroprotector effects. Sakuranetin (SAK) is a flavanone with antiparasitic, anti-inflammatory, antimutagenic, antiallergic, and antioxidant activity. In the present work, the effect of SAK on seizures in a model of status epilepticus induced by bicuculline (BIC) in mice was evaluated. Male Swiss mice received an intracerebroventricular injection (i.c.v.) of SAK (1, 10, or 20 mg/kg-SAK1, SAK10, or SAK20). Firstly, animals were evaluated in the open field (OF; 20 min), afterwards in the elevated plus maze (EPM) test (5 min). Next, 30 min prior the administration of BIC (1 mg/kg), mice received an injection of SAK (1 or 10 mg/kg, i.c.v.) and were observed in the OF (20 min) for seizures assessment. After behavioral procedures, immunohistochemical analysis of c-Fos was performed. Our main results showed that the lowest doses of SAK (1 and 10 mg/kg) increased the total distance traveled in the OF, moreover protected against seizures and death on the BIC-induced seizures model. Furthermore, SAK treatment reduced neuronal activity on the dentate gyrus of the BIC-treated animals. Taken together, our results suggest an anticonvulsant effect of SAK, which could be used for the development of anticonvulsants based on natural products from herbal source.

癫痫是一种慢性神经系统疾病，其特征是异常的、自发的和同步的神经元过度活跃。控制癫痫发作的治疗方法与药物耐药性和副作用负担有关。以前的研究报告说，不同的天然产物可能具有神经保护作用。Sakuranetin (SAK) 是一种黄烷酮，具有抗寄生虫、抗炎、抗诱变、抗过敏和抗氧化活性。在目前的工作中，评估了 SAK 对荷包牡丹碱 (BIC) 诱导的小鼠癫痫持续状态模型中癫痫发作的影响。雄性瑞士小鼠接受 SAK（1、10 或 20 mg/kg-SAK1、SAK10 或 SAK20）的脑室内注射 (icv)。首先，动物在开阔场地（OF；20 分钟）中进行评估，然后在高架十字迷宫（EPM）测试（5 分钟）中进行评估。接下来，在 BIC（1 mg/kg）给药前 30 分钟，小鼠接受 SAK（1 或 10 mg/kg，icv）注射，并在 OF（20 分钟）中观察癫痫发作评估。在行为程序之后，进行了 c-Fos 的免疫组织化学分析。我们的主要结果表明，最低剂量的 SAK（1 和 10 mg/kg）增加了 OF 中的总行进距离，而且在 BIC 诱导的癫痫发作模型中，还可以防止癫痫发作和死亡。此

外，SAK 治疗降低了 BIC 治疗动物齿状回的神经元活动。总之，我们的结果表明 SAK 具有抗惊厥作用，可用于开发基于草药来源的天然产物的抗惊厥药。) 并在 OF（20 分钟）中观察到癫痫发作评估。在行为程序之后，进行了 c-Fos 的免疫组织化学分析。我们的主要结果表明，最低剂量的 SAK（1 和 10 mg/kg）增加了 OF 中的总行进距离，此外，在 BIC 诱导的癫痫发作模型中，还可以防止癫痫发作和死亡。此外，SAK 治疗降低了 BIC 治疗动物齿状回的神经元活动。总之，我们的结果表明 SAK 具有抗惊厥作用，可用于开发基于草药来源的天然产物的抗惊厥药。) 并在 OF（20 分钟）中观察到癫痫发作评估。在行为程序之后，进行了 c-Fos 的免疫组织化学分析。我们的主要结果表明，最低剂量的 SAK（1 和 10 mg/kg）增加了 OF 中的总行进距离，此外，在 BIC 诱导的癫痫发作模型中，还可以防止癫痫发作和死亡。此外，SAK 治疗降低了 BIC 治疗动物齿状回的神经元活动。总之，我们的结果表明 SAK 具有抗惊厥作用，可用于开发基于草药来源的天然产物的抗惊厥药。我们的主要结果表明，最低剂量的 SAK（1 和 10 mg/kg）增加了 OF 中的总行进距离，此外，在 BIC 诱导的癫痫发作模型中，还可以防止癫痫发作和死亡。此外，SAK 治疗降低了 BIC 治疗动物齿状回的神经元活动。总之，我们的结果表明 SAK 具有抗惊厥作用，可用于开发基于草药来源的天然产物的抗惊厥药。

15. 抗癫痫发作药物的发现：近期和未来的转变

Antiseizure medication discovery: Recent and future paradigm shifts. *Epilepsia Open. 2022 Aug;7 Suppl 1(Suppl 1):S133-S141. doi: 10.1002/epi4.12581. Epub 2022 Feb 7*.

Talevi A.

Despite the ever-increasing number of available options for the treatment of epilepsies and the remarkable advances on the understanding of their pathophysiology, the proportion of refractory patients has remained approximately unmodified during the last 100 years. How efficient are we translating positive outcomes from basic research to clinical trials and/or the clinical scenario? It is possible that fresh thinking and exploration of new paradigms are required to arrive at truly novel therapeutic solutions, as seemingly proven by recently approved first-in-class antiseizure medications and drug candidates undergoing late clinical trials. Here, the author discusses some approximations in line with the network pharmacology philosophy, which may result in highly innovative (and, hopefully, safer and/or more efficacious) medications for the control of seizures, as embodied with some recent examples in the field, namely tailored multi-target agents and low-affinity ligands.

尽管可用于治疗癫痫的可选药物的数量不断增加，对其病理生理学的理解也取得了显著进展，但在过去 100 年中，难治性患者的比例几乎没有改变。我们将基础研究的积极成果转化为临床试验和/或临床情景的效率如何？有可能需要进行新的思考和探索，以获得真正新颖的治疗方案，最近批准的一流抗癫痫发作药物和正在进行后期临床试验的候选药物似乎证明了这一点。在这里，作者讨论了一些符合网络药理学原理的近似方法，这可能会产生用于控制癫痫发作的高度创新（希望更安全和/或更有效）的药物，正如该领域最近的一些例子所体现的，即定制的多靶点药物和低亲和力配体。

16. 用于治疗癫痫的生物可降解纳米颗粒：从当前进展到未来挑战

Biodegradable nanoparticles for the treatment of epilepsy: From current advances to future challenges. *Epilepsia Open. 2022 Aug;7 Suppl 1(Suppl 1):S121-S132.doi: 10.1002/epi4.12567.Epub 2021 Dec 13.*

Bonilla L, Esteruelas G, Ettcheto M, Espina M, García ML, Camins A, Souto EB, Cano A, Sánchez-López E

Epilepsy is the second most prevalent neurological disease worldwide. It is mainly characterized by an electrical abnormal activity in different brain regions. The massive entrance of Ca2+ into neurons is the main neurotoxic process that lead to cell death and finally to neurodegeneration. Although there are a huge number of antiseizure medications, there are many patients who do not respond to the treatments and present refractory epilepsy. In this context, nanomedicine constitutes a promising alternative to enhance the central nervous system bioavailability of antiseizure medications. The encapsulation of different chemical compounds at once in a variety of controlled drug delivery systems gives rise to an enhanced drug effectiveness mainly due to their targeting and penetration into the deepest brain region and the protection of the drug chemical structure. Thus, in this review we will explore the recent advances in the development of drugs associated with polymeric and lipid-based nanocarriers as novel tools for the management of epilepsy disorders.

癫痫是全球第二大常见的神经系统疾病。其主要特征是不同脑区的电异常活动。Ca2+大量进入神经元是导致细胞死亡并最终导致神经变性的主要神经毒性过程。虽然有大量的抗癫痫发作药物，但仍有许多患者对治疗无效，出现难治性癫痫。在这种情况下，纳米药物构成了增强抗癫痫发作药物中枢神经系统生物利用度的有希望的替代品。将不同化合物同时包封在各种药物控释系统中，主要由于其靶向性和渗透到大脑最深区域以及药物化学结构的保护，从而提高了药物的有效性。因此，在这篇综述中，我们将探讨与聚合物和基于脂质的纳米载体相关的药物作为癫痫疾病治疗新工具的最新进展。

17. 对当前癫痫耐药假说的复杂系统观点

A complex systems view on the current hypotheses of epilepsy pharmacoresistance.*Epilepsia Open. 2022 Aug;7 Suppl 1(Suppl 1):S8-S22. doi: 10.1002/epi4.12588. Epub 2022 Mar 11.*

Servilha-Menezes G, Garcia-Cairasco N.

Drug-resistant epilepsy remains to this day as a highly prevalent condition affecting around one-third of patients with epilepsy, despite all the research and the development of several new antiseizure medications (ASMs) over the last decades. Epilepsies are multifactorial complex diseases, commonly associated with psychiatric, neurological, and somatic comorbidities. Thus, to solve the puzzling problem of pharmacoresistance, the diagnosis and modeling of epilepsy and comorbidities need to change toward a complex system approach. In this review, we have summarized the sequence of events for the definition of epilepsies and comorbidities, the search for mechanisms, and the major

hypotheses of pharmacoresistance, drawing attention to some of the many converging aspects between the proposed mechanisms, their supporting evidence, and comorbidities-related alterations. The use of systems biology applied to epileptology may lead to the discovery of new targets and the development of new ASMs, as may advance our understanding of the epilepsies and their comorbidities, providing much deeper insight on multidrug pharmacoresistance.

尽管在过去的几十年里研究和开发了几种新的抗癫痫发作药物(ASMs)，但至今耐药性癫痫仍然是一种高度流行的疾病，影响着约三分之一的癫痫患者。癫痫是一种多因素的复杂疾病，通常与精神、神经和躯体共病有

关。因此，为了解决令人困惑的耐药性问题，癫痫和共病的诊断和建模需要向复杂的系统方法转变。在这篇综述中，我们总结了癫痫和共病定义的事件顺序、对机制的探索和耐药的主要假设，并注意到所提出的机制、支持证据和共病相关的改变之间的一些趋同情况。系统生物学在癫痫学中的应用可能会导致新靶点的发现和新的 ASMs 的发展，从而促进我们对癫痫及其共病的理解，为更深入地了解多药耐药提供更深入的认识。

18. 丙戊酸治疗对小儿癫痫患者体重增加的影响

The impact of valproic acid treatment on weight gain in pediatric patients with epilepsy.*Minerva Pediatr (Torino). 2022 Aug. doi: 10.23736/S2724-5276.17.04938-6.*

Ferrara P, Gatto A, Blasi V, DI Ruscio F, Battaglia D.

BACKGROUND: Valproic acid (VPA) is an antiepileptic drug, used for focal and generalized seizure. VPA treatment resulted in significant weight gain but there are no systematic data about the prevalence of this side effect. The aim of the study was to evaluate the weight gain of a pediatric population with epilepsy.

METHODS: We enrolled 38 patients, 17 females and 21 males with a mean age of 8.2±4.4 years. We evaluated data about height, weight and BMI at beginning of treatment and at 24, 36 and 48 months of follow-up.

RESULTS: There is a statistically significant difference between the percentile value of weight and BMI at baseline and at 36 and 48 months of follow-up (P<0.01) but there is not statistically significant difference between the percentile value of height (P=0.22 and P=0.18).

CONCLUSIONS: We believe that a nutritional support should be guaranteed to the pediatric patients with epilepsy that begin the VPA therapy.

背景：丙戊酸（VPA）是一种抗癫痫药物，用于治疗局灶性和全面性的癫痫发作。VPA 治疗导致体重明显增加，但没有关于这种副作用发生率的系统数据。该研究的目的是评估儿科癫痫患者的体重增加情况。

方法：我们招募了 38 名患者，17 名女性和 21 名男性，平均年龄为（8.2±4.4）岁。我们评估了治疗开始时和随访 24、36 和 48 个月时的身高、体重和 BMI 数据。

结果：在基线和随访的 36 个月和 48 个月时，体重和 BMI 的百分位数有统计学上的显著差异（P<0.01），但身高的百分位数没有统计学上的显著差异（P=0.22 和 P=0.18）。

结论：我们认为，对于开始接受 VPA 治疗的小儿癫痫患者，应保证其营养支持。

19. 快速脑电图对抗癫痫发作药物使用的影响

Effect of rapid EEG on anti-seizure medication usage.Epileptic Disord. *2022 Oct 1. doi: 10.1684/epd.2022.1463.*

Kurup D, Davey Z, Hoang P, Wu C, Werbaneth K, Shah V, Hirsch KG, Govindarajan P, Meador KJ.

OBJECTIVE: To study how early diagnoses from rapid EEG (rEEG) during the initial evaluation of patients with suspected non-convulsive seizures correlates with changes in anti-seizure medication (ASM) use.

METHODS: We performed a retrospective chart review of 100 consecutive adult patients at an academic medical center who underwent rEEG monitoring for suspected non-convulsive seizures. We collected information on the timing of ASM

administration and categorized EEG diagnoses as seizures (SZ), highly epileptiform patterns (HEP), or normal or slow activity (NL/SL). We used a χ^2 test to determine whether the use of ASMs was significantly different between SZ/HEP and NL/SL cases.

RESULTS: Of 100 patients, SZ were found in 5%, HEP in 14%, and no epileptiform/ictal activity in 81%. Forty-six percent of patients had received ASM(s) before rEEG. While 84% of HEP/SZ cases were started or continued on ASMs, only 51% of NL/SL cases were started or continued on ASMs after rEEG (χ^2 [1, n=100] = 7.09, p=0.008). Thirty-seven patients had received sedation (i.e., propofol or dexmedetomidine) prior to rEEG. In 15 patients (13/30 NL/SL, 2/7 HEP/SZ), sedation was discontinued following rEEG.SIGNIFICANCE: Our study demonstrates that seizures were rapidly ruled out with rEEG in 81% of patients while 19% of patients were rapidly identified as having seizures or being at higher risk for seizures. The rapid evaluation of patients correlated with a significant reduction in ASM treatment in NL/SL cases compared to HEP/SZ cases. Thus, early access to EEG information may lead to more informed and targeted management of patients suspected to have nonconvulsive seizures.

Epilepsy is a chronic neurological disorder characterized by an abnormal, spontaneous, and synchronized neuronal hyperactivity. Therapeutic approaches for controlling epileptic seizures are associated with pharmacoresistance and side effects burden. Previous studies reported that different natural products may have neuroprotector effects. Sakuranetin (SAK) is a flavanone with antiparasitic, anti-inflammatory, antimutagenic, antiallergic, and antioxidant activity. In the present work, the effect of SAK on seizures in a model of status epilepticus induced by bicuculline (BIC) in mice was evaluated. Male Swiss mice received an intracerebroventricular injection (i.c.v.) of SAK (1, 10, or 20 mg/kg-SAK1, SAK10, or SAK20). Firstly, animals were evaluated in the open field (OF; 20 min), afterwards in the elevated plus maze (EPM) test (5 min). Next, 30 min prior the administration of BIC (1 mg/kg), mice received an injection of SAK (1 or 10 mg/kg, i.c.v.) and were observed in the OF (20 min) for seizures assessment. After behavioral procedures, immunohistochemical analysis of c-Fos was performed. Our main results showed that the lowest doses of SAK (1 and 10 mg/kg) increased the total distance traveled in the OF, moreover protected against seizures and death on the BIC-induced seizures model. Furthermore, SAK treatment reduced neuronal activity on the dentate gyrus of the BIC-treated animals. Taken together, our results suggest an anticonvulsant effect of SAK, which could be used for the development of anticonvulsants based on natural products from herbal source.

目的：研究在对疑似非惊厥性发作患者进行初步评估时，快速脑电图（rEEG）的早期诊断与抗癫痫发作药物（ASM）使用的变化有何关联。

方法：我们对一个学术性医疗中心的 100 名连续的成人患者进行了回顾性的图表审查，这些患者因疑似非惊厥性发作而接受了 rEEG 监测。我们收集了关于 ASM 给药时间的信息，并将脑电图诊断分为癫痫发作（SZ）、高度癫痫样模式（HEP）或正常或缓慢活动（NL/SL）。我们用χ^2检验来确定 ASM 的使用在 SZ/HEP 和 NL/SL 病例之间是否有显著不同。

结果：在 100 名患者中，有 5%的患者发现有 SZ，14%的患者发现有 HEP，而 81%的患者没有癫痫样/发作活动。46%的患者在接受 rEEG 之前曾接受过 ASM（s）的治疗。而 84%的 HEP/SZ 病例是开始或继续使用 ASM，只有 51%的 NL/SL 病例在 rEEG 后开始或继续使用 ASMs（χ^2 [1, n=100] = 7.09, p=0.008）。37 名患者在进行 rEEG 之前使用了镇静剂（即丙泊酚或右美托咪定）。在 15 名患者中（13/30 NL/SL，2/7 HEP/SZ），在 rEEG 之后停止了使用镇静剂。

意义：我们的研究表明，81%的患者通过 rEEG 快速排除了癫痫发作，而 19%的患者被快速确定为有癫痫发作或有较高的癫痫发作风险。与 HEP/SZ 病例相比，对患者的快速评估与 NL/SL 病例中 ASM 治疗的显著减少有关。因此，早期获得脑电图信息可能能够更熟悉和更有针对性地管理疑似是非惊厥性发作的病人。

20. 抗癫痫药物的生物传感技术

Biosensors technology for anti-epileptic drugs. *Clin Chim Acta. 2022 Aug 1. doi: 10.1016/j.cca.2022.06.027.*

Mobed A, Shirafkan M, Charsouei S, Sadeghzadeh J, Ahmadalipour A.

A broad group of antiepileptic drugs (AEDs) often controls the frequency of seizures. Given the variability of pharmacokinetics, narrow target range, and the difficulty of identifying signs of toxicity from laboratory responses, therapeutic monitoring of AEDs plays a vital role in optimizing drug administration. Nanomaterials, especially biosensor-based methods, can facilitate the analysis of these agents with unique advantages such as rapid analysis, sensitivity, selectivity, and low cost. This review describes recent advances in biosensors developed to analyze AEDs. First, we described common electrochemical measurement techniques and types of deposited electrode substrates. Additionally, various chemical and biological modifiers to improve the sensitivity and selectivity of the sensor have been categorized and briefly described. Finally, the prospects for developing an electrochemical platform for quantifying AEDs are presented.

一组广泛的抗癫痫药物（AEDs）经常用于控制癫痫发作的频率。鉴于药代动力学的多变性、目标范围窄和从实验室反应中识别毒性迹象的难度，AEDs 的治疗监测在优化用药方面起着重要作用。特别是基于生物传感器方法的纳米材料，可以促进这些制剂的分析，具有独特的优势，如快速分析、灵敏度、选择性和低成本。这篇综述描述了为分析 AEDs 而开发的生物传感器的最新进展。首先，我们描述了常见的电化学测量技术和沉积电极基板。此外，用于提高传感器灵敏度和选择性的各种化学和生物调节剂已被归类并简要描述。最后，介绍了开发一个用于量化 AEDs 的电化学平台的前景。

21. 磷酸酶和张力蛋白同源物（PTEN）变异与癫痫：一个多中心病例系列研究

Phosphatase and tensin homolog (PTEN) variants and epilepsy: A multicenter case series.*Seizure. 2022 Aug. doi: 10.1016/j.seizure.2022.06.013.*

Ronzano N, Scala M, Abiusi E, Contaldo I, Leoni C, Vari MS, Pisano T, Battaglia D, Genuardi M, Elia M, Striano P, Pruna D.

PURPOSE: EEG anomalies and epilepsy are a not so rare clinical manifestation in patients with Phosphatase and tensin homolog (PTEN) variants. The main aim of this study is to analyze the characteristics of EEG traces, neuroimaging findings and epilepsy to better define the neurological aspects in a set of patients with PTEN variants collected in four Italian Centres. As a secondary aim, we describe the neurodevelopmental profile and the psychiatric comorbidities of this cohort.

METHODS: Patients with PTEN variants, identified by Sanger sequencing or target resequencing, were enrolled. For each subjects, clinical data were retrospectively extracted from medical charts, with a focus on epilepsy and neuroimaging data.

RESULTS: 54 patients with PTEN variants were enrolled, with a mean age of 18.8 years. 72.2% have at least one psychiatric diagnosis, being Autism Spectrum Disorder and Intellectual Disability the most frequent diagnosis (29 and 25 cases, respectively). 22 subjects show an abnormal EEG and 8 received a diagnosis of epilepsy, mainly focal epilepsy (7/8), with a mean age at seizure onset of 3.8 years. 3/8 subjects have a drug resistant epilepsy, independently from the underlying

neuroimaging pattern. The finding of a Focal cortical dysplasia is significantly associated with both an abnormal EEG (p = 0.02) and

the occurrence of seizures (p = 0.002).

CONCLUSION: EEG should be taken into consideration in the first-line diagnostic flowchart of subjects with PTEN variants. The onset of a focal epilepsy, independently from its response to antiepileptic drugs, highly recommends to carry out a neuroimaging exam.

目的：脑电图异常和癫痫是磷酸酶和张力蛋白同源物（PTEN）变异患者中一种并不罕见的临床表现。本研究的主要目的是分析脑电图轨迹、神经影像学结果和癫痫的特点，来更好地确定在四个意大利中心收集的一组 PTEN 变异患者的神经系统方面的情况。作为次要目的，我们描述了这一队列的神经发育状况和精神疾病的并发症。

方法：通过 Sanger 测序或靶向重测序确定的 PTEN 变异的患者被纳入。对于每个受试者，从病历中回顾性地提取临床数据，重点是癫痫和神经影像学数据。

结果：54 名 PTEN 变异的患者被纳入，平均年龄为 18.8 岁。72.2%的患者至少有一种精神病诊断，自闭症谱系障碍和智力障碍是最常见的诊断（分别为 29 和 25 例）。22 名受试者显示脑电图异常，8 人诊断为癫痫，主要是局灶性癫痫（7/8），发作的平均年龄为 3.8 岁。3/8 的受试者有耐药性癫痫，与潜在的神经影像学模式无关。局部皮质发育不良与脑电图异常（p = 0.02）和癫痫发作（p = 0.002）都有显著关系。

结论：在 PTEN 变异体受试者的一线诊断流程图中应考虑到 EEG。局灶性癫痫的发作与它对抗癫痫发作药物的反应无关，强烈建议进行神经影像学检查。

22. Geijigadaehwang-tang 对三甲基锡诱导的海马神经变性的神经保护作用：体外和体内研究

Neuroprotective effect of Geijigadaehwang-tang against trimethyltin-induced hippocampal neurodegeneration: An in vitro and in vivo study. *J Ethnopharmacol. 2022 Oct 5;296:115451. doi: 10.1016/j.jep.2022.115451.*

Lee S, Ryu SM, Kim DH, Lee YE, Lee SJ, Kang S, Kim JS, Lee SI.

Ethnopharmacological relevance: Patients with dementia are diagnosed with deficiency patterns and interior patterns in traditional Chinese medicine due to decreased physical strength, mental atrophy including cognitive function, and decreased motor function in the gastrointestinal tract. Since "greater yin symptom" in Shanghanlun has been interpreted as interior, deficiency, and cold pattern in traditional Chinese medicine, it is necessary to determine whether Geijigadaehwang-tang (GDT) has therapeutic effects on neurodegenerative diseases and the underlying mechanism if it has such effects.

Aims of the study: Trimethyltin (TMT), a neurotoxic organotin compound, has been used to induce several neurodegenerative diseases, including epilepsy and Alzheimer's disease. This study aimed to evaluate the therapeutic efficacy of GDT for TMT-induced hippocampal neurodegeneration and seizures and to determine the mechanisms involved at the molecular level.

Materials and methods: The main components of GDT were analyzed using ultra-performance liquid chromatography. TMT was used to induce neurotoxicity in microglial BV-2 cells and C57BL6 mice. GDT was administered at various doses to determine its neuroprotective and seizure inhibition effects. The inhibitory effects of GDT on TMT-induced apoptosis, inflammatory pathways, and oxidative stress pathways were determined in the mouse hippocampal tissues.

Results: GDT contained emodin, chrysophanol, albiflorin, paeoniflorin, 6-gingerol, and liquiritin apioside. In microglial BV-2 cells treated with TMT, GDT showed dose-dependent neuroprotective effects. Oral administration of GDT five times for 2.5 days before and after TMT injection inhibited seizures at doses of 180 and 540 mg/kg and inhibited neuronal death in the hippocampus. In hippocampal tissues extracted from mice, GDT inhibited the protein expression of ionized calcium binding adaptor molecule 1, glial fibrillary acidic protein, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing protein 3, and phosphorylated nuclear factor (NF)-κB/total-NFκB ratio. Additionally, GDT inhibited the messenger RNA levels of tumor necrosis factor-α, inducible nitric oxide synthase, apoptosis-associated speck-like protein containing a caspase recruitment domain, caspase-1, interleukin-1β, nuclear factor erythroid-2-related factor 2, and heme oxygenase-1.

Conclusion: This study's results imply that GDT might have neuroprotective potential in neurodegenerative diseases through neuronal death inhibition and anti-inflammatory and antioxidant mechanisms.

民族药理学相关性：痴呆症患者被诊断为由于体力下降、包括认知功能在内的精神萎缩以及胃肠道运动功能下降而导致的中医虚证和内证。由于《伤寒论》中的“大阴症状”在中医学中被解释为“内虚寒型”，因此有必要确定 Geijigadaehwang-tang（GDT）是否对神经退行性疾病具有治疗作用，以及是否具有这种作用的潜在机制。

研究目的：三甲基锡（TMT）是一种神经毒性有机锡化合物，已被用于诱发多种神经退行性疾病，包括癫痫和阿尔茨海默病。本研究旨在评估 GDT 对 TMT 诱导的海马神经退行性变和癫痫发作的治疗效果，并从分子水平确定相关机制。

材料和方法：采用超高效液相色谱法分析 GDT 的主要成分。TMT 用于诱导小胶质细胞 BV-2 细胞和 C57BL6 小鼠的神经毒性。给予不同剂量的 GDT 以确定其神经保护和癫痫抑制作用。在小鼠海马组织中测定了 GDT 对 TMT 诱导的凋亡、炎症途径和氧化应激途径的抑制作用。

结果：GDT 中含有大黄素、大黄酚、白花苷、芍药苷、6-姜辣素和甘草苷。在用 TMT 处理的小胶质细胞 BV-2 细胞中，GDT 显示出剂量依赖性神经保护作用。注射 TMT 前后口服 GDT 5 次，持续 2.5 天，以 180 和 540mg/kg 的剂量抑制癫痫发作，并抑制海马神经元死亡。在从小鼠提取的海马组织中，GDT 抑制游离钙结合衔接分子 1、胶质纤维酸性蛋白、核苷酸结合寡聚结构域样受体家族含吡喃结构域蛋白 3 和磷酸化核因子（NF）-κB/总 NFκB 比率的蛋白表达。此外，GDT 抑制肿瘤坏死因子-α、诱导型一氧化氮合酶、含有半胱天冬酶募集结构域的凋亡相关斑点样蛋白、半胱天蛋白酶-1、白细胞介素-1β、核因子红系-2 相关因子 2 和血红素加氧酶-1 的信使 RNA 水平。

结论：本研究结果表明，GDT 可能通过抑制神经元死亡以及抗炎和抗氧化机制在神经退行性疾病中具有神经保护潜力。

23. 研究慢性唑尼沙胺、噻嗪磺胺、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组织叶状体发生的影响

An investigation of the effects of chronic zonisamide, sultiam, lacosamide, clobazam, and rufinamide anti-seizure medications on foliculogenesis in ovarian tissue in prepubertal non-epileptic rats. *Int J Dev Neurosci. 2022 Aug;82(5):436-446. doi: 10.1002/jdn.10200.*

Kart PÖ, Gürgen SG, Esenülkü G, Dilber B, Yıldız N, Yazar U, Sarsmaz HY, Topsakal AS, Kamaşak T, Arslan EA, Şahin S, Cansu A.

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 divided into six experimental groups as control, zonisamide, sultiam, lacosamide, clobazam, and rufinamide groups; control solution and drugs were administered by gavage for 90 days. The number of healthy follicles in the control group was significantly higher than in the anti-medication groups ($p < 0.001$), and the number of corpus luteum was significantly lower ($p < 0.001$). There was a significant difference in the number of TUNEL positive apoptotic follicles between the control and drug groups ($p < 0.001$). With 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 compared to the drug group ($p < 0.001$). Long-term anti-seizure medication 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、噻嗪磺胺、拉考沙胺、氯巴占和卢非酰胺对大鼠卵巢卵泡发育的形态学和组织学影响。将 60 只雌性 Wistar 大鼠分为 6 个实验组，分别为对照组、唑尼沙胺组、噻嗪磺胺组、拉考沙胺组、氯巴占组和卢非酰胺组；对照溶液和药物灌胃给药 90 天。对照组的健康卵泡数显著高于耐药组（$p<0.001$），黄体数显著低于对照组（$p>0.001$）。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（$p<0.001$）。通过 EGF、IGF-1 和 GDF-9 染色，与药物组相比，对照组的卵巢多层初级卵泡颗粒细胞和卵母细胞中观察到非常强的免疫反应（$p<0.001$）。从青春期前到成年期，使用唑尼沙胺、噻嗪磺胺、拉考沙胺、氯巴占和卢非酰胺的长期抗癫痫药物可导致非排卵大鼠卵泡凋亡和卵泡发育中断。

24. 苯巴那酯对既往癫痫相关手术患者不受控制的局灶性癫痫发作的疗效：一项 3 期、多中心、开放标记研究的事后分析

Efficacy of cenobamate for uncontrolled focal seizures in patients with previous epilepsy-related surgery: Post hoc analysis of a phase 3, multicenter, open-label study. *Epilepsy Res. 2022 Aug;184:106952. doi: 10.1016/j.eplepsyres.2022.106952.*

Abou-Khalil B, Aboumatar S, Klein P(3), Krauss GL, Sperling MR, Rosenfeld WE.

Objective: This post hoc analysis of 10 US study sites from a long-term open-label phase 3 study of adjunctive cenobamate evaluated the efficacy of cenobamate in patients with prior epilepsy-related surgery.

Methods: Patients with uncontrolled focal seizures despite taking stable doses of 1-3 concomitant antiseizure medications (ASMs) received increasing doses of cenobamate (12.5, 25, 50, 100, 150, 200 mg/day) at 2-week intervals over 12 weeks (target dose, 200 mg/day). Further increases up to 400 mg/day using biweekly 50-mg/day increments were allowed during the maintenance phase. Dose adjustments of cenobamate and concomitant ASMs were allowed. Data were assessed until the last clinic visit on or after September 1, 2019.

Results: Of the 240 eligible patients, 85 had prior epilepsy-related surgery and 155 were nonsurgical patients. Baseline focal seizure frequency per 28 days was numerically higher among prior surgery (mean=25.9/median=4.1/range=0.3-562.3) versus nonsurgical (mean=13.8/median=2.4/range=0.2-534.2) patients. Among all patients, 100 % seizure reduction ≥ 12 months at any consecutive month interval occurred in 30.6 % (26/85) prior surgery and 39.4 % (61/155; p > 0.05) nonsurgical patients (cenobamate treatment median duration=32.9 months). Among the 177 patients still receiving cenobamate at the data cutoff, 29.2 % (19/65) of prior surgery and 36.6 % (41/112; p > 0.05) of nonsurgical patients had 100 % seizure reduction ≥ 12 months at the data cutoff. Cenobamate was well tolerated.

Conclusions: This post hoc analysis supports the efficacy of cenobamate in patients with refractory focal seizures despite prior surgery. These findings suggest cenobamate may be considered early in the treatment regimen, including, in some patients, before surgery is considered.

目的：对 10 个美国研究地点进行事后分析，这些研究地点来自一项长期的、开放性第三期研究，该研究是对曾接受癫痫相关手术的患者使用苯巴那酯的疗效进行评估。

方法：尽管服用了稳定剂量的 1-3 种联合抗癫痫发作药物（ASM），但未得到控制的局灶性癫痫发作患者在 12 周内（目标剂量，200mg/天）每隔 2 周接受递增剂量的苯巴那酯（12.5、25、50、100、150、200mg/日）。在维护阶段，允许使用每两周 50 mg/天的增量进一步增加至 400 mg/天。允许对苯巴那酯和同时服用的 ASM 进行剂量调整。数据评估直到 2019 年 9 月 1 日或之后的最后一次就诊。

结果：240 名符合条件的患者中，85 名曾接受过癫痫相关手术，155 名为非手术患者。与非手术（平均值=13.8/中位数=2.4/范围=0.2-534.2）患者相比，术前患者每 28 天的基线局灶性发作频率在数值上更高（平均值=25.9/中位数=4.1/范围=0.3-562.3）。在所有患者中，发作减少 100%≥ 术前 30.6%（26/85）和 39.4%（61/155；p>0.05）非手术患者（苯巴那酯治疗中位持续时间=32.9 个月）在任何连续的月间隔内出现 12 个月。在数据截止时仍接受苯巴那酯治疗的 177 名患者中，29.2%（19/65）的既往手术患者和 36.6%（41/112；p>0.05）的非手术患者癫痫发作减少率为 100%≥ 数据截止时为 12 个月。苯巴那酯耐受性良好。

结论：这项事后分析支持了苯巴那酯对既往手术后顽固性局灶性癫痫患者的有效。这些发现表明，在治疗方案的早期，包括在考虑手术之前，可以考虑使用苯巴那酯。

25. 鼻内 Niosomal 原位凝胶作为提高胞二磷胆碱疗效和脑给药治疗癫痫的新策略：体外和离体特征和体内药效学研究

Intranasal Niosomal In Situ Gel As A Novel Strategy for Improving Citicoline Efficacy and Brain Delivery in Treatment of Epilepsy: In Vitro and Ex Vivo Characterization and In Vivo Pharmacodynamics Investigation.*J Pharm Sci. 2022 Aug;111(8):2258-2269. doi: 10.1016/j.xphs.2022.02.012. Epub 2022 Feb 27..*

Bekhet MA, Ali AA, Kharshoum RM, El-Ela FIA, Salem HF.

The high hydrophilicity of citicoline and its rapid metabolism are the two main obstacles hindering intact molecules from passing the blood-brain barrier. This study aimed to formulate citicoline-loaded niosomes (CTCNSMs) for efficient brain delivery via the intranasal route to improve management of epilepsy. CTCNSMs were formulated via thin-film hydration method, optimized using d-optimal design, and characterized for entrapment efficiency, vesicle size, drug release, and cumulative amount permeated. The entrapment efficiency ranged from 19.44 to 61.98% with sustained drug release, and the vesicle size ranged from 125.4 to 542.5 nm with enhanced drug permeation. Cholesterol: Span ratio of 1:1.19 and cholesterol amount of 20 mg were predicted to produce optimal characteristics. Subsequently, the optimized formulation permeation confirmed a high nasal penetration using confocal laser scanning microscopy (CLSM). Afterward, the optimized CTCNSM formulation was integrated into in situ gel to boost the residence time in the nasal cavity. Additionally, Computed Tomography (CT) was performed by labeling the optimized formulation with gold nanoparticles (GNPs) to assess brain uptake and cellular translocation after intranasal administration of CTC. Furthermore, the protection against pentylenetetrazole-induced generalized seizures and mortality were determined in rats and compared with the oral drug solution at the exact dosage. The in vivo results revealed that a low dose of CTCNSM in situ gel had a powerful protective effect with delayed the latency for the start of convulsions. Collectively, NSM in situ gel is a potentially valuable intranasal drug delivery system that can boost the efficacy of CTC in epilepsy management..

胞磷胆碱的高亲水性及其快速代谢是阻碍完整分子通过血脑屏障的两个主要障碍。本研究旨在制备胞磷胆碱负载的囊泡（CTCNSMs），通过鼻内途径有效地进行脑递送，以改善癫痫的疗效。CTCNSMs 通过薄膜水合法配制，使用 D-最优设计优化，其特征包括包封效率、囊泡大小、药物释放和累积渗透量。药物缓释时包封率为 19.44-61.98%，药物渗透增强时囊泡大小为 125.4-542.5nm。胆固醇与跨度之比为 1:1.19，胆固醇含量为 20mg，预测可产生最佳特性。随后，使用共焦激光扫描显微镜（CLSM）证实优化配方的渗透性较高。然后，将优化的 CTCNSM 配方整合到原位凝胶中，以延长在鼻腔中的停留时间。此外，通过用金纳米颗粒（GNP）标记优化的配方进行计算机断层扫描（CT），以评估鼻腔给药四氯化碳后的脑摄取和细胞移位。此外，在大鼠中测定了其对戊四唑诱导的全面性癫痫发作和死亡率的保护作用，并与精确剂量的口服药物溶液进行了比较。体内结果显示，低剂量的 CTCNSM 原位凝胶具有强大的保护作用，可延迟惊厥开始的潜伏期。总之，NSM 原位凝胶是一种潜在的有价值的鼻内给药系统，可以提高四氯化碳在癫痫治疗中的疗效。

26. 神经外科手术后丙戊酸会增加肝损伤的风险：一项前瞻性嵌套病例对照研究

Valproic Acid After Neurosurgery Induces Elevated Risk of Liver Injury: A Prospective Nested Case-Control Study.*Ann Pharmacother. 2022 Aug;56(8):888-897. doi: 10.1177/10600280211055508. Epub 2021 Nov 8.*

Guo J, Ma J, Wang S, Li X, Ji H, Li Y, Peng F, Sun Y.

BACKGROUND: Valproic acid (VPA) has been widely used to prevent epileptic seizures after neurosurgery in China. We have found that the incidence of liver injury (LI) in patients using VPA after neurosurgery is higher than that in other patients.

OBJECTIVE: The objective of this study was to investigate the risk factors of LI in patients using VPA after neurosurgery.

METHODS: A nested case-control study was conducted in patients using VPA after neurosurgery between September 2019 and March 2021. Cases of LI were matched to controls by age and body mass index (BMI). Conditional logistic regression was used to estimate matched odds ratios representing the odds of LI. A receiver operating characteristic curve was used to analyze the optimal cutoff condition.

RESULTS: A total of 248 people (62 LI and 186 control) were enrolled. Among patients with vs without LI, the matched odds ratio for trough concentration of VPA was significant (matched odds ratio [OR], 1.09; 95% confidence interval [CI]: 1.01-1.19). The course of treatment (OR: 1.17, 95% CI: 1.02-1.33), Glasgow score (OR: 0.26, 95% CI: 0.10-0.67), gene polymorphisms of CYP2C19 (OR: 2.09, 95% CI: 1.03-146.93), and UGT1A6 (OR: 34.61, 95% CI: 1.19-1003.23) were all related to the outcome. The optimal cutoff of the course of treatment was 10 days, while the trough concentration of VPA was determined to be 66.16 mg/L.

CONCLUSION: Length of treatment, VPA trough concentration, and Glasgow score were associated with LI in patients after neurosurgery. A gene test may be necessary for people who are prescribed VPA for a long time.

背景：在中国，丙戊酸（VPA）已广泛用于预防神经外科手术后癫痫发作。我们发现神经外科手术后使用 VPA 的患者的肝损伤（LI）发生率高于其他患者。

目的：本研究的目的是调查神经外科手术后使用 VPA 患者发生 LI 的危险因素。

方法：2019 年 9 月至 2021 年 3 月，对神经外科手术后使用 VPA 的患者进行嵌套病例对照研究。根据年龄和体重指数（BMI）将肝损伤患者与对照组进行匹配。条件 logistic 回归用于估计代表 LI 几率的匹配优势比。接收器工作特性曲线用于分析最佳截止条件。

结果：共纳入 248 人（62 例 LI 和 186 例对照）。在有 LI 和无 LI 的患者中，VPA 谷浓度的匹配优势比显著（匹配优势比[OR]，1.09；95%置信区间[CI]：1.01-1.19）。治疗过程（OR:1.17，95%可信区间：1.02-1.33）、格拉斯哥评分（OR:0.26，95%置信区间：0.10-0.67）、CYP2C19 基因多态性（OR:2.09，95%CI:1.03-146.93）和 UGT1A6（OR:34.61，95%CI:1-1003.23）均与结果相关。治疗过程的最佳截止时间为 10 天，而 VPA 的谷浓度确定为 66.16 mg/L。

结论：神经外科手术后患者的治疗时间、VPA 谷浓度和格拉斯哥评分与肝损伤相关。长期服用 VPA 的患者可能需要进行基因检测。

27. 抗癫痫发作药物对局灶性癫痫儿童智力的累积效应

Cumulative effects of antiseizure medication on intelligence in children with Focal epilepsy. *Epileptic Disord. 2022 Oct 1;24(5):1-12. doi: 10.1684/epd.2022.1467.*

Stevering CH(1), Lamberink HJ(1), Woodfield J(2)(3), van Schooneveld M(4), Otte WM(1)(5), Chin RFM(2)(3)(6), Bastin ME(2)(3), Geleijns K(1), Braun KPJ(1).

OBJECTIVE: Antiseizure medication may have long-term effects on the neurodevelopment of children. We aimed to investigate the association between cumulative antiseizure medication load and intelligence quotient (IQ) in relation to brain volume and cortical thickness.

METHODS: A retrospective analysis of children with focal epilepsy who underwent neuropsychological assessment and MRI between the ages of 5-12 years in a tertiary epilepsy centre was performed. Cumulative medication load was presented in medication years. We studied the association between total medication load and IQ with multivariable linear regression, corrected for epilepsy-related confounders: age at first treatment, aetiology, maximum seizure frequency, duration of active epilepsy, history of secondary generalized seizures, history of status epilepticus, and the number of antiseizure medications used at time of neuropsychological assessment.

RESULTS: We included 59 children. Median medication load was 5.3 medication-years (interquartile range: 2.0 – 11.1) and mean total IQ (± standard deviation) was 77.4±18.9. A significant negative relation between medication load and total IQ was found with a decrease of 1.2 IQ-points per medication-year (95% confidence interval: -2.0 to -0.3) after correcting for confounders. Medication load and IQ were both not significantly associated with brain volume or cortical thickness.

SIGNIFICANCE: Higher cumulative medication load is associated with lower total IQ after adjusting for epilepsy-related confounders. We found no evidence to support the hypothesis that the medication-related IQ decrease was mediated by volumetric brain changes. However, these results should be interpreted with caution, and prospective, longitudinal confirmation of these findings is required. Lastly, it should be stressed that effective seizure prevention often outweighs the potential negative effects of antiseizure medication.

目的:抗癫痫发作药物对儿童的神经发育有着长期的影响，我们旨在研究抗癫痫发作药物累积负荷和智商（IQ）与脑体积和皮质厚度的关系。

方法: 对 5-12 岁在三级癫痫中心接受神经心理学评估和 MRI 检查的局灶性癫痫儿童进行回顾性分析。累积药物剂量以用药年的方式呈现，我们用多变量线性回归研究了总药物负荷与 IQ 之间的相关性，并校正了癫痫相关的混杂因素：首次治疗时的年龄、病因、最大发作频率、活动性癫痫的持续时间、继发全面性癫痫发作史、癫痫持续状态史以及神经心理学评估时使用的抗癫痫发作药物数量。

结果:我们纳入了 59 名儿童，中位药物负荷是 5.3 药物年(四分位间距：2.0-11.1)，平均总智商（±标准差）为 77.4±18.9，发现药物负荷和总智商间呈显著负性相关，即在调整了混杂因素后每一个药物年智商降低 1.2 分（95%置信区间：-2.0 至-0.3）。但是，药物负荷和智商与脑体积或皮质厚度均无显著相关性。

意义：调整癫痫相关混杂因素后，较高的累积药物负荷与较低的总智商相关。我们发现没有证据支持与药物相关的智商下降是由大脑体积变化介导的这种假设。然而，应谨慎解释这些结果，并且需要对这些结果进行前瞻性纵向确认。最后，应该强调的是，有效的癫痫预防，其益处往往超过抗癫痫发作药物的潜在负面影响。

28. 针对癫痫患者在抗癫痫发作药物短缺期间的治疗策略建议

Recommendations for treatment strategies in people with epilepsy during times of shortage of antiseizure medications.

Epileptic Disord. 2022 Oct 1;24(5):1-14. doi: 10.1684/epd.2022.1468.

Asadi-Pooya AA, Patel AA, Trinka E, Mazurkiewicz-Beldzinska M, Cross JH, Welty TE.

In times of severe antiseizure medication (ASM) shortage due to emergency situations (e.g., disasters, conflicts, sudden disruption to international supply chains), management of people with epilepsy with available ASMs can be difficult. A group of experts was brought together by the International League Against Epilepsy (ILAE) to formulate recommendations for such circumstances. Every effort was made to base these recommendations on direct published literature or extrapolations from basic information available about ASMs. Actual published literature in this area is, however, limited, and at times, assumptions were made by the experts to generate these recommendations. During times of shortage of ASMs, switching between different ASMs (e.g., oxcarbazepine and carbamazepine) can occasionally be considered as a mitigation procedure. However, for many ASMs, the option of an overnight switch to another drug does not exist. Switching from brand to generic or between generic products has often been shown to be safe, if required. Finally, when supplies of benzodiazepines or equipment to administer medications intravenously are not available, rectal administration of some ASMs may be an emergency alternative route for treating serial seizures and status epilepticus. Decision-making with regard to treatment and possible options should be driven by what is best for the patient.

由于一些紧急情况(比如，灾难，冲突，国际供应链突然中断)会导致抗癫痫发作药物严重短缺，在有限的抗癫痫发作药物情况下，癫痫患者的管理十分困难，抗癫痫国际联盟聚集了一批专家专门对这种情况提出了建议，已尽一切努力将这些建议建立在直接发表的文献或从可用的 ASM 基本信息推断的基础上，然而，在这个领域，实际出版的文献是有限的，同时，专家们为提出这些建议做出了假设。在 ASM 短缺期间，在不同的 ASM（如奥卡西平和卡马西平）之间切换偶尔可被视为缓解程序。然而，对于许多 ASM 来说，不存在隔夜改用另一种药物的选择。如果需要的话，从品牌到通用或在通用产品之间切换通常是安全的。最后，当无法提供苯二氮卓类药物或静脉给药设备时，一些 ASM 直肠给药可能是治疗癫痫连续发作和癫痫持续状态的紧急替代途径，关于治疗和可能选择的决策应以对患者最有利的方式为依据。

29. 抗癫痫发作药物与运动障碍

Antiseizure Drugs and Movement Disorders. *CNS Drugs. 2022 Aug;36(8):859-876. doi: 10.1007/s40263-022-00937-x. Epub 2022 Jul 21.*

Sáenz-Farret M, Tijssen MAJ, Eliashiv D, Fisher RS, Sethi K,Fasano A.

The relationship between antiseizure drugs and movement disorders is complex and not adequately reviewed so far. Antiseizure drugs as a treatment for tremor and other entities such as myoclonus and restless leg syndrome is the most common scenario, although the scientific evidence supporting their use is variable. However, antiseizure drugs also represent a potential cause of iatrogenic movement disorders, with parkinsonism and tremor the most common disorders. Many other antiseizure drug-induced movement disorders are possible and not always correctly identified. This review was conducted by searching for all the possible combinations between 15 movement disorders (excluding ataxia) and 24 antiseizure drugs. The main objective was to describe the movement disorders treated and worsened or induced by antiseizure drugs. We also summarized the proposed mechanisms and risk factors involved in the complex interaction between antiseizure drugs and movement disorders. Antiseizure drugs mainly used to treat movement disorders are clonazepam, gabapentin, lacosamide, levetiracetam, oxcarbazepine, perampanel, phenobarbital, pregabalin, primidone, topiramate, and zonisamide. Antiseizure drugs that worsen or induce movement disorders are cenobamate, ethosuximide, felbamate, lamotrigine, phenytoin, tiagabine, and vigabatrin. Antiseizure drugs with a variable effect on movement disorders are carbamazepine and valproate while no effect on movement disorders has been reported for brivaracetam, eslicarbazepine, lacosamide, and stiripentol. Although little information is available on the adverse effects or benefits on

movement disorders of newer antiseizure drugs (such as brivaracetam, cenobamate, eslicarbazepine, lacosamide, and rufinamide), the evidence collected in this review should guide the choice of antiseizure drugs in patients with concomitant epilepsy and movement disorders. Finally, these notions can lead to a better understanding of the mechanisms involved in the pathophysiology and treatments of movement disorders.

抗癫痫发作药物与运动障碍之间的关系是复杂的，到目前为止还没有足够的综述。抗癫痫发作药物是治疗震颤和其他疾病，如肌阵挛和不宁腿综合征最常见的方案，尽管支持其使用的科学证据不尽相同，然而，抗癫痫发作药物也是导致医源性运动障碍的潜在原因，其中帕金森症和震颤是最常见的，许多其他抗癫痫发作药物也可能引起运动障碍，但没有被正确认识到，这篇综述是通过搜索 15 种运动障碍（不包括共济失调）和 24 种抗癫痫发作药物的所有可能的组合，主要目的是描述抗癫痫发作药物治疗和恶化或诱发运动障碍。我们还总结了关于抗癫痫发作药物和运动障碍之间相互作用的已提出的机制和风险因素，抗癫痫发作药中主要用于治疗运动障碍的是氯硝西泮、加巴喷丁、拉科酰胺、左乙拉西坦、奥卡西平、吡仑帕奈、苯巴比妥、普瑞巴林、扑米酮、托吡酯和唑尼沙胺，加重或诱发运动障碍的抗癫痫药物是苯巴那酯、乙琥胺、非胺酯、拉莫三嗪、苯妥英、噻加宾和氨己烯酸。对运动障碍有不同影响的抗癫痫发作药物是卡马西平和丙戊酸盐，对运动障碍没有影响报道有布瓦西坦、艾司利卡西平、拉科酰胺和司替戊醇。尽管关于较新的抗癫痫发作药物（如布瓦西坦、辛诺巴酯、艾司利卡西平, 拉科酰胺和卢非酰胺）对运动障碍的益处或者不良反应的信息很少，在这篇综述中收集的证据应该指导癫痫和运动障碍合并症患者抗癫痫发作药物的选择。最后，这些概念可以促进我们更好的理解运动障碍的病理生理机制和治疗机制。

30. 抗癫痫发作药物治疗卒中后癫痫的有效性和安全性

Efficacy and safety of antiseizure medication in post-stroke epilepsy. *Seizure. 2022 Aug;100:109-114. doi: 10.1016/j.seizure.2022.07.003. Epub 2022 Jul.*

Winter Y, Uphaus T, Sandner K, Klimpe S, Stuckrad-Barre SV, Groppa S.

BACKGROUND: Specific antiseizure medications (ASM) would improve the outcome in post-stroke epilepsy (PSE). The aim of this multicenter observational study was to compare different antiseizure monotherapies in PSE.

METHODS: We collected the data from 207 patients with PSE who did not change their initial antiseizure monotherapy during the period of 12 months. Efficacy was assessed by a standardized three month seizure frequency and seizure freedom. Safety was estimated by the reported side effects.

RESULTS: The mean three month seizure frequency was 1.9 ± 3.1 on eslicarbazepine, 2.1 ± 3.2 on lacosamide, 3.4 ± 4.4 on levetiracetam, 4.3 ± 6.8 on lamotrigine, and 5.1 ± 7.3 on valproate ($p < 0.05$ for eslicarbazepine or lacosamide in comparison with levetiracetam, lamotrigine and valproate, respectively). The lowest seizure frequency and the highest seizure freedom was observed on ASMs acting via the slow inactivation of sodium channels in comparison to other mechanisms of action (0.7 ± 0.9 vs 2.2 ± 2.4, $p < 0.01$). Among side effects, the most frequently reported were vertigo (25%) and tiredness (15.9%). They were similar in all investigated groups of ASM. The independent factors increasing seizure frequency that were identified in multiple regression analyses were increased size of infarction, cortical involvement, hemorrhagic transformation, neurological deficits at admission and functional impairment. Administration of

ASM with the mechanism of action via the slow inactivation of sodium channels was an independent factor decreasing the seizure frequency.

CONCLUSION: Our data show that antiseizure medications acting via the slow inactivation of sodium channels, such as lacosamide and eslicarbazepine, are well tolerated and might be associated with better seizure control in PSE.

背景：特异性抗癫痫发作药物（ASM）可改善卒中后癫痫（PSE）的预后。这项多中心观察性研究的目的是比较 PSE 中不同的单药抗癫痫发作疗法。

方法：我们收集了 207 名 PSE 患者的数据。他们在 12 个月期间没有改变初始的单药抗癫痫发作治疗。通过标准化的三个月癫痫发作频率和无癫痫发作去评估有效性，通过报告的副作用估计其安全性。

结果：艾司利卡西平,其平均三个月癫痫发作频率为 1.9±3.1，拉科酰胺为 2.1±3.2，左乙拉西坦为 3.4±4.4，拉莫三嗪为 4.3±6.8，丙戊酸盐为 5.1±7.3（艾司利卡西平或拉科酰胺与左乙拉西坦、拉莫三嗪和丙戊酸盐相比，$P < 0.05$）。在抗癫痫发作药物中观察到最低癫痫发作频率和最高无癫痫发作与其他作用机制相比是通过钠通道的缓慢失活起作用（0.7±0.9vs2.2±2.4，$p<0.01$）。在副作用中，报告最多的是眩晕（25%）和疲倦（15.9%）。它们在所有被调查的 ASM 组中都是相似的，通过多元回归分析显示增加癫痫发作频率的独立因素有梗死面积增加，皮质受累、出血性转化、神经功能缺损和功能障碍。通过钠通道缓慢失活的作用机制管理 ASM 是降低癫痫发作频率的独立因素。

结论：我们的数据显示，通过钠通道缓慢失活发挥作用的抗癫痫发作药物，例如拉考沙胺和艾司利卡西平，其耐受性良好，可能与 PSE 中更好的癫痫发作控制有关。

副作用

1. 长期丙戊酸治疗对儿科癫痫患者脂质谱的影响：mate 分析

Effect of long-term valproic acid therapy on lipid profiles in paediatric patients with epilepsy: a meta-analysis. *Epileptic Disord. 2022 Oct 1;24(5):1-9. doi: 10.1684/epd.2022.1460.*

Guo HL, Dong N, Chen F, Zeng YY, Hu YH, Xia Y, Tian M, Lu XP, Qiu JC.

OBJECTIVE: Despite the potential role of valproic acid (VPA) in weight gain, the effects of VPA therapy on lipid profiles remain unclear. This study aimed to review the influence of VPA therapy on serum lipid profiles in children with epilepsy.

METHODS: This meta-analysis was conducted on data from PubMed, Web of Science, Cochrane Library, and Embase databases. Case-controlled studies, which assessed the effects of VPA therapy on lipid profiles, were included. All outcomes were recorded as continuous variables, and the effect size was measured.

RESULTS: VPA therapy was associated with a significant reduction in total cholesterol (mean difference [MD]=-6.34, 95% confidence interval [CI]: -12.30, -0.37, p=0.04) and low-density lipoprotein cholesterol levels (MD = -7.75, 95% CI: -13.48, -2.0, p=0.008). No significant effects were observed regarding the levels of high-density lipoprotein cholesterol and triglycerides.

SIGNIFICANCE: In conclusion, this meta-analysis indicates that VPA therapy causes a decrease in the levels of total cholesterol and low-density lipoprotein cholesterol.

目的：尽管丙戊酸（VPA）在体重增加中有潜在作用，但VPA疗法对血脂的影响仍不清楚。这项研究旨在评估VPA治疗对癫痫儿童血脂的影响。

方法：对来自 PubMed、Web of Science、Cochrane Library 和 Embase 数据库的数据进行 Mate 分析。包括评估 VPA 治疗对血脂的影响的病例对照研究。所有结果都被记录为连续变量，并测量效果大小。

结果：VPA 治疗与总胆固醇显著降低（平均差异[MD]=-6.34，95%置信区间[CI]：-12.30，-0.37，p=0.04）和低密度脂蛋白胆固醇水平（MD = -7.75，95%CI：-13.48，-2.0，p=0.008）显著降低有关。在高密度脂蛋白胆固醇和甘油三酯水平方面没有观察到显著影响。

意义：总之，这种 Meta 分析表明，VPA 治疗会导致总胆固醇和低密度脂蛋白胆固醇水平下降。

2. 分析抗癫痫发作药物制剂中辅料相关的不良事件

Analyzing excipient-related adverse events in antiseizure drug formulations.*Epilepsy Res. 2022 Aug;184:106947. doi: 10.1016/j.eplepsyres.2022.106947. Epub 2022 May 23.*

Ionova Y, Peterson T, Wilson L.

There have been several reports that switching formulations of antiseizuremedications (ASMs) has been associated with a deterioration of seizure control,seizure relapse or increased adverse effects. Considering recent findings that excipients, namely purported inactive ingredients, may nevertheless exert biological effects, it is possible that the variation in adverse event profile of antiseizure drugs may be related to differences in excipients. To test our hypothesis, we constructed a new research tool to connect FDA-compiled adverse event reports to the excipient in the medicine. Analysis of adverse events to formulations of five different second-generation antiseizure drugs - gabapentin, lamotrigine, levetiracetam, oxcarbazepine, and topiramate - showed several significant associations between specific excipient in the formulations and an adverse event when compared to the same medicine formulated with other excipients. Epilepsy and seizure adverse events were associated with multiple excipients across gabapentin, lamotrigine, and levetiracetam formulations. A different group of excipients were associated with reports of hypersensitivity reactions including urticaria, rash, erythema, and Stevens-Johnson syndrome. Our study provides a novel approach to analyzing post-market surveillance reports by including excipients. It may be useful to clinicians when evaluating select patient groups that may be refractory to pharmacological treatment or experience worsening adverse events when switching formulations of the same antiseizure medicine.

有几篇报道称，更换抗癫痫发作药物(ASMs)的配方与癫痫控制恶化、癫痫复发或不良反应增加有关。考虑到最近的研究发现，辅料(即所谓的非活性成分)可能发挥生物作用，抗癫痫发作药物不良事件的变化可能与辅料的差异有关。为了验证我们的假设，我们构建了一个新的研究工具，将 FDA 汇编的不良事件报告与药物中的辅料联系起来。对五种不同的第二代抗癫痫发作药物——加巴喷丁、拉莫三嗪、左乙拉西坦、奥卡西平和托吡酯制剂的不良事件分析显示，与使用其他辅料配制的相同药物相比，制剂中特定辅料与不良事件之间存在若干显著关联。癫痫和癫痫不良事件与加巴喷丁、拉莫三嗪和左乙拉西坦制剂中的多种辅料有关。另一组辅料与过敏反应相关，包括荨麻疹、皮疹、红斑和 Stevens-Johnson 综合征。我们的研究通过添加辅料提供了一种分析上市后监测报告的新方法。对于临床医生来说，当评估对药物治疗有困难的患者群体或在更换同一种抗癫痫发作药物配方时不良事件不断恶化时，这可能是有用的。

3. 阿那白滞素和托昔单抗在发热感染相关癫痫综合征（FIRES）慢性期的作用：一系列病例的有效性和安全性

Anakinra and tocilizumab in the chronic phase of febrile infection-related epilepsy syndrome (FIRES): Effectiveness and safety from a case-series. *Seizure. 2022 Aug;100:51-55. doi: 10.1016/j.seizure.2022.06.012.*

Aledo-Serrano A, Hariramani R, Gonzalez-Martinez A, Álvarez-Troncoso J, Toledano R, Bayat A, Garcia-Morales I, Becerra JL, Villegas-Martínez I, Beltran-Corbellini A, Gil-Nagel .

PURPOSE: There is scarce evidence of effective treatments for the chronic phase of Febrile infection-related epilepsy syndrome (FIRES). This study aimed to analyze the outcomes of treatment with anakinra and tocilizumab.

METHODS: Retrospective study including patients receiving either anti-interleukin-1 (anti-IL-1, anakinra) or anti-IL-6 (tocilizumab) during the chronic phase of FIRES. We evaluated seizure outcomes, non-seizure comorbidities, and adverse events. Additionally, an indirect control group including patients during the chronic phase of FIRES non-treated with-IL therapies was evaluated.

RESULTS: Five patients were included; three females. Median age at FIRES: 8 years (IQR: 6-10). Five patients received anakinra; one patient switched to tocilizumab after ineffectiveness. Median treatment duration was 9months (IQR: 7-20). While no patients became seizure-free, 20-50% reduction in seizure frequency was reported in 3/5 patients after 6

months with anakinra. Retention rate was 100% at 6 months and 40% at 12months. Three patients reported reduced seizure intensity and rescue medication needed, and better behavior/communication. Similar improvement was reported for the patient switching to tocilizumab. Patients with the best response received anti-IL a

median of 9 years after acute phase. All discontinuations were due to ineffectiveness. There were none relevant adverse events apart from one patient presenting transient seizure aggravation. Nine patients were included in the control group; none of them showed relevant improvement in seizure outcomes or cognitive/behavioral comorbidities. Only one presented mild improvement in seizure frequency during the 6-months follow-up.

CONCLUSION: This study provides promising data on effectiveness/safety of anakinra and tocilizumab in the chronic phase of FIRES. These findings warrant prospective/larger studies.

目的：对于发热感染相关癫痫综合征（FIRES）的慢性期，缺乏有效治疗的证据。本研究旨在分析 anakinra 和 tocilizumab 治疗的结果。

方法：回顾性研究包括在 FIRES 慢性期接受抗白细胞介素-1（抗 IL-1，阿那白滞素）或抗 IL-6（托昔单抗）治疗的患者。我们评估了癫痫结果、非癫痫合并症和不良事件。此外，还评估了一个间接对照组，包括慢性期未接受 IL 治疗的患者。

结果：包括 5 例患者；三名女性。FIRES 中位年龄：8 岁（IQR:6-10）。5 名患者接受了阿那白滞素治疗；一名患者在无效后改用托昔单抗。中位治疗时间为 9 个月（IQR:7-20）。虽然没有患者无癫痫发作，但据报道，阿那白滞素治疗 6 个月后，3/5 患者的癫痫发作频率降低了 20-50%。6 个月时保持率为 100%，12 个月时为 40%。三名患者报告降低了癫痫发作强度和抢救所需药物，并且恢复了行为/沟通能力。据报道，改用托昔单抗的患者也有类似的改善。对治疗反应最好的患者在急性期后接受抗 IL-1 治疗的时间中位数为 9 年。所有的中断都是由于无效。除一名患者出现短暂发作加重外，无相关不良事件发生。对照组包括 9 名患者；他们都没有表现出癫痫发作结果或认知/行为共病的相关改善。在 6 个月的随访中，只有 1 例癫痫发作频率略有改善。

结论：本研究提供了阿那白滞素和托昔单抗在 FIRES 慢性期的有效性/安全性的有希望的数据。这些发现值得进行前瞻性/大型研究。

机制研究

1. 一种乌墨水提取物可以保护红藻氨酸诱导的癫痫状态和失忆：抗氧化和抗炎干预的证据

An aqueous extract of Syzygium cumini protects against kainate-induced status epilepticus and amnesia: evidence for antioxidant and anti-inflammatory intervention. *Metab Brain Dis. 2022 Aug 2. doi: 10.1007/s11011-022-01052-y.*

Kandeda AK, Nodeina S, Mabou ST.

Temporal lobe epilepsy is the most common drug-resistant epilepsy. To cure epilepsy, drugs must target the mechanisms at the origin of seizures. Thus, the present investigation aimed to evaluate the antiepileptic- and anti-amnesic-like effects of an aqueous extract of Syzygium cumini against kainate-induced status epilepticus in mice, and possible mechanisms of action. Mice were divided into 7 groups and treated as follows: normal group or kainate group received po distilled water (10 mL/kg), four test groups received Syzygium cumini (28.8, 72, 144, and 288 mg/kg, po), and the positive control group treated intraperitoneally (ip) with sodium valproate (300 mg/kg). An extra group of normal mice was treated with piracetam (200 mg/kg, po). Treatments were administered 60 min before the induction of status epilepticus with kainate (15 mg/kg, ip), and continued daily throughout behavioral testing. Twenty-four hours after the induction, T-maze and Morris water maze tasks were successively performed. The animals were then sacrificed and some markers of oxidative stress and neuroinflammation were estimated in the hippocampus. The extract significantly prevented status epilepticus and mortality. In the T-maze, the aqueous extract markedly increased the time spent and the number of entries in the discriminated arm. In the Morris water maze, the extract significantly increased the time spent in the target quadrant during the retention phase. Furthermore, the aqueous extract induced a significant reduction of oxidative stress and neuroinflammation. These results suggest that the aqueous extract of Syzygium cumini has antiepileptic- and anti-amnesic-like effects, likely mediated in part by antioxidant and anti-inflammatory activities.

颞叶癫痫是最常见的耐药性癫痫。为了治愈癫痫，药物必须针对癫痫发作起源的机制。因此，本研究旨在评估乌墨水提物对红藻氨酸诱导的小鼠癫痫持续状态的抗癫痫和抗遗忘样作用，以及可能的作用机制。将小鼠分为 7 组，处理方法如下：正常组或红藻氨酸组口服蒸馏水（10 mL/kg），四个试验组给予乌墨（28.8、72、144 和 288 mg/kg，po），和阳性对照组用丙戊酸钠 (300 mg/kg) 腹腔内 (ip) 治疗。另有一组正常小鼠用吡拉西坦（200mg/kg，po）治疗。在用红藻氨酸 (15 mg/kg, ip) 诱导癫痫持续状态前 60 分钟进行治疗，并在整个行为测试中每天持续进行。诱导后 24 小时，依次进行 T 迷宫和 Morris 水迷宫任务。然后将动物处死，并在评估海马体中一些氧化应激和神经炎症的标志物。该提取物显著降低了癫痫持续状态和死亡率。在 T 型迷宫中，水提取物显著增加了在被识别臂中花费的时间和进入的次数。在莫里斯水迷宫中，提取物显着增加了保留阶段在目标象限中花费的时间。此外，水提取物可显着减少氧化应激和神经炎症。这些结果表明，乌墨水提物具有抗癫痫和抗失眠的作用，可能部分是由抗氧化和抗炎活动介导的。

2. 脑和外周器官中的外排转运蛋白和代谢酶在解释耐药性癫痫中的作用

The role of efflux transporters and metabolizing enzymes in brain and peripheral organs to explain drug-resistant epilepsy.

Epilepsia Open. 2022 Aug;7 Suppl 1(Suppl 1):S47-S58. doi: 10.1002/epi4.12542. Epub 2021 Oct 1.

Vázquez M, Fagiolino P.

Drug-resistant epilepsy has been explained by different mechanisms. The most accepted one involves overexpression of multidrug transporters proteins at the blood brain barrier and brain metabolizing enzymes. This hypothesis is one of the main pharmacokinetic reasons that lead to the lack of response of some antiseizure drug substrates of these transporters and enzymes due to their limited entrance into the brain and limited stay at the sites of actions. Although uncontrolled seizures can be the cause of the overexpression, some antiseizure medications themselves can cause such overexpression leading to treatment failure and thus refractoriness. However, it has to be taken into account that the inductive effect of some drugs such as carbamazepine or phenytoin not only impacts on the brain but also on the rest of the body with different intensity, influencing the amount of drug available for the central nervous system. Such induction is not only local drug concentration but also time dependent. In the case of valproic acid, the deficient disposition of ammonia due to a malfunction of the urea cycle, which would have its origin in an intrinsic deficiency of L-carnitine levels in the patient or by its depletion caused by the action of this antiseizure drug, could lead to drug-resistant epilepsy. Many efforts have been made to change this situation. In order to name some, the administration of once-daily dosing of phenytoin or the coadministration of carnitine with valproic acid would be preferable to avoid iatrogenic refractoriness. Another could be the use of anadjuvant drug that down-regulates the expression of transporters. In this case, the use of cannabidiol with antiseizure properties itself and able to diminish the overexpression of these transporters in the brain could be a novel therapy in order to allow penetration of other antiseizure medications into the brain.

耐药性癫痫已被不同的机制解释。最被接受是一种涉及多药转运蛋白在血脑屏障和脑代谢酶的过度表达。这一假设是导致这些转运蛋白和酶的一些抗癫痫药物底物由于其有限地进入大脑和在作用位点停留有限而导致缺乏反应的主要药代动力学原因之一。虽然不受控制的癫痫发作可能是过度表达的原因，但一些抗癫痫发作药物本身会导致这种过度表达，从而导致治疗失败并因此产生难治性。然而，必须考虑到一些药物如卡马西平或苯妥英的诱导作用不仅对大脑有影响，而且对身体其他部位也有不同程度的影响，影响中枢神经系统可用的药物量。这种诱导不仅是局部药物浓度，而且是时间依赖性的。在使用丙戊酸的治疗的情况下，由于尿素循环功能障碍导致氨的处置不足，这可能源于患者体内左旋肉碱水平的内在缺乏或由这种抗癫痫发作药物的作用引起的耗尽，可能导致耐药性癫痫。为了改变这种状况，人们做出了许多努力。为了避免医源性难治，最好每天服用一次苯妥英或同时服用肉碱和丙戊酸。另一种可能是使用下调转运蛋白表达的调节药物。在这种情况下，使用本身具有抗癫痫特性并能够减少这些转运蛋白在大脑中过度表达的大麻二酚可能是一种新的疗法，以允许其他抗癫痫发作药物渗透到大脑中。

3. microRNAs 序列或其中靶基因的单核苷酸变异可能影响癫痫的风险：一篇综述

Single-Nucleotide Variants in microRNAs Sequences or in their Target Genes Might Influence the Risk of Epilepsy: A Review.

Cell Mol Neurobiol. 2022 Aug. doi: 10.1007/s10571-021-01058-7.

Buainain RP, Boschiero MN, Camporeze B, de Aguiar PHP, Marson FAL, Ortega MM.

Single-nucleotide variant (SNV) is a single base mutation at a specific location in the genome and may play an import role in epilepsy pathophysiology. The aim of this study was to review case-control studies that have investigated the relationship between SNVs within microRNAs (miRs) sequences or in their target genes and epilepsy susceptibility from January 1, 2010 to October 31, 2020. Nine case-control studies were included in the present review. The mainly observed SNVs associated with drug-resistant epilepsy (DRE) risk were SNVs n.60G > C (rs2910164) and n.-411A > G (rs57095329), both located at miR-146a mature sequence and promoter region, respectively. In addition, the CC haplotype

(rs987195-rs969885) and the AA genotype at rs4817027 in the MIR155HG/miR-155 tagSNV were also genetic susceptibility markers for early-onset epilepsy. MiR-146a has been observed as upregulated in human astrocytes in epileptogenesis and it regulates inflammatory process through NF-κB signaling by targeting tumor necrosis factor-associated factor 6 (TRAF6) gene. The SNVs rs2910164 and rs57095329 may modify the expression level of mature miR-146a and the risk for epilepsy and SNVs located at rs987195-rs969885 haplotype and at rs4817027 in the MIR155HG/miR-155 tagSNV could interfere in the miR-155 expression modulating inflammatory pathway genes involved in the development of early-onset epilepsy. In addition, SNVs rs662702, rs3208684, and rs35163679 at 3'untranslated region impairs the ability of miR-328, let-7b, and miR-200c binding affinity with paired box protein PAX-6 (PAX6), BCL2 like 1 (BCL2L1), and DNA methyltransferase 3 alpha (DNMT3A) target genes. The SNV rs57095329 might be correlated with DRE when a larger number of patients are evaluated. Thus, we concluded that the main drawback of most of studies is the small number of individuals enrolled, which lacks sample power.

单核苷酸变异（SNV）是基因组中特定位置的单碱基突变，可能在癫痫的病理生理中发挥重要作用。本研究的目的是回顾 2010 年 1 月 1 日至 2020 年 10 月 31 日期间调查 microRNAs（miRs）序列内或其靶基因的 SNVs 与癫痫易感性之间关系的病例对照研究。本综述包括了 9 项病例对照研究。主要观察到的与耐药性癫痫（DRE）风险相关的 SNVs 是 n.60G（rs2910164）和 n.-411A > G（rs57095329），两者分别位于 miR-146a 成熟序列和启动子区域。此外，CC 单倍型（rs987195-rs969885）和 MIR155HG/miR-155 标记 SNV 中 rs4817027 的 AA 基因型也是早发癫痫的遗传易感性标记。MiR-146a 在人体星形胶质细胞中被观察到在癫痫发生中上调，它通过靶向肿瘤坏死相关因子 6（TRAF6）基因的 NF-κB 信号调控炎症过程。SNVs rs2910164 和 rs57095329 可能改变成熟 miR-146a 的表达水平和癫痫风险，位于 rs987195-rs969885 单倍型和 MIR155HG/miR-155 tagSNV 中的 rs4817027 可能干扰 miR-155 表达调节参与早发癫痫发病的炎症通路基因。此外，3'非翻译区的 SNVs rs662702、rs3208684 和 rs35163679 削弱了 miR-328、let-7b、miR-200c 与配对盒蛋白 PAX-6（PAX6）、BCL2 like 1（BCL2L1）和 DNA 甲基转移酶 3α（DNMT3A）靶基因结合的能力。当对更多的患者进行评估时，SNV rs57095329 可能与 DRE 相关。因此，我们得出结论，大多数研究的主要缺点是入选人数少，缺乏样本力量。

4. 铜锌超氧化物歧化酶抑制匹罗卡品诱导的大鼠癫痫并改变 SCN2A/Nrf2/HO-1 的表达

Cu-Zn SOD suppresses epilepsy in pilocarpine-treated rats and alters SCN2A/Nrf2/HO-1 expression. *Epileptic Disord. 2022 Aug 1;24(4):1-10. doi: 10.1684/epd.2022.1434.*

Wen F, Tan ZG, Xiang J.

OBJECTIVE: Copper-zinc superoxide dismutase (Cu-Zn SOD) is downregulated in epilepsy, however, the role of Cu-Zn SOD in epilepsy remains unclear.

METHODS: Based on the pilocarpine hydrochloride-induced rat model of epilepsy, cortical-striatum brain slices of rats were examined based on field excitatory post-synaptic potentials. Pathological changes were observed by transmission electron microscope. Also using SH-SY5Y cells, flow cytometry and TUNEL staining were applied to investigate cell apoptosis, and ELISA was applied to detect SOD activity. In addition, qRT-PCR and western blot were performed to detect SCN2A/Nrf2/HO-1 gene and protein expression levels, respectively.

RESULTS: Cu-Zn SOD over-expression suppressed epilepsy in vivo. In addition, Cu-Zn SOD knockdown notably decreased SOD activity and induced apoptosis in SH-SY5Y cells. Moreover, Cu-Zn SOD silencing decreased the levels of SCN2A, Nrf2 and HO-1. Lastly, Cu-Zn SOD was shown to modulate the NaV1.2/Nrf2/HO-1 axis in rats.

SIGNIFICANCE: In this model, Cu-Zn SOD attenuated epilepsy and was shown to alter the expression level of proteins of the NaV1.2 /Nrf2/HO-1 signalling pathway, indicating that Cu-Zn SOD might be a target for the treatment of epilepsy.

目的：在癫痫中，铜锌超氧化物歧化酶(Cu–Zn SOD)的表达下调，然而，它在癫痫中的作用尚不清楚的。

方法：应用盐酸匹罗卡品诱导的癫痫大鼠模型，以及场兴奋性突触后电位检查大鼠皮质纹状体脑切片，透射电子显微镜观察病理变化，同时使用 SH-SY5Y 细胞，流式细胞仪和 TUNEL 染色检测细胞凋亡，ELISA 检测 SOD 活动，此外，分别用 qRT–PCR 和 WB 检测 SCN2A/Nrf2/HO-1 基因和蛋白表达水平。

结果: Cu-Zn-SOD 过度表达抑制了体内癫痫。此外，Cu-Zn-SOD 基因敲除显著降低 SH-SY5Y 细胞的 SOD 活性并诱导细胞凋亡。此外，铜锌超氧化物歧化酶沉默降低了 SCN2A、Nrf2 的水平，最后，铜锌超氧化物歧化酶显示可调节大鼠的 NaV1.2/Nrf2/HO-1 轴。

意义:在该模型中，Cu–Zn SOD 可抑制癫痫，同时可改变 SCN2A/Nrf2/HO-1 信号通路的蛋白表达水平，表明 Cu–Zn SOD 可能是癫痫治疗的一个靶点。

5. 戊四氮点燃大鼠模型：miR-182 和 miR-27b-3p 介导的百里醌在海马区的神经保护作用

Pentylenetetrazole-induced kindling rat model: miR-182 and miR-27b-3p mediated neuroprotective effect of thymoquinone in the hippocampus.*Neurol Res. 2022 Aug;44(8):726-737. doi: 10.1080/01616412.2022.2051129. Epub 2022 Mar 13.*

Pala M, Meral I, Pala Acikgoz N, Gorucu Yilmaz Ş, Taslidere E, Okur SK, Acar S, Akbas F.

OBJECTIVES: Epilepsy is a neurological disease that pathologically affects brain functions. The epileptic hippocampus has modified microRNA(miRNA) levels. Therefore, we aimed to evaluate the neuroprotective effect of thymoquinone (TQ) in PTZ-induced epilepsy and to demonstrate the overlap between miRNA and mRNA expression profiles.

METHODS: Male adult Wistar albino rats (200-230 g, n = 20) were divided into three groups as control (n = 6), PTZ (n = 7), and TQ + PTZ (n = 7). The PTZ kindling model was created by injecting PTZ in sub convulsive doses to rats on days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, and 24 of the study into animals.

Clonic and tonic seizures were induced by injecting a convulsive dose of PTZ on day 26 of the study. Rats in the TQ+PTZ group were treated by oral gavage with a 20 mg/kg TQ 2 h before each PTZ injection. The rats in the control group were treated with 0.5 ml saline. Seizure severity was evaluated with the Racine scale. The genes and signaling pathways targeted by miRNAs were determined by bioinformatics analysis.

RESULTS: In the rat hippocampus, mature 728 miRNAs were analyzed by microarray and the nine miRNA were verified by quantitative Real-Time PCR. rno-miR-182 and rno-miR-27b-3p were up-regulated in the PTZ group and down-regulated in the TQ + PTZ group.

DISCUSSION: In the PTZ kindling epilepsy model, the expression of these two miRNAs was regulated by TQ and exerted a neuroprotective effect by controlling the activities of target genes.

目的：癫痫是一种从病理上影响脑功能的神经系统疾病。癫痫患者海马区微小 RNA(miRNA)水平发生改变。因此，我们的目的是评估百里醌(TQ)在 PTZ 诱导的癫痫中的神经保护作用，并证明 miRNA 和 mRNA 表达谱之间的重叠。

方法：成年雄性 Wistar 大鼠 20 只，体重 200-230g 随机分为对照组(n=6)、PTZ 组(n=7)和 TQ+PTZ 组(n=7)。在实验的第 1、3、5、8、10、12、15、17、19、22 和 24 天分别向大鼠注射亚惊厥剂量的 PTZ，建立 PTZ 点燃模型。在研究的第 26 天，通过注射惊厥剂量的 PTZ 来诱发阵挛发作和强直发作。TQ+PTZ 组在每次注射 PTZ 前 2 h 灌胃给予 TQ 20 mg/kg。对照组给予 0.5ml 生理盐水。用 Racine 评分评估癫痫发作严重程度。通过生物信息学分析确定 miRNAs 靶向的基因和信号通路。

结果：用基因芯片技术分析了大鼠海马区成熟的 728 个 miRNAs，用实时定量 PCR 验证了 9 个 miRNAs 的表达。PTZ 组 rno-miR-182 和 rno-miR-27b-3p 表达上调，TQ+PTZ 组 rno-miR-182 和 rno-miR-27b-3p 表达下调。

讨论：在 PTZ 点燃癫痫模型中，这两种 miRNAs 的表达受 TQ 调控，并通过调控靶基因的活性发挥神经保护作用。

6. 鞘内注射乙琥胺能够在失神癫痫的基因模型中高效抑制癫痫发作

Intrathecal application of ethosuximide is highly efficient in suppressing seizures in a genetic model of absence epilepsy.*Epilepsy Res. 2022 Aug;184:106967. doi: 10.1016/j.eplepsyres.2022.106967. Epub 2022 Jun 15.*

Buschhoff AS, Scherließ R, de Mooij-van Malsen JG, Schiffelholz T, Stephani U, Wulff P.

Systemic drug application is the main approach in epilepsy treatment. However, the central nervous system (CNS) is a challenging target for drug delivery as the blood-brain barrier (BBB) restricts the transfer of drugs into the brain. Accordingly, there is a general interest in developing new therapeutic strategies to improve CNS drug accessibility. Intrathecal administration of antiseizure drugs (ASDs) e.g. via pumps or advanced materials could be a possible approach to bypass the BBB and increase the availability of neuroactive compounds in the CNS. The aim of this study was the evaluation of intracerebroventricular (i.c.v.) compared to systemic drug application in generalized epilepsy. The i.c.v. administration of the established ASD ethosuximide (ETX) in Genetic Absence Epilepsy Rats from Strasbourg (GAERS) caused a robust and dose-dependent reduction of spike-wave discharges (SWDs) without causing obvious behavioral abnormalities. Additionally, we could show that i.c.v. treatment with ETX is significantly more effective in seizure suppression than systemic treatment with the same dose. The localized application resulted in reduced systemic drug exposure compared to standard systemic ETX therapy. The tracing of dye distribution throughout the CNS supported the view that i.c.v. applied drugs cross into brain tissue surrounding the ventricles but largely remain restricted to the siteof injection. Our data suggest that intrathecal application represents a possible route for the treatment in generalized epilepsy through direct drug penetration from CSF into brain tissue.

全身用药是癫痫治疗的主要方法。然而，血脑屏障的存在使药物向大脑的转运受到限制，这使得中枢神经系统成为给药的挑战性的靶点。因此，提高的中枢神经系统对药物的可及性已成为药物开发的普遍兴趣点。通过泵或其他先进材料进行鞘内注射抗癫痫发作药物，可能成为药物绕过血脑屏障并提高中枢神经系统中神经活性物质的途径。本研究的目的是在全面性癫痫中评价侧脑室注射及全身用药的效果。在失神性发作斯特拉斯堡癫痫大鼠基因模型中使用侧脑室注射抗癫痫发作药乙琥胺，可以发生显著的剂量依赖的棘波发放减少且不引起显著的异常行为。此外，我们可以发现相同剂量的乙琥胺侧脑室注射与全身给药相比对于减少癫痫发作更有效。与标准的全身性乙琥胺治疗相比，局部给药可以减少全身药物的暴露。对整个中枢神经系统染料分布的追踪支持了以下观点，即侧脑室注射将药物进入脑室周围的脑组织，但很大程度上局限于注射部位。我们的数据表明鞘内给药通过药物从脑脊液直接渗透到脑组织，成为一种治疗全面性癫痫的可能途径。

7. 食欲素 A 与癫痫发作的关系

Relation between orexin A and epileptic seizures.*Epilepsy Res. 2022 Aug;184:106972. doi: 10.1016/j.eplepsyres.2022.106972. Epub 2022 Jun 26.*

Arslan GA, Saygi S, Bodur E, Cicek C, Tezer FI.

INTRODUCTION: One of the unknown mechanisms in epilepsy pathogenesis is the involvement of the hypothalamic neuropeptide orexin. Although the relationship between orexin and sleep has been revealed, its effect in epilepsy has not been fully clarified. In this study, we aimed to show the relationship between orexin A and the seizures that occur during sleep and wakefulness.

MATERIAL AND METHODS: This study included 40 patients with drug-resistant focal epilepsy and 37 healthy controls. Night basal orexin (NBO) and morning basal orexin (MBO) levels were measured using enzyme-linked immunosorbent assay in patients and controls. Serum samples were collected from patients after epileptic seizures during sleep and wakefulness.

RESULTS: In both patients and controls, MBO levels (median: 1039 pg/mL, interquartile ranges [IQR] (899-1078)) were higher than NBO levels (median 989 pq/mL, IQR (893-1078) ($p = 0.02$). Basal orexin levels were lower in patients than in controls ($p < 0.001$). However, while the duration of seizures was shortened in awake seizures, the level of orexin increased ($p = 0.007$). Additionally, orexin levels after nocturnal seizure were higher in patients who had an ictal electroencephalography onset in the left hemisphere or a lesion in the left temporal lobe ($p = 0.02$; $p = 0.01$, respectively). There was no relationship between postictal somnolence and orexin levels. Although there was no significant difference, the level of post-seizure orexin increased compared to the basal values, especially in seizures during sleep.

DISCUSSION: The increase in serum orexin levels, especially after seizures, suggests that orexin may be associated with the epileptogenic effect. In further studies, determination of orexin from cerebrospinal fluid (CSF) and correlation of CSF and serum orexin levels may provide more useful information regarding the relationship between orexin and epilepsy.

目的：癫痫的未知发病机制之一是下丘脑神经肽食欲素的参与。虽然食欲素与睡眠的关系已被揭露，但是其与癫痫的关系仍然不明确。在这项研究中，我们旨在阐明在睡眠与觉醒中食欲素 A 与癫痫发作的关系。

材料和方法：该研究纳入 40 名耐药性癫痫患者及 37 名健康对照人群。应用酶联免疫吸附试验检测患者及健康人群的夜间基础食欲素（NBO）及日间基础食欲素（MBO）水平。癫痫患者在睡眠和清醒期间癫痫发作后采集血清样本。

结果：在疾病组和正常对照组，MBO 水平（中位数 1039pg/ml，四分位数[IQR]（899-1078））均较 NBO 水平（中位数 989pg/ml，四分位数[IQR]（893-1078））高（p=0.02）。疾病组基础食欲素水平较正常对照组水平低（p < 0.001）。然而，虽然清醒期癫痫发作的持续时间更短，但是食欲素水平更高（p=0.007）。此外，伴随发作期脑电图发作起源于左侧大脑半球或病灶位于左侧颞叶的夜间癫痫发作患者的食欲素水平较高（分别为 p=0.02；p=0.01）。发作后嗜睡与食欲素水平间无相关性。特别在睡眠期间的癫痫发作，其癫痫发作后食欲素水平较基线期水平的升高并无显著性差异。

讨论：癫痫发作后的血清中食欲素水平升高，表明食欲素可能与致痫作用相关。在未来的的研究中，测定脑脊液中食欲素水平并探讨脑脊液和血清中食欲素水平的相关性可能为食欲素及癫痫的相关性的研究提供更有价值的信息。

8. Na（+）-K（+）ATP 酶在癫痫大脑中扮演的角色

The role of Na(+) -K(+) -ATPase in the epileptic brain.*CNS Neurosci Ther. 2022 Sep;28(9):1294-1302. doi: 10.1111/cns.13893. Epub 2022 Jun 25.*

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Na+-K+-ATPase, a P-type ATP-powered ion transporter on cell membrane, plays a vital role in cellular excitability. Cellular hyperexcitability, accompanied by hypersynchronous firing, is an important basis for seizures/epilepsy. An increasing number of studies point to a significant contribution of Na+-K+-ATPase to epilepsy, although discordant results exist. In this review, we comprehensively summarize the structure and physiological function of Na+-K+-ATPase in the central nervous system and critically evaluate the role of Na+-K+-ATPase in the epileptic brain. Importantly, we further provide perspectives on some possible research directions and discuss its potential as a therapeutic target for the treatment of epilepsy.

Na+-K+-ATP 酶，是一种定位在细胞膜上，且在细胞兴奋性中有着重要作用的 P 型 ATP 驱动的离子转运体。细胞过度兴奋性伴有超同步放电，是癫痫发作/癫痫的重要基础。越来越多的研究指出 Na+-K+- atp 酶对癫痫的作用，虽然结果不一致。本文就 Na+-K+- atp 酶在中枢神经系统的结构和生理功能作一综述，并评价其在癫痫大脑中的作用。本文还对其可能的研究方向进行了展望，并探讨了其作为癫痫治疗靶点的潜力。

其他药物

1. 托吡酯和其他红藻氨酸受体拮抗剂治疗抑郁症：随机对照试验的系统回顾

Topiramate and other kainate receptor antagonists for depression: A systematic review of randomized controlled trials.
Neuropsychopharmacol Rep. 2022 Aug 1. doi: 10.1002/npr2.12284.

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BACKGROUND: Depression is a common disorder that affects patients' quality of life and incurs health system costs. Due to the resistance to treat depression, better understanding of neurophysiology was considered; one of the implications is the glutamatergic system. This study aims to systematically review clinical trials investigating the antidepressant effects of kainate receptor antagonists.

METHODS: The study protocol was registered in PROSPERO (CRD42021213912). Scopus, ISI, Embase, PubMed, Cochrane Library, Google Scholar, and two trial registries were searched for randomized controlled trials on the effectiveness of topiramate, phenobarbital, and other ten barbiturates in depression. The difference with control groups in terms of changing depressive symptoms was the primary outcome.

RESULTS: Nine trials were identified, in which 784 patients were studied. The efficacy of thiopental was comparable to that of imipramine, with fewer side effects. When administered with electroconvulsive therapy, it had fewer to similar effects and fewer side effects than ketamine. Both monotherapy and adjunctive therapy with topiramate were effective and tolerable in treating depressed patients. Phenobarbital had therapeutic effects compared to imipramine and amitriptyline with fewer side effects.

CONCLUSION: Regarding the glutamatergic hypothesis of depression and obtained promising results, further studies of kainate receptor antagonists in high-quality trials are recommended. Given the high prevalence of depression in epileptic patients, more problems with its treatment, and the fact that the studied agents were anticonvulsants, it is recommended that future studies prioritize depressed-epileptic patients.

背景：抑郁症是一种常见的疾病，影响患者的生活质量，并引起卫生系统的费用。由于治疗抑郁症的阻力，人们考虑对神经生理学有更好的了解；其中一个影响是谷氨酸系统。本研究旨在系统地回顾调查凯恩酸盐受体拮抗剂的抗抑郁作用的临床试验。

方法：研究方案已在 PROSPERO 注册（CRD42021213912）。在 Scopus、ISI、Embase、PubMed、Cochrane Library、Google Scholar 和两个试验登记处搜索了托吡酯、苯巴比妥和其他 10 种巴比妥类药物对抑郁症疗效的随机对照试验。与对照组在改变抑郁症状方面的差异是主要结果。

结果：确定了九项试验，其中研究了 784 名病人。戊硫代巴比妥的疗效与丙咪嗪相当，但副作用较少。当与电休克疗法一起使用时，它的效果较少或相似，副作用也比氯胺酮少。单一疗法和托吡酯的辅助疗法在治疗抑郁症患者方面都是有效和可承受的。与丙咪嗪和阿米替林相比，苯巴比妥具有治疗效果，且副作用较少。

结论：关于抑郁症的谷氨酸假说和获得的有希望的结果，建议在高质量的试验中进一步研究凯恩酸盐受体拮抗剂。鉴于癫痫患者的抑郁症发病率较高，其治疗存在较多问题，且所研究的药物均为抗惊厥药，建议今后的研究优先考虑抑郁症共病癫痫患者。

2. 普瑞巴林治疗危重病复发性癫痫：一种有前途的辅助药物治疗，尤其是周期性发作

Pregabalin for Recurrent Seizures in Critical Illness: A Promising Adjunctive Therapy, Especially for cyclic Seizures. *Neurocrit Care. 2022 Aug;37(1):140-148. doi: 10.1007/s12028-022-01459-6. Epub2022 Feb 25.*

Busl KM, Fong MWK, Newcomer Z, Patel M, Cohen SA, Jadav R, Smith CN, Mitropanopoulos S, Bruzzone M, Hella M, Eisenschenk S, Robinson CP, Roth WH, Ameli PA, Babi MA, Pizzi MA, Gilmore EJ, Hirsch LJ, Maciel CB.

BACKGROUND: Pregabalin (PGB) is an effective adjunctive treatment for focal epilepsy and acts by binding to the alpha2-delta subunit of voltage-gated calcium channels to reduce excitatory neurotransmitter release. Limited data exist on its use in the neurocritical care setting, including cyclic seizures-apattern of recurrent seizures occurring at nearly regular intervals. Although the mechanism underpinning cyclic seizures remains elusive, spreading excitation linked to spreading depolarizations may play a role in seizure recurrence and periodicity. PGB has been shown to increase spreading depolarization threshold; hence, we hypothesized that the magnitude of antiseizure effect from PGB is more pronounced in patients with cyclic versus noncyclic seizures in a critically ill cohort with recurrent seizures.

METHODS: We conducted a retrospective case series of adults admitted to two academic neurointensive care units between January 2017 and March 2019 who received PGB for treatment of seizures. Data collected included demographics, etiology of brain injury, antiseizure medications, and outcome. Continuous electroencephalogram recordings 48 hours before and after PGB administration were reviewed by electroencephalographers blinded to the administration of antiseizure medications to obtain granular data on electrographic seizure burden. Cyclic seizures were determined quantitatively (i.e., < 50% variation of interseizure intervals for at least 50% of consecutive seizures). Coprimary outcomes were decrease in hourly seizure burden in minutes and decrease in seizure frequency in the 48 hours after PGB initiation. We used nonparametric tests for comparison of seizure frequency and burden and segmented linear regression to assess PGB effect.

RESULTS: We included 16 patients; the median age was 69 years, 11 (68.7%) were women, three (18.8%) had undergone a neurosurgical procedure, and five (31%) had underlying epilepsy. All seizures had focal onset; ten patients (62.5%) had cyclic seizures. The median hourly seizure burden over the 48 hours prior to PGB initiation was 1.87 min/hour (interquartile range 1.49-8.53), and the median seizure frequency was 1.96 seizures/hour (interquartile range 1.06-3.41). In the 48 hours following PGB (median daily dose 300 mg, range 75-300 mg), the median number of seizures per hour was reduced by 0.80 seizures/hour (95% confidence interval 0.19-1.40), whereas the median hourly seizure burden decreased by 1.71 min/hour (95% confidence interval 0.38-3.04). When we compared patients with cyclic versus noncyclic seizures, there was a relative decrease in hourly seizure frequency (- 86.7% versus - 2%, p = 0.04) and hourly seizure burden (- 89% versus - 7.8%, p = 0.03) at 48 hours.

CONCLUSIONS: PGB was associated with a relative reduction in seizure burden in neurocritically ill patients with recurrent seizures, especially those with cyclic seizures, and may be considered in the therapeutic arsenal for refractory seizures. Whether this effect is mediated via modulation of spreading depolarization requires further study.

背景：普瑞巴林 (PGB) 是一种有效的局灶性癫痫辅助治疗药物，通过与电压门控钙通道的 alpha2-delta 亚基结合来减少兴奋性神经递质的释放。关于其在神经重症监护环境中的使用数据有限，包括周期性癫痫发作——一种几乎定期发生的复发性癫痫发作模式。尽管支持周期性癫痫发作的机制仍然难以捉摸，但与扩散去极化相关的扩散兴奋可能在癫痫发作的复发和周期性中起作用。PGB 已被证明可以增加扩散去极化阈值；因此，我们假设 PGB 的抗癫痫发作作用力度在反复发作的危重患者队列中的周期性与非周期性癫痫发作患者中更为明显。

方法： 我们对 2017 年 1 月至 2019 年 3 月期间入住两个学术神经重症监护病房且接受 PGB 治疗癫痫发作的成人进行了回顾性病例系列。收集的数据包括人口统计学、脑损伤病因、抗癫痫发作药物和结果。PGB 给药前后 48 小时的连续脑电图记录由对抗癫痫发作药物给药不知情的脑电图仪进行审查，以获得关于脑电图癫痫发作负担的详细数据。周期性癫痫发作是定量测定的（即，对于至少 50% 的连续癫痫发作，癫痫发作

间隔的变化 < 50%）。主要结果是在数分钟内减少每小时癫痫发作负担，并在 PGB 开始后 48 小时内减少癫痫发作频率。

结果： 我们纳入了 16 名患者；中位年龄为 69 岁，11 人 (68.7%) 为女性，3 人 (18.8%) 接受过神经外科手术，5 人 (31%) 患有潜在的癫痫。所有癫痫发作都有局灶性发作；10 名患者（62.5%）有周期性癫痫发作。在 PGB 开始前的 48 小时内，中位癫痫发作负担为 1.87 分钟/小时（四分位距 1.49-8.53），中位癫痫发作频率为 1.96 次/小时（四分位距 1.06-3.41）。在 PGB 后的 48 小时内（中位日剂量 300 毫克，范围 75-300 毫克），中位每小时癫痫发作次数减少了 0.80 次/小时（95% 置信区间 0.19-1.40），而中位每小时癫痫发作负担减少 1.71 分钟/小时（95% 置信区间 0.38-3.04）。当我们比较周期性与非周期性癫痫发作的患者时，

结论： PGB 与复发性癫痫发作的神经危重症患者的癫痫发作负担相对减轻有关，尤其是那些周期性癫痫发作的患者，并且可以考虑在难治性癫痫发作的治疗库中。这种效应是否通过扩散去极化的调制来介导需要进一步研究。

3. 卢非酰胺在日本癫痫患者中的监测：关注药物相互作用、耐受性和临床有效性

Therapeutic Drug Monitoring for Rufinamide in Japanese Patients With Epilepsy: Focus on Drug Interactions, Tolerability, and Clinical Effectiveness. *Ther Drug Monit. 2022 Aug 1;44(4):585-591. doi: 10.1097/FTD.0000000000000977.*

Yamamoto Y, Inoue Y, Usui N, Imai K, Kagawa Y, Takahashi Y.

BACKGROUND: The purposes of this study were to assess drug interactions between rufinamide and concomitant antiepileptic drugs (AEDs) and to identify the therapeutic window for rufinamide.

METHODS: Serum samples (n = 1531) were obtained from 178 patients (aged 2-57 years), and clinical records were retrospectively reviewed to evaluate the safety and efficacy of rufinamide (mean observation time, 1073 ± 846 days).

RESULTS: Rufinamide exhibited linear pharmacokinetics at doses of up to 60 mg/kg (range, 50-3200 mg/d). Concomitant use of the enzyme-inducing AEDs such as phenytoin, carbamazepine, and phenobarbital reduced rufinamide concentrations by 43.4%, 13.2%, and 30.3%, respectively. By contrast, concomitant use of valproate significantly elevated rufinamide concentrations. Clinical response was seen in 41 patients (23.0%), with a median therapeutic concentration (interquartile range) of 20.6 mcg/mL (13.3-27.0). There was no difference in the therapeutic concentrations between seizure types, but patients with tonic/atonic seizures tended to have higher rufinamide concentrations. During the study period, adverse events were reported in 64 patients (35.8%), including somnolence, gastrointestinal disorders, dizziness, and irritability/behavior disorders.

Conditional logistic regression analysis showed that patients administered a concentration greater than 20 mcg/mL had an 8.6-fold higher incidence of adverse events.

CONCLUSIONS: Therapeutic drug monitoring for rufinamide is clinically useful for predicting drug interactions between rufinamide and concomitant AEDs. When a patient has tonic/atonic seizures, careful titration is required for concentrations greater than 20 mcg/mL.

背景：本研究的目的是评估卢非酰胺和伴随的抗癫痫药物 (AED) 之间的药物相互作用，并确定卢非酰胺的治疗窗口。

方法：从 178 名患者（年龄 2-57 岁）中获取血清样本（n = 1531），并临床回顾性记录以评估卢非胺的安全性和有效性（平均观察时间，1073 ± 846 天）。

结果：卢非酰胺在高达 60 mg/kg（范围，50-3200 mg/d）的剂量下表现出线性药代动力学。同时使用苯妥英、卡马西平和苯巴比妥等酶诱导 AED 可将卢非酰胺浓度分别降低 43.4%、13.2% 和 30.3%。相比之下，同时使用丙戊酸盐会显着提高卢非酰胺的浓度。41 名患者 (23.0%) 出现临床疗效，中位治疗浓度（四分位距）为 20.6 mcg/mL (13.3-27.0)。癫痫发作类型之间的治疗浓度没有差异，但强直性/失张力性癫痫发作的患者往往具有较高的卢非酰胺浓度。在研究期间，64 名患者（35.8%）报告了不良事件，包括嗜睡、胃肠道疾病、头晕和易怒/行为障碍。

结论：卢非酰胺 治疗的药物监测在临床上可用于预测卢非酰胺 和同时给药的其他 AEDs 之间的药物相互作用。当患者出现强直/失张力发作时，浓度大于 20 mcg/mL 时需要仔细滴定。

4. 氯巴占在小儿人群中的有效性和耐受性：一项大队列多中心研究中的辅助治疗和单药治疗

The effectiveness and tolerability of clobazam in the pediatric population: Adjunctive therapy and monotherapy in a large-cohort multicenter study. *Epilepsy Res. 2022 Aug;184:106963. doi: 10.1016/j.eplepsyres.2022.106963.*

Kamaşak T, Serdaroğlu E, Yılmaz Ö, Kılıç BA, Polat BG, Erdoğan I, Yücel Şen AD, Özen N, Durgut BD, Yıldız N(, Özkan Kart P, Dilber B, Arslan EA, Şahin S, Topçu Y, Gencpinar P, Serin HM, Hız SA, Çarman KB, Dündar NO, Okuyaz Ç, Aydın K, Serdaroğlu A, Tekgül H, Cansu A.

Objective: To evaluate the effectiveness and tolerability of clobazam therapy in the pediatric population in terms of seizure semiology, epileptic syndromes, and etiological subgroups.

Methods: A retrospective cohort study was conducted consisting of 1710 epileptic children from eight centers in seven geographic regions of Turkey. The initial efficacy of clobazam therapy was evaluated after three months of treatment. The long-term effectiveness of the drug, overall seizure outcomes, and overall therapeutic outcomes were evaluated during 12 months of therapy.

Results: Analysis of initial efficacy after the first three months of clobazam therapy showed that 320 (18.7 %) patients were seizure-free, 683 (39.9 %) had > 50 % seizure reductions, and 297 (17.4 %) had < 50 % seizure reductions. A positive response (seizure-free and >50 % seizure reduction) was determined for focal-onset (62.3 %) seizures, epileptic spasms (61.5 %), and generalized onset seisures (57.4). The highest positive response rate among the epileptıc syndromes was for self-limited epilepsy with centrotemporal spikes (SeLECTS). The highest negative response rate was for developmental and/or epileptic encephalopathies (DEEs). Magnetic resonance imaging (MRI) revealed a structural etiological diagnosis in 25.8 % of the cohort. A higher positive response rate was observed at MRI in patients with sequelae lesions than in those with congenital lesions. The seizure recurrence rate was higher in the patient group with epilepsy wıth genetic and metabolic causes, in individuals with more than one seizure type, and in those using three or more antiseizure drugs.

Conclusions: This cohort study provides additional evidence that clobazam is an effective and well-tolerable drug with a high seizure-free rate (18.7 %), a significant seizure reduction rate (57.3 %), and with excellent overall therapeutic outcomes with a low seizure relapse rate and considerable reversible benefits in the pediatric population.

目的：从癫痫症状学、癫痫综合征和病因学亚组的角度评估氯巴占治疗在儿科人群中的有效性和耐受性

方法：对来自土耳其七个地理区域八个中心的 1710 名癫痫儿童进行回顾性队列研究。在三个月的治疗后，对氯巴占治疗的初始疗效进行评估。在 12 个月的治疗期间，评估药物的长期有效性、总体癫痫发作结果和总体治疗结果。

结果：氯巴占治疗后的前三个月的初步疗效分析显示，320 例（18.7%）患者无癫痫发作，683 例（39.9%）癫痫发作减少>50%，297 例（17.4%）癫痫发作减轻<50%。确定局灶性发作（62.3%）、癫痫痉挛（61.5%）和全面性发作（57.4%）的阳性反应（无发作，发作减少>50%）。癫痫综合征中阳性反应率最高的是具有中央-颞棘波的自限性癫痫（SeLECTS），发育性和/或癫痫性脑病（DEE）的阴性反应率最高。磁共振成像（MRI）显示 25.8%的队列中有结构性病因诊断，后遗症病变患者的 MRI 阳性反应率高于先天性病变患者。具有遗传和代谢原因的癫痫患者组、具有一种以上癫痫发作类型的个体以及使用三种或三种以上抗癫痫发作药物的患者的癫痫复发率较高。

结论：这项队列研究提供了额外的证据，证明氯巴占是一种有效且耐受性良好的药物，无癫痫发作率高（18.7%），显著减少癫痫发作率（57.3%），总体治疗效果良好，癫痫复发率低，在儿科人群中具有相当大的可逆益处。

5. 癫痫大鼠齿状回中左乙拉西坦对海马 CA1 突触可塑性及分子变化的差异效应

Differential effects of levetiracetam on hippocampal CA1 synaptic plasticity and molecular changes in the dentate gyrus in epileptic rats.*Neurochem Int. 2022 Sep;158:105378. doi: 10.1016/j.neuint.2022.105378. Epub 2022 Jun 24.*

Salaka RJ, Nair KP, Sasibhushana RB, Udayakumar D, Kutty BM, Srikumar BN, Shankaranarayana Rao BS.

Temporal lobe epilepsy (TLE) is the most common form of focal epilepsies. Pharmacological treatment with anti-seizure drugs (ASDs) remains the mainstay in epilepsy management. Levetiracetam (LEV) is a second-generation ASD with a novel SV2A protein target and is indicated for treating focal epilepsies. While there is considerable literature in acute models, its effect in chronic epilepsy is less clear. Particularly, its effects on neuronal excitability, synaptic plasticity, adult hippocampal neurogenesis, and histological changes in chronic epilepsy have not been evaluated thus far, which formed the basis of the present study. Six weeks post-lithium-pilocarpine-induced status epilepticus (SE), epileptic rats were injected with levetiracetam (54 mg/kg b.w. i.p.) once daily for two weeks. Following LEV treatment, Schaffer collateral - CA1 (CA3-CA1) synaptic plasticity and structural changes in hippocampal subregions CA3 and CA1 were evaluated. The number of doublecortin (DCX+) and reelin (RLN+) positive neurons was estimated. Further, mossy fiber sprouting was evaluated in DG by Timm staining, and splash test was performed to assess the anxiety-like behavior. Chronic epilepsy resulted in decreased basal synaptic transmission and increased paired-pulse facilitation without affecting post-tetanic potentiation and long-term potentiation. Moreover, chronic epilepsy decreased hippocampal subfields volume, adult hippocampal neurogenesis, and increased reelin expression and mossy fiber sprouting with increased anxiety-like behavior. LEV treatment restored basal synaptic transmission and paired-pulse facilitation ratio in CA3-CA1 synapses. LEV also restored the CA1 subfield volume in chronic epilepsy. LEV did not affect epilepsy-induced abnormal adult hippocampal neurogenesis, ectopic migration of newborn granule cells, mossy fiber sprouting in DG, and anxiety-like behavior. Our results indicate that in addition to reducing seizures, LEV has favorable effects on synaptic transmission and structural plasticity in chronic epilepsy. These findings add new dimensions to the use of LEV in chronic epilepsy and paves way for further research into its effects on cognition and affective behavior.

颞叶癫痫（TLE）是最常见的局灶性癫痫发作形式。抗癫痫发作药物（ASDs）的药物治疗方法仍然是癫痫管理的主要手段。左乙拉西坦是一种主要用于治疗局灶性癫痫发作的靶向 SV2A 蛋白的第二代抗癫痫发作药物。虽然在急性模型中有相当多的文献，但其对慢性癫痫的影响尚不清楚。尤其是其对慢性癫痫的神经元兴奋性、突触可塑

性、成年海马神经发生和组织学改变的影响尚未得到评估，这是本研究的基础。经过 6 周建立锂-匹罗卡品诱导的癫痫持续状态模型，向癫痫大鼠注射左乙拉西坦（54mg/kg b.w.i.p.），一天一次，共注射两周。LEV 治疗后，评估海马 CA3 和 CA1 亚区的突触可塑性和结构变化。计数双生素（DCX+）及络丝蛋白（RLN+）阳性的神经元数量。进一步用 Timm 染色评估 DG 的苔藓纤维出芽情况，飞溅试验评估焦虑样行为。慢性癫痫发作导致基线突触传递减少及成对脉冲易化的增加，且不影响强直后增强及长时程增强。此外，慢性癫痫降低了海马亚单位体积，成年海马神经发生，增加了络丝蛋白表达和苔藓纤维发芽，增加了焦虑样行为。LEV 治疗可恢复 CA3-CA1 突触的基线突触传递和成对脉冲易化率。LEV 还可恢复慢性癫痫模型 CA1 亚单位体积。LEV 不影响癫痫诱导的异常成年海马神经发生、新生颗粒细胞异位迁移、DG 中苔藓纤维发芽和焦虑样行为。我们的结果表明，除了减少癫痫发作外，LEV 对慢性癫痫的突触传递和结构可塑性有良好的影响。这些发现为 LEV 在慢性癫痫中的应用提供了新的维度，并为进一步研究其对认知和情感行为的影响铺平了道路。

药物检测

1. LC-MS/MS 法测定癫痫患者 TDM 中左乙拉西坦、拉莫三嗪和 10-羟卡西平的含量

LC-MS/MS quantification of levetiracetam, lamotrigine and 10-hydroxycarbazepine in TDM of epileptic patients. *Biomed Chromatogr. 2022 Aug;36(8):e5393. doi: 10.1002/bmc.5393. Epub 2022 May 18.*

Zhou S, Li R, Chen Z, Ren R, Wang X, Dai Q, Wen D, Guan Y, Zhang X, Tang S, Zhou L, Huang M.

BACKGROUND: To minimize drug-related toxicity and monitor dosing regimens, an ultra-sensitive, simple and high-throughput analytical method for therapeutic drug monitoring is required. A novel LC-MS/MS bioassay of levetiracetam, lamotrigine and 10-hydroxycarbazepine in human plasma was established. The analytes were separated on a Hypersil GOLD™ C18 column under a 2.5 min isocratic elution after one-step protein precipitation. MS detection was performed under electrospray ionization positive-mode fitted with selected reaction monitoring. The validated ranges were 0.1-20 μg/ml for LTG, 0.3-60 μg/ml for 10-hydroxycarbazepine and levetiracetam. The intra- and inter-batches of precision and accuracy was within ±15%. The novel method met all other criteria.

CONCLUSION: This method can be used to monitor drug concentrations and decision-making in epileptic patients.

背景：为了最大限度地减少药物毒性和监测给药方案，需要一种超灵敏、简单、高通量的分析方法来监测药物治疗。建立了一种新型的液相色谱-质谱联用法(LC-MS/MS)生物测定人血浆中左乙拉西坦、拉莫三嗪和 10-羟基卡西平。分析物经一步蛋白沉淀后，在 Hypersil GOLD ™ C18 柱上等度洗脱 2.5 min。质谱检测在电喷雾正离子模式下进行，并配合选定的反应监测。10-羟卡西平和左乙拉西坦的有效范围分别为 0.1-20μg/ml 和 0.3-6 0μg/ml。批内、批间精密度和准确度均在±15%以内。这种新方法符合所有其他标准。

结论：该方法可用于癫痫患者的血药浓度监测和决策。

2. 使用带丝网印刷碳电极的电化学传感器在未稀释的人类唾液中检测卡马西平的信号增强策略的比较

Comparison of signal enhancement strategies for carbamazepine detection in undiluted human saliva using an electrochemical sensor with stencil-printed carbon electrodes. *Anal Methods. 2022 Aug 2. doi: 10.1039/d2ay00926a.*

Wentland L, Downs C, Fu E.

Carbamazepine (CBZ), a drug prescribed to prevent seizures in people with epilepsy, has a narrow therapeutic range such that patients would greatly benefit from personalized drug dosage recommendations. Saliva is an excellent sample for personalized monitoring of CBZ levels because saliva CBZ concentration correlates with the free concentration of CBZ in blood, and can be collected non-invasively. CBZ level quantification using electrochemical detection has been demonstrated in a variety of electrode systems and samples, however, human saliva presents a particular challenge in terms of its complex composition that can result in signal interference via a high background current at the potentials of interest for CBZ detection. Previous demonstrations of electrochemical detection of CBZ in saliva have included rigorous pre-treatment of the sample using centrifugation and high levels of dilution, which is not compatible with lower-resource

field settings for patient monitoring of CBZ levels. In this work, we systematically investigate several strategies to improve the detection of CBZ in a background of undiluted human saliva using polymeric laminate-based devices with stencil-printed carbon electrodes; (i) adding the anionic surfactant sodium dodecyl sulfate to the saliva, (ii) filtering saliva to remove larger molecular weight species, (iii) plasma pretreatment of the device electrodes, and (iv) incubation of the sample on the electrodes. These methods enabled the quantification of therapeutically-relevant concentrations of CBZ in a background of human saliva without the need for saliva preprocessing like dilution.

卡马西平 (CBZ) 是一种用于预防癫痫患者癫痫发作的药物，其治疗范围较窄，因此患者将从个性化的药物剂量建议中受益匪浅。唾液是用于个性化监测 CBZ 水平的优秀样本，因为唾液 CBZ 浓度与血液中 CBZ 的游离浓度相关，并且可以无创收集。使用电化学检测的 CBZ 水平定量已在各种电极系统和样品中得到证实，然而，人类唾液的复杂成分是一个特殊的挑战，它可能通过 CBZ 检测所关注的电位的高背景电流导致信号干扰。以前对唾液中 CBZ 进行电化学检测的手段包括用离心法和高度稀释法对样品进行严格的预处理，这与用于患者监测 CBZ 水平的资源较低的现场设置不兼容。在这项工作中，我们系统地研究了几种策略，以改进在未稀释的人类唾液背景下使用带有丝网印刷碳电极的聚合物层压设备来检测 CBZ；(i) 将阴离子表面活性剂十二烷基硫酸钠添加到唾液中，(ii) 过滤唾液以去除较大分子量的物质，(iii) 对设备电极进行等离子体预处理，以及 (iv) 在电极上孵育样品。这些方法使治疗浓度的 CBZ 在人类唾液的背景中得到了量化，而不需要像稀释那样对唾液进行预处理。

大麻二酚

1. 大麻二酚和钠通道药理学：一般概述、机制以及临床意义

Cannabidiol and Sodium Channel Pharmacology: General Overview, Mechanism, and ClinicalImplications. *Neuroscientist. 2022 Aug;28 doi: 10.1177/10738584211017009.*

Ghovanloo MR, Ruben PC.

Voltage-gated sodium (Nav) channels initiate action potentials in excitable tissues. Altering these channels' function can lead to many pathophysiological conditions. Nav channels are composed of several functional and structural domains that could be targeted pharmacologically as potential therapeutic means against various neurological conditions. Mutations in Nav channels have been suggested to underlie various clinical syndromes in different tissues and in association with conditions ranging from epileptic to muscular problems. Treating those mutations that increase the excitability of Nav channels requires inhibitors that could effectively reduce channel firing. The main non-psychotropic constituent of the cannabis plant, cannabidiol (CBD), has recently gained interest as a viable compound to treat some of the conditions that are associated with Nav malfunctions. In this review, we discuss an overview of Nav channels followed by an in-depth description of the interactions of CBD and Nav channels. We conclude with some clinical implications of CBD use against Nav hyperexcitability based on a series of preclinical studies published to date, with a focus on Nav/CBD interactions.

电压门控钠（Nav）通道在可兴奋的组织中发起动作电位，改变这些通道的功能会导致许多病理生理状况。钠通道由几个功能区和结构域组成，这些功能区和结构域可以作为潜在的治疗手段对各种神经系统疾病进行药理定位。电压门控钠通道的的突变已被认为是不同组织的各种临床综合征的基础，并与从癫痫到肌肉问题的各种情况有关。治疗那些增加电压门控钠通道兴奋性的突变需要能够有效减少通道开放的抑制剂。大麻植物主要的非精神药物成分—大麻二酚（CBD），最近受到了人们的关注，作为一种活性化合物来治疗一些与 Nav 功能失常有关的疾病。在本综述中，我们讨论了电压门控钠通道的概况，然后深入描述了大麻二酚和电压门控钠通道的相互作用。最后，我们根据迄今发表的一系列临床前研究，提出了使用大麻二酚对抗 Nav 过度兴奋的一些临床意义，重点是 Nav/CBD 的相互作用。

2. 在大麻二酚辅助治疗条件下的非惊厥性癫痫持续状态

Non-convulsive status epilepticus in the setting of cannabidiol adjunctive therapy. *Epileptic Disord. 2022 Aug 1;24(4):1-6. doi: 10.1684/epd.2022.1435.*

Tanwir A, Szabó CÁ.

Anti-seizure medications (ASMs) can cause non-convulsive status epilepticus (NCSE), but account for less than 5% of all NCSE cases. We present a 63-year-old, right-handed male with a history of intractable focal epilepsy since age seven years old, whose bouts of NCSE were triggered by cannabidiol (CBD) adjunctive therapy. His most common seizure types included focal myoclonic or tonic seizures with vocalization, usually with awakening, which occurred on a monthly basis despite the combination of tiagabine, perampanel, levetiracetam, lacosamide and clonazepam. After CBD was initiated, he began to exhibit episodes of prolonged confusion, at times with myoclonic or tonic seizures. Increasing CBD doses led to more frequent and prolonged episodes. The confusional episodes occurred predominantly in the morning, with

spontaneous resolution by the afternoon. During one of these episodes, he was hospitalized, and NCSE was confirmed by video-EEG monitoring. CBD was withdrawn and the patient had no further episodes of NCSE. While CBD can cause NCSE, the medication interaction between CBD and tiagabine also needs to be considered

抗癫痫发作药物（ASMs）可以导致非惊厥性癫痫持续状态（NCSE），但只占所有非惊厥性癫痫持续状态病例的不到 5%。我们提出一名 63 岁的右利手男患，从 7 岁起有难治性局灶性癫痫病史，他的 NCSE 发作是由大麻二酚（CBD）的辅助治疗诱发的。他通常在清醒时发作，其最普遍的发作类型包括局灶性肌阵挛发作和伴发声的强直发作，尽管联用了硫加宾、吡仑帕奈、左乙拉西坦、拉考沙胺及氯硝西泮，但每月均有发作。加用 CBD 后，他开始出现长时间的意识模糊发作，间断的肌阵挛发作和强直发作。增加 CBD 剂量后出现更加频繁及持续时间的发作。意识模糊的发作主要发生在早上，直到下午就会自发缓解。其中一次发作期间，他正在住院，并通过视频脑电图监测证实了 NCSE。当 CBD 被撤除后，患者再无 NCSE 发作。除了 CBD 引起 NCSE 的同时，CBD 与硫加宾之间的药物相互作用也需要考虑。

吡仑帕奈

1. 日本癫痫青少年吡仑帕奈有效性的真实评估

Real-world evaluation of perampanel effectiveness in Japanese adolescents with epilepsy. *Epileptic Disord. 2022 Oct 1;24(5):1-9. doi: 10.1684/epd.2022.1454.*

Inoue Y, Sumitomo K, Matsutani K, Ishii M

OBJECTIVE: Real-world data from adolescents treated with perampanel in a routine clinical setting are lacking in Japan. We evaluated the safety and efficacy of perampanel for adolescent patients (aged 12-17 years) with drug-resistant, refractory epilepsy in real-world settings.

METHODS: This was a large-scale, prospective, observational post-marketing study, with a 104-week observation period. Safety was assessed by monitoring adverse effects (adverse drug reactions). For efficacy assessments, seizure frequency was compared between the four weeks immediately prior to the last observation and the four weeks before the commencement of perampanel.

RESULTS: In total, 519 patients were enrolled; 505 and 484 patients were included in the safety and efficacy analysis sets, respectively. The mean age was 14.4 years. The mean daily dose of perampanel was 4.4 mg/day. The main reasons for discontinuation at 104 weeks were adverse events (48.4%) and inadequate efficacy (46.8%). The retention rate at 104 weeks was 50.5%. Adverse effect and severe adverse effect incidences were 42.2% and 1.8%, respectively. The most common adverse effects were somnolence (13.5%), irritability (8.5%), dizziness (5.1%), and agitation (4.8%). There were significant differences in the occurrence of adverse effects between the initial titration interval of <2 weeks and 2-4 weeks (odds ratio=0.441, p=0.029) and 4-8 weeks (odds ratio=0.462, p=0.027). The median percent change in seizure frequency at the last observation carried forward was −50.0 for focal aware seizures with motor signs, −73.3 for focal aware seizures without motor signs, −28.6 for focal impaired awareness seizures, −62.6 for focal to bilateral tonic-clonic seizures, and −20.0 for generalized tonic-clonic seizures.

SIGNIFICANCE: In adolescent patients, perampanel was well tolerated and efficacious in reducing seizure frequency. No unexpected safety issues were observed, and slow titration may reduce the incidence of adverse effects.

目的：日本缺乏常规临床环境中接受吡仑帕奈治疗的青少年的真实数据。我们评估了吡仑帕奈对青少年患者（12-17 岁）在真实世界中患有耐药性难治性癫痫的安全性和有效性。方法：这是一项大规模、前瞻性的观察性上市后研究，观察期为 104 周。通过监测不良反应（药物不良反应）来评估安全性。为了评估疗效，比较了最后一次观察前四周和吡仑帕奈开始前四周的缉获的发作频率。

结果：共有 519 名患者注册；505 名和 484 名患者分别被纳入安全性和有效性分析集，人均年龄为 14.4 岁。吡仑帕奈日均剂量为 4.4 毫克/天。104 周停用的主要原因是不良事件（48.4%）和疗效不足（46.8%）。104 周的保留率为 50.5%。不良反应和严重不良反应的发生率分别为 42.2%和 1.8%。最常见的副作用是嗜睡（13.5%）、易怒（8.5%）、头晕（5.1%）和躁动（4.8%）。初始滴定间隔<2 周至 2-4 周（比值比为 0.441，p=0.029）和 4-8 周（比值比=0.462，p=0.027）之间不良反应的发生率存在显著差异。在最后一次观察时癫痫发作频率的中位数百分比变化为:具有运动迹象的局灶知觉性癫痫发作为-50.0，没有运动迹象

的局灶知觉性癫痫发作为-73.3，局灶性意识障碍性癫痫发作为-28.6，局灶性到双侧强直性癫痫发作为-62.6，全面性强直性癫痫发作为-20.0。

意义：在青少年患者中，耐受良好，在降低癫痫发作频率方面有效。没有观察到意想不到的安全问题，缓慢滴定可能会减少不利影响的发生率。

2. 吡仑帕奈在临床实践中用于治疗肌阵挛性癫痫发作：来自 PERMIT 研究的证据

Perampanel for the treatment of patients with myoclonic seizures in clinical practice: Evidence from the PERMIT study.

Seizure. 2022 Aug;100:56-66. doi: 10.1016/j.seizure.2022.06.008. Epub 2022 Jun 15.

D'Souza W, Alsaadi T, Montoya J, Carreño M, Di Bonaventura C, Mohanraj R, Yamamoto T, McMurray R, Shastri O, Villanueva V; PERMIT study group.

PURPOSE: To investigate the effectiveness, safety and tolerability of perampanel (PER) in treating myoclonic seizures in clinical practice, using data from the PERaMpanel pooled analysIs of effecTiveness and tolerability (PERMIT) study.

METHODS: PERMIT was a pooled analysis of 44 real-world studies from 17 countries, in which patients with focal and generalised epilepsy were treated with PER. This post-hoc analysis included patients with myoclonic seizures at baseline. Retention and effectiveness were assessed after 3, 6, and 12 months; effectiveness was additionally assessed at the last visit (last observation carried forward). Effectiveness assessments included responder rate (≥50% seizure frequency reduction from baseline) and seizure freedom rate (no seizures since at least the prior visit). Safety and tolerability were assessed by evaluating adverse events (AEs) and discontinuation due to AEs.

RESULTS: 156 patients had myoclonic seizures (59.0% female; mean age, 32.1 years; idiopathic generalised epilepsy, 89.1%; Juvenile Myoclonic Epilepsy, 63.1%; monthly median myoclonic seizure frequency [interquartile range], 1.7 [1.0-10.0]; mean [standard deviation] prior antiseizure medications, 2.9 [2.6]). Retention was assessed for 133 patients (mean time, 12.1 months), effectiveness for 142, and safety/tolerability for 156. Responder and seizure freedom rates were, respectively, 89.5% and 68.8% at 12 months, and 85.9% and 63.4% at the last visit. Incidence of AEs was 46.8%, the most frequent being dizziness/vertigo (19.2%), irritability (18.6%) and somnolence (9.6%). AEs led to discontinuation of 14.0% of patients over 12 months.

CONCLUSION: PER was associated with reduction in myoclonic seizure frequency in patients with myoclonic seizures treated in everyday clinical practice.

目的：使用吡仑帕奈有效性和耐受性汇总分析 (PERMIT) 研究的数据，研究(PER) 在临床实践中治疗肌阵挛性癫痫发作的有效性、安全性和耐受性。

方法：PERMIT 是对来自 17 个国家的 44 项真实世界研究的汇总分析，其中局灶性和全身性癫痫患者接受了 PER 治疗。这项事后分析包括基线时肌阵挛发作的患者。在 3、6 和 12 个月后评估保留率和有效性；在最后一次访问时额外评估了有效性（末次观察推进法）。有效性评估包括反应率（癫痫发作频率从基线降低≥50%）和癫痫无发作率（至少自上次访问以来没有癫痫发作）。通过评估不良事件 (AE) 和因 AE 引起的停药来评估安全性和耐受性。

结果：156 名患者出现肌阵挛发作（59.0% 女性；平均年龄 32.1 岁；特发性全身性癫痫，89.1%；青少年肌阵挛性癫痫，63.1%；每月平均肌阵挛发作频率 [四分位距]，1.7 [1.0-10.0]；平均 [标准偏差] 先前的抗癫痫药物，2.9 [2.6]）。评估了 133 名患者的保留时间（平均时间 12.1 个月）、142 名患者的有效性和 156 名患者的安全性/耐受性。12 个月时的应答率和无癫痫发作率分别为 89.5% 和 68.8%，最后一次访问时为 85.9% 和 63.4%。AE 的发生率为 46.8%，最常见的是头晕/眩晕 (19.2%)、易怒 (18.6%) 和嗜睡 (9.6%)。AE 导致 14.0% 的患者在 12 个月内停药。

结论：在日常临床实践中，PER 与接受治疗的肌阵挛发作患者的肌阵挛发作频率降低有关。

3. 吡仑帕奈辅助治疗等待癫痫手术的患有耐药性癫痫儿童和青少年：泰国的一项多中心观察研究

Perampanel as adjunctive therapy in drug resistant epilepsy in adolescents and children waiting for epilepsy surgery: A multicenter observational study in Thailand. *Seizure. 2022 Aug;100:103-108. doi: 10.1016/j.seizure.2022.06.015. Epub 2022 Jun 27.*

Suwanpakdee P, Saksritavee B, Likasitthananon N, Simasathien T, Deesudchit T, Khongkhatithum C, Viravan S, Nabangchang C.

PURPOSE: To evaluate the effectiveness and tolerability of perampanel (PER) in real-world settings in patients between 1 month and 18 years of age with drug resistant epilepsy (DRE) waiting for epilepsy surgery.

METHODS: In this multicenter study, patients between 1 month and 18 years of age with DRE treated with PER between January 2020 and June 2021 were selected. The study outcome was effectiveness of PER treatment reported as reduction in seizure frequency and seizure freedom rate. Effectiveness was assessed at 30, 60, 90, 120, 150 and 180 days after initiation of PER. Tolerability profiles were reported as adverse events according to the observations of the patients' family members and physician.

RESULTS: Eighty-five patients treated with PER were included in the study. The mean initial dose and mean maximum dose of adjunctive PER was 2 mg/day and 5.8mg/day, respectively. The mean seizure frequency (rate/week) was 41.3, 25.4,18.9, 14.3, 11.2, 11.1 and 8.9 seizures at baseline, 30, 60, 90, 120, 150 and 180 days, respectively; the reduction in the mean seizure frequency at all timepoints was significant compared at the baseline ($p<0.001$). At 180 days, ≥75% seizure reduction was seen in 64.9% (37/57) of the patients and seizure freedom was achieved in 36.8% (21/57). Drowsiness, ataxia, and behavioral changes were the common adverse events observed, and these improved after the dose of PER was reduced. No discontinuation of PER was required due to side effects or intolerance.

CONCLUSION: In real-world settings, PER is well tolerated and effective in seizure control in pediatric and adolescent patients with DRE.

目的：评估在真实世界中，1 个月至 18 岁等待癫痫手术的耐药性癫痫（DRE）患者中，吡仑帕奈（PER）的有效性和耐受性。

方法：在这项多中心研究中，选择了 2020 年 1 月至 2021 年 6 月期间接受 PER 治疗的 1 个月至 18 岁的 DRE 患者。研究结果是 PER 在减少癫痫发作频率和无癫痫发作率方面的有效性，其有效性评估在开始用药后 30，60、90、120、150 和 180 天，耐受性报告为家庭成员和医生观察到的不良事件。

结果：85 名接受 PER 治疗的患者被纳入研究，其平均初始剂量和平均最大剂量分别为 2mg/天和 5.8 毫克/天。在基线水平,使用后 30，60、90、120、150 和 180 天，平均癫痫发作频率分别为（率/周）41.3、25.4、18.9、14.3、11.2、11.1 和 8.9 次癫痫发作，在所有时间点，与基线水平相比，平均癫痫发作频率显著降低（$p<0.001$）。在 180 天时，在 64.9%(37/57)的患者中，其癫痫发作减少≥75%，36.8%(21/57)的患者获得了无癫痫发作。嗜睡、共济失调和行为改变是观察到的常见不良事件，并且这些在减少 PER 剂量后得到改善，由于副作用或不耐受，不需要停止使用 PER。

结论：在现实环境中，PER 耐受性良好，且有效控制儿童和青少年中耐药性癫痫的癫痫发作。

4. 吡仑帕奈治疗肌阵挛癫痫发作及症状性肌阵挛疗效的系统性综述

A systematic review of the efficacy of perampanel as treatment for myoclonic seizures and symptomatic myoclonus.

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Epileptic myoclonus or myoclonic seizures can occur in idiopathic generalized epilepsy (IGE) and progressive myoclonus epilepsy (PME). However, symptomatic myoclonus which is stimulus-sensitive and provoked by movement is typically seen in PME and Lance-Adams syndrome. Symptomatic myoclonus is not always associated with epileptiform discharges on the electroencephalogram. Therapeutic interventions such as anti-seizure medications (ASMs), the ketogenic diet and vagus nerve stimulation are not always effective. There is emerging evidence

that perampanel (PER), an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, may be effective for the treatment of myoclonic seizures and symptomatic myoclonus. We performed a systematic review of the literature to assess the efficacy of PER as treatment for myoclonic seizures and symptomatic myoclonus. Twenty-seven studies with a total sample size of 260 patients were included. The efficacy of PER was analysed separately for myoclonic seizures and symptomatic myoclonus. In the group with myoclonic seizures, 50% responder, 75% responder and seizure freedom rates were reported as 74.3% (101/ 136), 60.3% (82/136) and 57.4% (78/136), respectively, with a follow-up duration of 6-12 months. However, in one post-hoc analysis of data from patients with IGE, the efficacy of PER as treatment for myoclonic seizures during the double-blind phase showed no significant difference compared to placebo. The efficacy of PER for symptomatic myoclonus was reported in a total of 119 patients. Four studies (n=88 patients) reported the efficacy of PER as a decrease in myoclonus score/scale. In the remaining 31 patients, symptomatic myoclonus resolved in three patients, decreased in 21 patients and seven patients showed no improvement. We also analysed the number of patients who were already on levetiracetam (LEV) or valproic acid (VPA) at the time of PER initiation; these data were available for 153 patients. Of these, 56.8% were on LEV and 75.1% were on VPA when PER was initiated. This systematic review suggests that PER maybe effective as treatment for drug-resistant myoclonic seizures and symptomatic myoclonus. It may also be effective in patients who have already failed to respond to LEV and VPA. These findings are preliminary yet encouraging. This study has several limitations, particularly given the scarcity of high-quality randomized controlled trials and marked heterogeneity regarding the type and results of the studies. Hence, the findings of this review should be viewed with considerable reservation.

痫性肌阵挛或肌阵挛性发作可发生在特发性全面性癫痫（IGE）和进行性肌阵挛性癫痫(PME)中。然而，症状性肌阵挛是 PME 及 Lance-Adams 综合征中的典型表现，对刺激敏感及由运动诱发。症状性肌阵挛在脑电图上并不总是与癫痫样放电相关。治疗干预如抗癫痫发作药物（ASMs）、生酮饮食和迷走神经刺激并不总是有效。最新证据表明，吡仑帕奈作为一种α-氨基-3 羟基-5-甲基-4-异噁唑丙酸（AMPA）受体拮抗剂可能对治疗肌阵挛性发作及症状性肌阵挛有效。我们对相关文献进行了系统回顾，以评估 PER 治疗肌阵挛发作和症状性肌阵挛的疗效。共纳入 27 项研究，总样本量 260 名患者。分别评估 PER 对肌阵挛性发作及症状性肌阵挛的疗效。在 6-12 个月的随访期中，50%应答者，75%应答者及癫痫发作完全控制的占比分别为 74.3% (101/ 136), 60.3% (82/136) 及 57.4% (78/136)。然而，在一项全面性癫痫患者的随机双盲因果分析中，与对照组相比 PER 对于肌阵挛性发作的疗效并无显著性差异。共计在 119 名患者中进行了 PER 对于症状性肌阵挛发作的疗效分析。4 项研究（n=88 名患者）表明 PER 的疗效可以减少肌阵挛评分/计分。在其余的 31 名患者中，3 名患者的症状性肌阵挛发作得到完全缓解，21 名患者发作减少，7 名患者的发作无改善。我们还分析了在启动 PER 治疗时已经在使用左乙拉西坦或丙戊酸治疗的患者数量；这些数据的患者数量为 153 名。其中，在启动 PER 治疗时 56.8%患者正在服用左乙拉西坦，75.1%正在服用丙戊酸。这项系统性综述表明 PER 对于治疗耐药性肌阵挛性发作及全面性肌阵挛发作有效。且对于使用左乙拉西坦及丙戊酸治疗无效的患者有效。这些初步发现是令人鼓舞的。这项研究有几个局限性，特别是考虑到缺乏高质量的随机对照试验以及研究类型和结果的显著异质性。因此，对这项综述的结果应当持保留态度。