癫痫药物时讯

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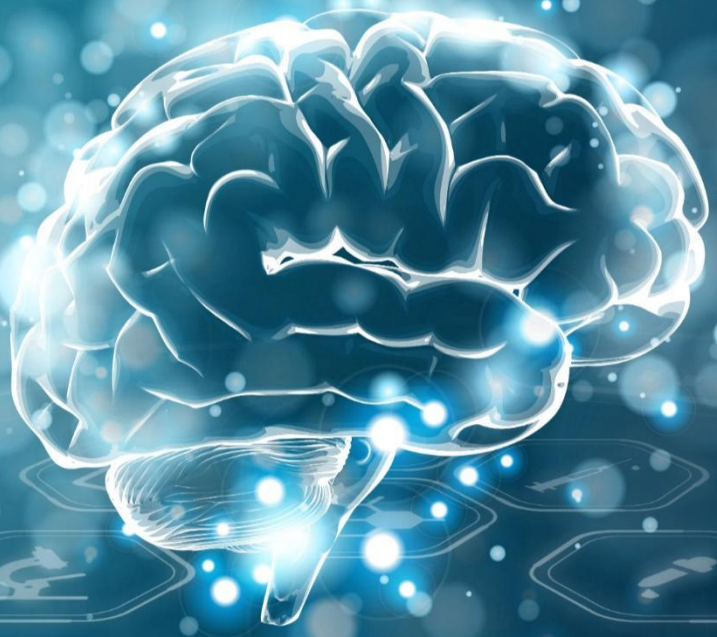

中国抗癫痫协会药物治疗专业委员会
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目录 1-3

药物

大麻二酚

1.大麻二酚去核：PPARγ 的作用

Cannabidiol goes nuclear： The role of PPARγ

Khosropoor S, Alavi MS, Etemad L, Roohbakhsh A. Cannabidiol goes nuclear： The role of PPARγ. Phytomedicine. 2023 Jun;114：154771. doi： 10.1016/j.phymed.2023.154771. Epub 2023 Mar 15. PMID： 36965374.

Abstract

Background：Cannabidiol (CBD) is one of the main phytocannabinoids found in Cannabis sativa. In contrast to Δ9-tetrahydrocannabinol, it has a low affinity for cannabinoid receptors CB1 and CB2, thereby it does not induce significant psychoactive effects. However, CBD may interact with other receptors, including peroxisome proliferator-activated receptor gamma (PPARγ). CBD is a PPARγ agonist and changes its expression. There is considerable evidence that CBD's effects are mediated by its interaction with PPARγ. So, we reviewed studies related to the interaction of CBD and PPARγ.

Methods：In this comprehensive literature review, the term 'cannabidiol' was used in combination with the following keywords including 'PPARγ', 'Alzheimer's disease', 'Parkinson's disease', 'seizure', 'multiple sclerosis', 'immune system', 'cardiovascular system', 'cancer', and 'adipogenesis'. PubMed, Web of Science, and Google Scholar were searched until December 20, 2022. A total of 78 articles were used for the reviewing process.

Results：CBD, via activation of PPARγ, promotes significant pharmacological effects. The present review shows that the effects of CBD on Alzheimer's disease and memory, Parkinson's disease and movement disorders, multiple sclerosis, anxiety and depression, cardiovascular system, immune system, cancer, and adipogenesis are mediated, at least in part, via PPARγ.

Conclusion：CBD not only activates PPARγ but also affects its expression in the body. It was suggested that the late effects of CBD are mediated via PPARγ activation. We suggested that CBD's chemical structure is a good backbone for developing new dual agonists. Combining it with other chemicals enhances their biological effectiveness while reducing their dosage. The present study indicated that PPARγ is a key target for CBD, and its activation by CBD should be considered in all future studies.

背景：大麻二酚(CBD)是大麻中发现的主要植物大麻素之一。与 δ9-四氢大麻酚相比，它对大麻素受体 CB1 和 CB2 的亲和力较低，因此不会诱发明显的精神作用。然而，CBD 可能与其他受体相互作用，包括过氧化物酶体增殖物激活受体 γ(PPARγ)。CBD 是 PPARγ 激动剂并改变其表达。大量证据表明 CBD 的作用是通过与 PPARγ 的相互作用来介导的。因此，我们对 CBD 和 PPARγ 相互作用的相关研究进行了综述。

方法：在这篇综合文献综述中，术语“大麻二酚”与下列关键词结合使用，包括“PPARγ”、“阿尔茨海默病”、“帕金森病”、“癫痫发作”、“多发性硬化症”、“免疫系统”、“心血管系统”、“癌症”和“脂肪生成”。在 PubMed、Web of Science 和谷歌学术搜索到 2022 年 12 月 20 日。共有 78 篇文章用于综述过程。

结果：CBD 通过激活 PPARγ 产生显著的药理作用。目前的综述表明，CBD 对阿尔茨海默病和记忆、帕金森病和运动障碍、多发性硬化、焦虑和抑郁、心血管系统、免疫系统、癌症和脂肪生成的影响至少部分是通过 PPARγ 介导的。

结论：CBD 不仅激活 PPARγ，而且影响其在体内的表达。有人认为 CBD 的晚期效应是通过 PPARγ 激活介导的。我们认为 CBD 的化学结构是开发新的双重激动剂的良好基础。将它与其他化学物质结合在一起，可以增强它们的生物有效性，同时减少它们的用量。目前的研究表明 PPARγ 是 CBD 的一个关键靶点，在所有未来的研究中都应考虑 PPARγ 被 CBD 激活。

2.大麻二酚治疗伴肌阵挛-失张力发作的儿童难治性癫痫

Cannabidiol in children with treatment-resistant epilepsy with myoclonic-atonic seizures

Caraballo RH, Reyes Valenzuela G, Fortini S, Espeche A, Gamboni B, Silva W, Semprino M, Fasulo L, Chacón S, Gallo A, Galicchio S, Cachia P. Cannabidiol in children with treatment-resistant epilepsy with myoclonic-atonic seizures. Epilepsy Behav. 2023 Jun;143：109245. doi： 10.1016/j.yebeh.2023.109245. Epub 2023 May 12. PMID： 37182500.

Abstract

Purpose： This multicenter study aimed to evaluate the efficacy and tolerability of add-on cannabidiol (CBD) in treatment-resistant patients with epilepsy with myoclonic-atonic seizures (EMAtS) (n = 22) and Sturge Weber syndrome (SWS) with myoclonic-atonic seizures (n = 4).

Methods：Patients who met the diagnostic criteria of treatment-resistant EMAtS or SWS with myoclonic-atonic seizures were included. Cannabidiol was added in doses ranging from 8 to 40 mg/kg/day. Efficacy was assessed by comparing seizure frequency before and after initiating CBD therapy. Neurologic examinations, brain magnetic resonance imaging, repeated prolonged electroencephalography (EEG) and/or video-EEG recordings, and neurometabolic studies were performed in all patients, and genetic investigations in 15.

Results：After a mean follow-up of 19 months, 15/26 patients (57.7%) who received add-on CBD had a >50% seizure decrease; three (11.5%) became seizure-free. The remaining 11 patients (42.3%) had a 25-50% seizure reduction. Drop attacks, including myoclonic-atonic seizures and generalized tonic-clonic seizures, as well as atypical absences and nonconvulsive status epilepticus responded well to CBD. In SWS patients, focal motor seizures without consciousness impairment and focal non-motor seizures with consciousness impairment were recognized in two each; in three a 30% reduction of focal seizures was observed. Side effects were mild and did not lead to CBD discontinuation.

Conclusion：This study evaluating the use of add-on CBD in children with EMAtS or SWS with myoclonic-atonic seizures found that 15/26 (57.7%) had a >50% seizure reduction with good tolerability; three (11.5%) became seizure-free.

目的：本项多中心研究旨在评估添加大麻二酚(CBD)对伴有肌阵挛-失张力发作(EMAtS) (n = 22)的难治性癫痫和 Sturge Weber 综合征(SWS)(n = 4)的疗效和耐受性。

方法：纳入符合难治性 EMAtS 或 SWS 伴肌阵挛-失张力发作诊断标准的患者。大麻二酚的添加剂量为 8 至 40mg/kg/d。通过比较开始 CBD 治疗前后的癫痫发作频率来评估疗效。对所有患者进行了神经系统检查、脑磁共振成像、多次长程脑电图和/或视频脑电图记录以及神经代谢研究，并对 15 名患者进行了基因检测。

结果：经过平均 19 个月的随访，接受添加 CBD 治疗的 26 例患者中有 15 例(57.7%)癫痫发作减少了 50%以上；3 例(11.5%)无癫痫发作。其余 11 名患者(42.3%)的癫痫发作减少了 25-50%。跌倒发作，包括肌阵挛-失张力发作和全身强直-阵挛发作，以及非典型失神发作和非惊厥性癫痫持续状态对 CBD 反应良好。在 SWS 患者中，无知觉障碍的局灶性运动性发作和伴知觉障碍的局灶性非运动性发作各有 2 例；在三个病例中，观察到局灶性癫痫发作减少了 30%。副作用轻微，不会导致 CBD 停药。

结论：本研究评估了在患有肌阵挛-失张力发作的 EMAtS 或 SWS 儿童中使用添加 CBD 的情况，发现 15/26 (57.7%)的癫痫发作减少了 50%以上，且耐受性良好；3 例(11.5%)无癫痫发作。

3.大麻二酚用于发热性感染相关癫痫综合征(FIRES)急性期

Cannabidiol in the acute phase of febrile infection-related epilepsy syndrome (FIRES)

Fetta A, Crotti E, Campostrini E, Bergonzini L, Cesaroni CA, Conti F, Di Pisa V, Gentile V, Mondardini MC, Vezzoli C, Giordano L, Cordelli DM. Cannabidiol in the acute phase of febrile infection-related epilepsy syndrome (FIRES). Epilepsia Open. 2023 Jun;8(2)：685-691. doi： 10.1002/epi4.12740. Epub 2023 Apr 24. PMID： 37042946; PMCID：PMC10235155.

Febrile infection-related epilepsy syndrome (FIRES) is a prolonged refractory status epilepticus (SE) that develops among healthy individuals after a febrile infection. FIRES treatment is challenging due to its poor response to antiseizure medications (ASMs) and anesthetic drugs. The use of cannabidiol (CBD) as an adjunctive treatment has been suggested, albeit data about its role in the acute phase is lacking. This report describes the use of purified CBD in the acute phase of two pediatric cases of FIRES and their long-term outcome. Both children were treated with several ASMs, immunomodulators, anesthetics, and nonpharmacological treatment (ketogenic diet). CBD was administered, as an adjunctive treatment, through nasogastric tube about 30 days after onset. SE resolved within 3 days of reaching the target dose and both were seizure-free for 1 year after. Although it is difficult to define the extent to which each previous therapy contributed to recovery, in both cases CBD therapy was a turning point, reinforcing its potential role as add-on treatment in the acute phase of FIRES.

发热性感染相关癫痫综合征(FIRES)是健康个体在发热性感染后出现的一种长期难治性癫痫持续状态(SE)。由于对抗癫痫发作药物(ASMs)和麻醉药物的反应差，FIRES 治疗具有挑战性。有人建议使用大麻二酚(CBD)作为辅助

治疗，尽管还缺乏关于其在急性期作用的数据。本报告描述了在两例儿科 FIRES 的急性期使用纯化 CBD 及其长期结果。两个孩子都接受了一些 ASMs、免疫调节剂、麻醉剂和非药物治疗(生酮饮食)。CBD 作为一种辅助治疗，在发病后 30 天左右通过鼻胃管给药。SE 在达到目标剂量的 3 天内缓解，且两位患者在此后的 1 年内均无癫痫发作。虽然很难确定每种先前治疗对康复的贡献程度，但在这两个病例中，CBD 治疗都是一个转折点，加强了其作为 FIRES 急性期添加治疗的潜在作用。

4.大麻二酚治疗各种癫痫亚型的真实世界数据：一项回顾性、多中心研究

Real-world data on cannabidiol treatment of various epilepsy subtypes： A retrospective, multicenter study

Kühne F, Becker LL, Bast T, Bertsche A, Borggraefe I, Boßelmann CM, Fahrbach J, Hertzberg C, Herz NA, Hirsch M, Holtkamp M, Janello C, Kluger GJ, Kurlemann G, Lerche H, Makridis KL, von Podewils F, Pringsheim M, Schubert-Bast S, Schulz J, Schulze-Bonhage A, Steinbart D, Steinhoff BJ, Strzelczyk A, Syrbe S, De Vries H, Wagner C, Wagner J, Wilken B, Prager C, Klotz KA, Kaindl AM. Real-world data on cannabidiol treatment of various epilepsy subtypes： A retrospective, multicenter study. Epilepsia Open. 2023 Jun;8(2)：360-370. doi： 10.1002/epi4.12699. Epub 2023 Feb 6. PMID： 36693811; PMCID： PMC10235575.

Objective：Cannabidiol (CBD) is approved for treatment of Dravet syndrome (DS), Lennox-Gastaut syndrome (LGS), and tuberous sclerosis complex (TSC). Several studies suggest antiseizure effects also beyond these three epilepsy syndromes.

Methods：In a retrospective multicenter study, we analyzed the efficacy and tolerability of CBD in patients with epilepsy at 16 epilepsy centers.

Results：The study cohort comprised 311 patients with epilepsy with a median age of 11.3 (0-72) years (235 children and adolescents, 76 adults). Therapy with CBD was off-label in 91.3% of cases due to age, epilepsy subtype, lack of adjunct therapy with clobazam, and/or higher dose applied. CBD titration regimens were slower than recommended, with good tolerability of higher doses particularly in children. Of all patients, 36.9% experienced a reduction in seizure frequency of >50%, independent of their epilepsy subtype or clobazam co-medication. The median observation period was 15.8 months. About one third of all patients discontinued therapy within the observation period due to adverse effects or lack of efficacy. Adverse effects were reported frequently (46.9%).

Significance：Our study highlights that CBD has an antiseizure effect comparable to other antiseizure medications with a positive safety profile independent of the epilepsy subtype. Comedication with clobazam was not associated with a better outcome. Higher doses to achieve seizure frequency reduction were safe, particularly in children. These findings call for further trials for an extended approval of CBD for other epilepsy subtypes and for children <2 years of age.

目的：大麻二酚(CBD)被批准用于治疗 Dravet 综合征(DS)、Lennox-Gastaut 综合征(LGS)和结节性硬化症(TSC)。几项研究表明，其抗癫痫作用已超出了这三种癫痫综合征。

方法：在一项回顾性多中心研究中，我们分析了 CBD 在 16 个癫痫中心的癫痫患者中的疗效和耐受性。

结果：研究队列包括 311 名癫痫患者，中位年龄为 11.3 (0-72)岁(235 名儿童和青少年，76 名成人)。由于年龄、癫痫亚型、缺少氯巴占联合治疗和/或应用剂量较高，在 91.3%的病例中 CBD 治疗是开放标签的。CBD 滴定方案比推荐的慢，高剂量组的耐受性良好，特别是在儿童中。在所有患者中，36.9%患者的癫痫发作频率降低了 50%以上，这与他们的癫痫亚型或合用氯巴占无关。中位观察期为 15.8 个月。约三分之一的患者在观察期内由于不良反应或缺乏疗效而停止治疗。不良反应较多(46.9%)。

意义：我们的研究强调 CBD 具有与其他抗癫痫药物相当的抗癫痫作用，其安全性与癫痫亚型无关。联用氯巴占与更好的结果无关。使用更高的剂量以达到减少癫痫发作频率是安全的，特别是对儿童。需要进一步试验来扩展批准 CBD 用于其他癫痫亚型和 2 岁以下儿童。

5.外周注射大麻二酚减轻小鼠神经病性疼痛：5-HT1A 和 TRPV1 受体的作用

Peripherally injected canabidiol reduces neuropathic pain in mice： Role of the 5-HT1A and TRPV1 receptors

Aguiar DD, da Costa Oliveira C, Fonseca FCS, de Almeida DL, Campos Pereira WV, Guimarães FS, Perez AC, Duarte IDG, Romero TRL. Peripherally injected canabidiol reduces neuropathic pain in mice： Role of the 5-HT1A and TRPV1 receptors. Biochem Biophys Res Commun. 2023 Jun 11;660：58-64. doi： 10.1016/j.bbrc.2023.04.022. Epub 2023 Apr 11. PMID： 37068389.

Cannabidiol (CBD) is the most abundant non-psychoactive component found in plants of the genus Cannabis. Its analgesic effect for the treatment of neuropathy has been widely studied. However, little is known about its effects in the acute treatment when Cannabidiol is administered peripherally. Because of that, this research was aimed to evaluate the antinociceptive effects of the CBD when administered peripherally for the treatment of acute neuropathic pain and check the involvement of the 5-HT1A and the TRPV1 receptors in this event. Neuropathic pain was induced with the constriction of the sciatic nerve while the nociceptive threshold was measured using the pressure test of the mouse paw. The technique used proved to be efficient to induce neuropathy, and the CBD (5, 10 and 30 μg/paw) induced the antinociception in a dosage-dependent manner. The dosage used that induced a more potent effect (30 μg/paw), did not induce a systemic response, as demonstrated by both the motor coordination assessment test (RotaRod) and the antinociceptive effect restricted to the paw treated with CBD. The administration of NAN-190 (10 μg/paw), a selective 5-HT1A receptor antagonist, and SB-366791 (16 μg/paw), a selective TRPV1 antagonist, partially reversed the CBD-induced antinociception. The results of the research suggest that the CBD produces the peripheral antinociception during the acute treatment of the neuropathic pain and it partially involved the participation of the 5-HT1A and TRPV1 receptors.

大麻二酚(CBD)是大麻属植物中发现的最丰富的非精神活性成分。其治疗神经病变的镇痛作用已被广泛研究。然而，当大麻二酚外周施用时，对其在急性治疗中的作用知之甚少。正因为如此，本研究旨在评估 CBD 外周给药治疗急性神经病性疼痛时的作用，并检测 5-HT1A 和 TRPV1 受体是否参与该作用。通过坐骨神经收缩诱导神经病性疼痛，用鼠爪压力试验测量痛觉阈值。该技术可有效诱导神经病变， CBD(5、10、30 μg/爪)以剂量依赖性诱导抗痛觉作用。运动协调性评估试验(RotaRod)表明，使用 30 μg/爪的剂量诱导更强的作用并未引起全身反应，抗痛觉作用仅限于注射 CBD 的爪。给予选择性 5-HT1A 受体拮抗剂 NAN-190 (10 μg/爪)和选择性 TRPV1

拮抗剂 SB-366791 (16 μg/爪)，部分逆转了 CBD 诱导的抗疼痛作用。研究结果表明，CBD 在神经病性疼痛急性治疗过程中产生外周抗痛觉作用，部分涉及 5-HT1A 和 TRPV1 受体的参与。

6.大麻二酚β-环糊精复合物胶束鼻喷剂对体外 SARS-CoV-2 诱导的细胞因子风暴的抑制作用

Aqueous cannabidiol β-cyclodextrin complexed polymeric micelle nasal spray to attenuate in vitro and ex vivo SARS-CoV-2-induced cytokine storms

Changsan N, Sawatdee S, Suedee R, Chunhachaichana C, Srichana T. Aqueous cannabidiol β-cyclodextrin complexed polymeric micelle nasal spray to attenuate in vitro and ex vivo SARS-CoV-2-induced cytokine storms. Int J Pharm. 2023 Jun 10;640：123035. doi： 10.1016/j.ijpharm.2023.123035. Epub 2023 May 12. PMID： 37182795; PMCID：PMC10181874.

Cannabidiol (CBD) has a number of biological effects by acting on the cannabinoid receptors CB1 and CB2. CBD may be involved in anti-inflammatory processes via CB1 and CB2 receptors, resulting in a decrease of pro-inflammatory cytokines. However, CBD's poor aqueous solubility is a major issue in pharmaceutical applications.The aim of the present study was to develop and evaluate a CBD nasal spray solution. A water-soluble CBD was prepared by complexation with β-cyclodextrin (β-CD) at a stoichiometric ratio of 1：1 and forming polymeric micelles using poloxamer 407.The mixture was then lyophilized and characterized using FT-IR, DSC, and TGA.CBD-β-CD complex-polymeric micelles were formulated for nasal spray drug delivery. The physicochemical properties of the CBD-β-CD complex-polymeric micelle nasal spray solution (CBD-β-CDPM-NS) were assessed. The results showed that the CBD content in the CBD-β-CD complex polymeric micelle powder was 102.1 ± 0.5% labeled claim.The CBD-β-CDPM-NS was a clear colorless isotonic solution. The particle size, zeta potential, pH value, and viscosity were 111.9 ± 0.7 nm, 0.8 ± 0.1 mV, 6.02 ± 0.02, and 12.04 ± 2.64 cP, respectively.This formulation was stable over six months at ambient temperature. The CBD from CBD-β-CDPM-NS rapidly released to 100% within 1 min. Ex vivo permeation studies of CBD-β-CDPM-NS through porcine nasal mucosa revealed a permeation rate of 4.8 μg/cm2/min, which indicated that CBD was effective in penetrating nasal epithelial cells. CBD-β-CDPM-NS was tested for its efficacy and safety in terms of cytokine production from nasal immune cells and toxicity to nasal epithelial cells.The CBD-β-CDPM-NS was not toxic to nasal epithelial at the concentration of CBD equivalent to 3.125-50 μg/mL. When the formulation was subjected to bioactivity testing against monocyte-like macrophage cells, it proved that the CBD-β-CDPM-NS has the potential to inhibit inflammatory cytokines. CBD-β-CDPM-NS demonstrated the formulation's ability to reduce the cytokine produced by S-RBD stimulation in ex vivo porcine nasal mucosa in both preventative and therapeutic modes.

大麻二酚(CBD) 具有许多生物学效应，作用于大麻素受体 CB1 和 CB2。CBD 可能通过 CB1 和 CB2 受体参与抗炎过程，导致促炎细胞因子减少。然而，CBD 的水溶性差是制药应用中的一个主要问题。本研究的目的是开发和评估 CBD 鼻喷雾剂溶液。以 CBD 与 β-环糊精(β-CD)按 1：1 的化学量配比，以 407 为辅料形成聚合物胶束，制备成水溶性 CBD。然后将混合物冻干，并使用 FT-IR, DSC 和 TGA 进行表征。制备 CBD-β-CD 复合物-聚合物胶束，用于鼻腔喷雾给药。对 CBD-β-CD 复合物-聚合物胶束鼻腔喷雾溶液(CBD-β-CDPM-NS)的理化性质进行评价。结果表明，CBD-β-CD 复合聚合物胶束粉中 CBD 含量为 102.1±0.5%。CBD-β-CDPM-NS 为透明无色等渗溶液。粒径为 111.9±0.7 nm，电动电位为 0.8±0.1 mV，pH 值为 6.02±0.02，粘度为 12.04±2.64 cP。 该配方在室温下稳定 6

个月以上。CBD-β-CDPM-NS 在 1 分钟内迅速释放至 100%，体外通过猪鼻粘膜渗透实验显示，CBD-β-CDPM-NS 的渗透率为 4.8 μg/cm2/min，表明 CBD 对鼻上皮细胞有渗透作用。研究了 CBD-β-CDPM-NS 在鼻免疫细胞产生细胞因子和对鼻上皮细胞毒性方面的有效性和安全性。CBD-β-CDPM-NS 在 CBD 浓度为 3.125 ~ 50 μg/mL 时对鼻上皮细胞无毒性。通过对单个核样巨噬细胞的生物活性测试，证明了 CBD-β-CDPM-NS 具有抑制炎症细胞因子的潜力。CBD-β-CDPM-NS 证明该制剂在预防和治疗两种模式下减少体外猪鼻黏膜 S-RBD 刺激产生的细胞因子的能力。

丙戊酸

1.丙戊酸导致的肾小管损伤：系统文献综述

Kidney tubular injury induced by valproic acid： systematic literature review

Anguissola G, Leu D, Simonetti GD, Simonetti BG, Lava SAG, Milani GP, Bianchetti MG, Scoglio M. Kidney tubular injury induced by valproic acid： systematic literature review. Pediatr Nephrol. 2023 Jun;38(6)：1725-1731. doi：10.1007/s00467-022-05869-8. Epub 2023 Jan 16. PMID： 36645492; PMCID： PMC10154265.

Abstract

Background：Valproic acid is prescribed for epilepsy and as prophylaxis for bipolar disorder and migraine headaches. It has also been implicated as a cause of a kidney tubular injury.

Methods：We undertook a review of the literature to characterize the biochemical and histopathological features of the overt kidney tubular injury and to evaluate the possible existence of a pauci-symptomatic injury. The pre-registered review (CRD42022360357) was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology. Searches were conducted in Excerpta Medica, the National Library of Medicine, and Web of Science. The gray literature was also considered.

Results：For the final analysis, we retained 36 articles： 28 case reports documented 48 individuals with epilepsy on valproic acid for 7 months or more and presenting with features consistent with an overt kidney tubular injury. The following disturbances were noted： hypophosphatemia (N = 46), normoglycemic glycosuria (N = 46), total proteinuria (N = 45), metabolic acidosis (N = 36), hypouricemia (N = 27), tubular proteinuria (N = 27), hypokalemia (N = 23), and hypocalcemia (N = 8). A biopsy, obtained in six cases, disclosed altered proximal tubular cells with giant and dysmorphic mitochondria. Eight case series addressed the existence of a pauci- or even asymptomatic kidney injury. In the reported 285 subjects on valproic acid for 7 months or more, an isolated tubular proteinuria, mostly N-acetyl-β-glucosaminidase, was often noted.

Conclusions：Valproic acid may induce an overt kidney tubular injury, which is associated with a proximal tubular mitochondrial toxicity. Treatment for 7 months or more is often associated with a pauci- or oligosymptomatic kidney tubular injury. A higher resolution version of the Graphical abstract is available as Supplementary information.

背景：丙戊酸被用于癫痫以及双相情感障碍和偏头痛的预防。它也被认为是肾小管损伤的一个原因。

方法:我们对文献进行了回顾,以表征明显肾小管损伤的生化和组织病理学特征,并评估无症状损伤的可能性。预注册评价(CRD42022360357)按照系统评价和荟萃分析(PRISMA)方法的首选报告项目进行。在医学文摘、国家医学图书馆和科学网上进行搜索。灰色文献也被考虑。

结果：在最后的分析中，我们保留了 36 篇文章：28 篇病例报告记录了 48 例服用丙戊酸治疗 7 个月或更长时间的癫痫患者，表现出与明显肾小管损伤一致的特征。注意到以下异常：低磷血症(N = 46)、血糖正常的糖尿(N

= 46)、总蛋白尿(N = 45)、代谢性酸中毒(N = 36)、低尿酸血症(N = 27)、肾小管性蛋白尿(N = 27)、低钾血症(N = 23)和低钙血症(N = 8)。在六个病例中获得的组织活检揭示具有巨大和畸形线粒体改变的近端肾小管细胞。八个病例系列讨论了存在缺乏或甚至无症状肾损伤。在报告的 285 名服用丙戊酸 7 个月或更长时间的受试者中，经常发现孤立性肾小管性蛋白尿，主要是 N-乙酰-β-氨基葡萄糖苷酶。

结论：丙戊酸可诱导明显的肾小管损伤，这种损伤与近端肾小管线粒体毒性有关。治疗 7 个月或更长时间常伴有少症状或无症状肾小管损伤。高分辨率版本的图片摘要可作为补充信息。

2.一种预测非结合性丙戊酸浓度的新方法

A novel method for predicting the unbound valproic acid concentration

Ishikawa M, Uchida M, Asakawa T, Suzuki S, Yamazaki S, Shiko Y, Kawasaki Y, Suzuki T, Ishii I. A novel method for predicting the unbound valproic acid concentration. Drug Metab Pharmacokinet. 2023 Jun;50：100503. doi：10.1016/j.dmpk.2023.100503. Epub 2023 Mar 5. PMID： 37080137.

In this study, we constructed a prediction formula for unbound valproic acid (VPA) concentration that was more accurate and widely applicable than previously reported formulae. A total of 136 datasets from 75 patients were analyzed retrospectively. The median of free fraction of VPA was 0.16 (interquartile range： 0.07; range： 0.07-0.45). The parameter that combined total VPA concentration (CtVPA) and serum albumin (SA), (CtVPA [μM] - 2 × SA [μM]), was significantly related to the free fraction of VPA (r = 0.76, p < 0.001). We constructed a combined parameter-based prediction formula for unbound VPA concentration. Analysis using external datasets from patients without severe renal failure showed that the prediction errors of the unbound VPA concentration were lower than those of previously reported formulae. Although the previous formulae showed large prediction errors, especially in the specific range of CtVPA values, the constructed formula showed a weak trend with CtVPA or SA. The formula based on (CtVPA [μM] - 2 × SA [μM]) had high prediction accuracy and wide applicability in predicting the unbound VPA concentration in patients without severe renal failure.

在本研究中，我们构建了一个非结合性丙戊酸（VPA）浓度的预测公式，该公式比以前报道的公式更准确和更适用。我们回顾性分析了来自 75 例患者的数据集 136 例。VPA 的游离分数中位数为 0.16（四分位数范围：0.07；范围： 0.07-0.45）。结合性总 VPA 浓度（CtVPA）和血清白蛋白（SA）的参数（CtVPA [μM] - 2×SA [μM]）与 VPA 的游离分数显著相关（r = 0.76，p < 0.001）。我们构建了一个基于参数的非结合性 VPA 浓度预测公式。使用来自无严重肾功能衰竭患者的外部数据集进行分析显示，非结合 VPA 浓度的预测误差低于以前报道的公式。虽然之前的公式有较大的预测误差，特别是在特定的 CtVPA 值的范围内，但构建的公式在 CtVPA 或 SA 中呈现出微弱的趋势。基于（CtVPA [μM] - 2×SA [μM]）的公式在预测无严重肾功能衰竭患者的非结合 VPA 浓度方面具有较高的预测准确性和广泛的适用性。

3.两名局灶性癫痫兄弟的新 SYN1 变异体及其对丙戊酸钠的快速应答

Novel SYN1 Variant in Two Brothers with Focal Epilepsy and Their Prompt Response to Valproate

Leuschner UV, Kleinle S, Holzinger A, Neef J. Novel SYN1 Variant in Two Brothers with Focal Epilepsy and Their Prompt Response to Valproate. Neuropediatrics. 2023 Jun;54(3)：206-210. doi： 10.1055/a-2019-0136. Epub 2023 Jan 24. PMID： 36693418.

Synapsins are neuron-specific phosphoproteins that modulate neurotransmitter release, synaptic plasticity, and molecular processes shaping higher brain functions. Pathogenic synapsin-1 (SYN1) variants are associated with epilepsy, intellectual disabilities, and behavioral problems. We detected a novel SYN1 variant [c.477_479delTGG (p.Gly160del)] in brothers with focal epilepsy with secondary generalization. The deleted amino acid was found to be highly conserved among mammalian species. In electroencephalography, the older brother showed a bioelectrical status epilepticus and was also diagnosed with attention deficit hyperactivity disorder. Behavioral abnormalities were seen before or after the seizures. Both patients responded quickly to treatment with valproate. Our case reports are consistent with the clinical heterogeneity of the pathogenic SYN1 variants described in the literature.

突触蛋白是神经元特异性磷蛋白，调节神经递质释放、突触可塑性和塑造高级脑功能的分子过程。致病性突触蛋白-1 (SYN1)变异与癫痫、智力残疾和行为问题有关。我们在患有局灶性继发泛化的癫痫兄弟中检测到一种 SYN1 新发变异[c.477_479delTGG (p.Gly160del)]，发现缺失的氨基酸在哺乳动物中高度保守。在脑电图中，哥哥表现为电癫痫持续状态，也被诊断为注意缺陷多动障碍。癫痫发作前后都有行为异常。两名患者对丙戊酸钠治疗应答迅速。我们的病例报告与文献中描述的致病性 SYN1 变异体的临床异质性一致。

4.丙戊酸钠、奥卡西平或左乙拉西坦单药治疗癫痫儿童 Apo B100/A1 比值的变化

Change in Apo B100/A1 Ratio in Children With Epilepsy on Monotherapy With Sodium Valproate, Oxcarbazepine or Levetiracetam

Lekhwani S, Dhama A, Kaushik JS. Change in Apo B100/A1 Ratio in Children With Epilepsy on Monotherapy With Sodium Valproate, Oxcarbazepine or Levetiracetam. Indian Pediatr. 2023 Jun 15;60(6)：492-495. PMID：37293912.

A prospective longitudinal study was conducted to assess the Apo B100/A1 ratio as a marker of cardiovascular risk in children with epilepsy aged 5-14 years on long-term anti-seizure medication monotherapy with either sodium valproate, oxcarbazepine, or levetiracetam. Apo B100/A1 ratio showed an increase after six months of monotherapy with oxcarbazepine (P=0.05).

这是一项前瞻性纵向研究，5-14 岁癫痫儿童服用丙戊酸钠、奥卡西平或左乙拉西坦长期单药治疗时，对作为心血管风险指标的 Apo B100/A1 比值进行评估。单药奥卡西平治疗 6 个月后，Apo B100/A1 比值升高(P=0.05)。

5.丙戊酸对人胎盘滋养层细胞合胞化的影响

Effects of valproic acid on syncytialization in human placental trophoblast cell lines

Ohyama N, Furugen A, Sawada R, Aoyagi R, Nishimura A, Umazume T, Narumi K, Kobayashi M. Effects of valproic acid on syncytialization in human placental trophoblast cell lines. Toxicol Appl Pharmacol. 2023 Jun 27：116611. doi：10.1016/j.taap.2023.116611. Epub ahead of print. PMID： 37385477.

The placenta is a critical organ for fetal development and a healthy pregnancy, and has multifaceted functions (e.g., substance exchange and hormone secretion). Syncytialization of trophoblasts is important for maintaining placental

functions. Epilepsy is one of the most common neurological conditions worldwide. Therefore, this study aimed to reveal the influence of antiepileptic drugs, including valproic acid (VPA), carbamazepine, lamotrigine, gabapentin, levetiracetam, topiramate, lacosamide, and clobazam, at clinically relevant concentrations on syncytialization using in vitro models of trophoblasts. To induce differentiation into syncytiotrophoblast-like cells, BeWo cells were treated with forskolin. Exposure to VPA was found to dose-dependently influence syncytialization-associated genes (ERVW-1, ERVFRD-1, GJA1, CGB, CSH, SLC1A5, and ABCC4) in differentiated BeWo cells. Herein, the biomarkers between differentiated BeWo cells and the human trophoblast stem model (TSCT) were compared. In particular, MFSD2A levels were low in BeWo cells but abundant in TSCT cells. VPA exposure affected the expression of ERVW-1, ERVFRD-1, GJA1, CSH, MFSD2A, and ABCC4 in differentiated cells (ST-TSCT). Furthermore, VPA exposure attenuated BeWo and TSCT cell fusion. Finally, the relationships between neonatal/placental parameters and the expression of syncytialization markers in human term placentas were analyzed. MFSD2A expression was positively correlated with neonatal body weight, head circumference, chest circumference, and placental weight. Our findings have important implications for better understanding the mechanisms of toxicity of antiepileptic drugs and predicting the risks to placental and fetal development.

胎盘是胎儿发育和健康妊娠的关键器官，具有多方面的功能(如物质交换和激素分泌)。滋养层细胞合胞化对维持胎盘功能非常重要。癫痫是世界上最常见的神经系统疾病之一。因此，本研究旨在揭示抗癫痫药物，包括丙戊酸（VPA）、卡马西平、拉莫三嗪、加巴喷丁、左乙拉西坦、托吡酯、拉考沙胺和氯巴占，在临床相关浓度下对体外滋养细胞模型合胞化的影响。弗司可林诱导 BeWo 细胞向合体滋养层样细胞分化。发现暴露于 VPA 对分化的 BeWo 细胞中的合胞化相关基因(ERVW-1，ERVFRD-1，GJA1，CGB，CSH，SLC1A5 和 ABCC4)具有剂量依赖性影响。比较分化的 BeWo 细胞与人滋养层干细胞模型(TSCT)的生物标志物。特别是在 BeWo 细胞中 MFSD2A 水平较低，但在 TSCT 细胞中较丰富。VPA 的暴露影响 ERVW-1，ERVFRD-1，GJA1，CSH，MFSD2A 和 ABCC4 在分化细胞(ST-TSCT)中的表达。此外，VPA 暴露减弱了 BeWo 和 TSCT 细胞融合。最后，分析新生儿/胎盘参数与人足月胎盘合胞化标志物表达的关系。MFSD2A 表达与新生儿体重、头围、胸围、胎盘重量呈正相关。我们的研究结果对于更好地理解抗癫痫药物的毒性机制和预测胎盘和胎儿发育的风险具有重要意义。

吡仑帕奈

1.低剂量滴定对吡仑帕奈耐受性和安全性的影响

Effects of low-dose titration on the tolerability and safety of perampanel

Yamamoto Y, Shiratani Y, Nishida T, Usui N, Imai K, Kagawa Y, Takahashi Y. Effects of low-dose titration on the tolerability and safety of perampanel. Epilepsy Behav. 2023 Jun;143：109213. doi： 10.1016/j.yebeh.2023.109213. Epub 2023 Apr 29. PMID： 37126869.

Abstract

Purpose：To evaluate the effects of low-dose titration on the tolerability and safety of perampanel.

Methods：We retrospectively reviewed the records of 1065 patients who started perampanel therapy and compared the incidence of adverse events after standard titration (Group A： starting dose, 2 mg/day; titration speed, 2 mg/2 weeks or longer) and low-dose titration (Group B： starting dose, < 1 mg/day; titration speed, < 1 mg/2 weeks or longer).

Results：Adverse events were reported in 158 patients (14.8%) within the initial first 90 days of starting perampanel (mean concentration, 331 ng/mL). At 90 days, the cumulative incidence of adverse events was significantly higher in Group A than in Group B (24.5% vs. 16.3%, respectively; log-rank test p < 0.001). A Cox proportional hazards model also showed that low-dose titration decreased the incidence risk of adverse events (adjusted hazard ratio, 0.49; 95% confidence interval, 0.35-0.69). When the groups were stratified by use of enzyme-inducing antiseizure medications (inducers), Group A patients without inducers had a significantly higher cumulative incidence of adverse events than the other three subgroups (26.7%, p < 0.001). In patients taking 2 mg of perampanel, median concentrations in patients with or without inducers were 43 ng/mL and 204 ng/mL, respectively.

Conclusion：Perampanel is generally initiated at 2 mg, but serum perampanel concentrations show substantial interindividual variation. Our study suggests that care must be taken when setting the starting dose of perampanel. In particular, low-dose titration is recommended in patients not taking inducers.

目的：评估低剂量滴定对吡仑帕奈耐受性和安全性的影响。

方法：我们回顾性分析了 1065 例开始吡仑帕奈治疗患者的记录，并比较了标准滴定（A 组：起始剂量，2mg/天；滴定速度，2 mg/2 周或更长)和低剂量滴定(B 组：起始剂量，< 1mg/天；滴定速度，< 1mg/2 周或更长）后不良事件的发生率。

结果：158 名患者(14.8%)在开始服用吡仑帕奈的最初 90 天内报告了不良事件(平均浓度为 331 ng/mL)。在 90 天时，A 组不良事件的累计发生率显著高于 B 组(分别为 24.5%和 16.3%；对数秩检验 p < 0.001)。Cox 比例风险模型也显示低剂量滴定降低了不良事件的发生风险(校正风险比，0.49；95%置信区间，0.35-0.69)。当使用酶诱导抗癫痫发作药物(诱导剂)对各组进行分层时，非酶诱导剂的 A 组患者不良事件累积发生率明显高于其他三个

亚组(26.7%，p < 0.001)。在服用2 mg吡仑帕奈的患者中，酶诱导剂和非酶诱导剂患者的中位浓度分别为43 ng/mL和204 ng/mL。

结论：吡仑帕奈一般起始剂量为 2 mg，但是血清吡仑帕奈浓度存在显著的个体差异。我们的研究表明，在设定吡仑帕奈的起始剂量时必须小心。特别是，建议服用非酶诱导剂的患者使用低剂量滴定。

2.吡仑帕奈在两种已建立的啮齿动物早发性癫痫模型中的抗癫痫作用

Anti-seizure efficacy of perampanel in two established rodent models of early-life epilepsy

Roberts NS, Handy MJ, Ito Y, Hashimoto K, Jensen FE, Talos DM. Anti-seizure efficacy of perampanel in two established rodent models of early-life epilepsy. Epilepsy Behav. 2023 Jun;143：109194. doi：10.1016/j.yebeh.2023.109194. Epub 2023 Apr 27. PMID： 37119576.

Early-life seizures can be refractory to conventional antiseizure medications (ASMs) and can also result in chronic epilepsy and long-term behavioral and cognitive deficits. Treatments targeting age-specific mechanisms contributing to epilepsy would be of clinical benefit. One such target is the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) subtype of excitatory glutamate receptor, which is upregulated in the developing brain. Perampanel is a non-competitive, selective AMPAR antagonist that is FDA-approved for focal onset seizures (FOS) or primary generalized tonic-clonic seizures (PGTC) in children and adults. However, the efficacy of perampanel treatment in epilepsy patients younger than 4 years has been less documented. We thus tested the efficacy of perampanel in two early-life seizure models： (1) a rat model of hypoxia-induced neonatal seizures and (2) a mouse model of Dravet syndrome with hyperthermia-induced seizures. Pretreatment with perampanel conferred dose-dependent protection against early-life seizures in both experimental models. These findings suggest that AMPAR-mediated hyperexcitability could be involved in the pathophysiology of early-life seizures, which may be amenable to treatment with perampanel.

早发性癫痫发作可能对常规抗癫痫发作药物(ASMs)无效，也可能导致慢性癫痫和长期的行为和认知缺陷。针对导致癫痫年龄特异性机制的治疗将具有临床益处。此类靶标之一是兴奋性谷氨酸受体的 α-氨基-3-羟基-5-甲基-4-异恶唑丙酸受体(AMPAR)亚型，其在发育中的大脑中上调。吡仑帕奈是一种非竞争性、选择性 AMPAR 拮抗剂，FDA 批准用于儿童和成人的局灶性发作(FOS)或原发性全身强直阵挛性发作(PGTC)。然而，吡仑帕奈治疗 4 岁以下癫痫患者的疗效却鲜有记载。因此，我们在两种早发性癫痫模型中测试了吡仑帕奈的疗效：(1)缺氧诱导的新生儿癫痫发作的大鼠模型；(2)高热诱导癫痫发作的 Dravet 综合征小鼠模型。在两种实验模型中，用吡仑帕奈预处理对早发性癫痫发作具有剂量依赖性的保护作用。这些发现表明，AMPAR 介导的过度兴奋可能与早发性癫痫发作的病理生理学有关，这可能适用于吡仑帕奈的治疗。

3.伴或不伴局灶进展为双侧强直-阵挛发作的患者，添加治疗后吡仑帕奈单药治疗的安全性、有效性及保留率：韩国的一项多中心回顾性研究

Safety and effectiveness of perampanel monotherapy after adjunctive therapy through retention rate in subjects with focal-onset seizures with or without focal to bilateral tonic-clonic seizures：A multicenter retrospective study in Korea

Lim SC, Lee WG, Kim DW, Kim KK, Shon YM, Park J, Lee Y, Seo DW. Safety and effectiveness of perampanel monotherapy after adjunctive therapy through retention rate in subjects with focal-onset seizures with or without focal to bilateral tonic-clonic seizures： A multicenter retrospective study in Korea. Epilepsy Behav. 2023 Jun 17;145：109291. doi： 10.1016/j.yebeh.2023.109291. Epub ahead of print. PMID： 37336136.

Objective：To assess the effectiveness and tolerability of perampanel monotherapy following conversion from adjunctive therapy.

Methods：This was a multicenter, retrospective, non-interventional study of Korean patients aged ≥12 years with focal-onset seizures (FOS) with or without focal to bilateral tonic-clonic seizures. Data were extracted from electronic medical records of perampanel-treated patients from 1 February 2016 to 31 October 2020. Kaplan-Meier estimated retention rates,effectiveness, and safety were recorded.

Results：Subjects (n = 66, mean age 46.2 years) were mostly male (68.2%) with focal to bilateral tonic-clonic seizure (71.2%). Mean duration of illness was 86.3 months. Retention rates after conversion to perampanel monotherapy at 3, 6, and 12 months (primary outcome) were 96.0%, 96.0%, and 75.6%, respectively. Overall retention rates in patients receiving perampanel as adjunctive or monotherapy at 3, 6, 12, 18, and 24 months after perampanel add-on were 100%, 98.3%, 95.9%, 92.6%, and 92.6%, respectively. Mean retention duration was 41.2 months (overall perampanel administration) and 21.4 months (monotherapy). Mean seizure frequency/28 days in the Full Analysis Set (n = 61) was comparable for adjunctive and monotherapy (0.2 ± 0.79 vs 0.2 ± 0.64; change between adjunctive and monotherapy periods： 0.0 ± 0.59; p = 0.498). Perampanel was well tolerated and no new safety signals were identified. Dizziness (4.6%), only reported during adjunctive therapy, was the most common treatment-emergent adverse event.

Conclusions：Conversion to perampanel monotherapy from adjunctive therapy showed promising results in subjects with FOS with/without focal to bilateral tonic-clonic seizures; further studies in a larger population are needed to confirm these encouraging data.

目的：评估从添加治疗转换为吡仑帕奈单药治疗的有效性和耐受性。

方法：这是一项多中心、回顾性、非干预性研究，研究对象为年龄≥12 岁的韩国局灶性发作(FOS)患者，伴或不伴局灶进展为双侧强直阵挛发作。数据提取自 2016 年 2 月 1 日至 2020 年 10 月 31 日使用吡仑帕奈治疗患者的电子病历。Kaplan-Meier 评估保留率、有效性和安全性。

结果：研究对象(n = 66，平均年龄 46.2 岁)主要为男性(68.2%)，伴有局灶性进展为双侧强直阵挛发作(71.2%)。平均病程为 86.3 个月。在 3 个月、6 个月和 12 个月(主要终点)转用单药治疗后保留率分别为 96.0%、96.0%和

75.6%。在使用吡仑帕奈添加治疗或单药治疗后 3、6、12、18 和 24 个月，患者的总保留率分别为 100%、98.3%、95.9%、92.6%和 92.6%。平均保留期为 41.2 个月(总给药)和 21.4 个月(单药)。全数据集(n = 61)中的平均癫痫发作频率/28 天与添加治疗和单药治疗相当(0.2±0.79 vs 0.2±0.64;添加和单药治疗期间的变化：0.0±0.59;P = 0.498)。吡仑帕奈的耐受性良好，没有发现新的安全信号。头晕(4.6%)仅在添加助治疗期间报道，是最常见的治疗相关性紧急不良事件。

结论： 在伴/不伴局灶性至双侧强直-阵挛性发作的 FOS 患者中，从吡仑帕奈添加治疗转为单药治疗显示出良好的效果;需要在更大人群中行进一步研究来证实这些令人鼓舞的数据。

4.自微乳化给药系统中吡仑帕奈经鼻至脑给药可改善其在小鼠中的抗惊厥和抗焦虑活性

Nose-to-brain delivery of perampanel formulated in a self-microemulsifying drug delivery system improves anticonvulsant and anxiolytic activity in mice

Meirinho S, Rodrigues M, Santos AO, Falcão A, Alves G. Nose-to-brain delivery of perampanel formulated in a self-microemulsifying drug delivery system improves anticonvulsant and anxiolytic activity in mice. Int J Pharm. 2023 Jun 15;642：123145. doi： 10.1016/j.ijpharm.2023.123145. Epub ahead of print. PMID： 37330157.

Perampanel (PER) is a potent third-generation antiepileptic drug only available for oral administration. Additionally, PER has shown potential in managing epilepsy comorbidities such as anxiety. Previously, we demonstrated that the intranasal (IN) administration of PER, loaded in a self-microemulsifying drug delivery system (SMEDDS), improved brain-targeting and exposure in mice. Herein, we investigated PER brain biodistribution, its anticonvulsant and anxiolytic effects, and its potential olfactory and neuromotor toxicity after IN administration to mice (1 mg/kg). PER showed a rostral-caudal brain biodistribution pattern when administered intranasally. At short times post-nasal dosing, high PER concentrations were found in olfactory bulbs (olfactory bulbs/plasma ratios of 1.266 ± 0.183 and 0.181 ± 0.027 after IN and intravenous administrations, respectively), suggesting that a fraction of the drug directly reaches brain through the olfactory pathway. In the maximal electroshock seizure test, IN PER protected 60% of mice against seizure development, a substantially higher value than the 20% protected after receiving oral PER. PER also demonstrated anxiolytic effects in open field and elevated plus maze tests. Buried food-seeking test showed no signs of olfactory toxicity. Neuromotor impairment was found in rotarod and open field tests at the times of PER maximum concentrations after IN and oral administrations. Nevertheless, neuromotor performance was improved after repeated administrations. Compared with IN vehicle, PER IN administration decreased brain levels of L-glutamate (0.91 ± 0.13 mg/mL vs 0.64 ± 0.12 mg/mL) and nitric oxide (100 ± 15.62% vs 56.62 ± 4.95%), without interfering in GABA levels. Altogether, these results suggest that the IN PER delivery through the developed SMEDDS can be a safe and promising alternative to the oral treatment, which supports the design of clinical studies to evaluate the IN PER delivery to treat epilepsy and neurological-related conditions as anxiety.

吡仑帕奈 (PER)是一种有效的第三代抗癫痫药物，只能口服。此外，PER 在控制癫痫共患病(如焦虑)方面显示出潜力。先前，我们证明了在自微乳化药物传递系统(SMEDDS)中装载 PER 的鼻内(IN)给药，可以改善小鼠的脑靶向性和暴露。在此，我们研究了 PER 的脑生物分布、抗惊厥和抗焦虑作用，以及给药(1 mg/kg)后对小鼠的潜在嗅觉和神经运动毒性。经鼻给药时，PER 显示喙端-尾端脑生物分布模式。在短时间内，经鼻给药后，嗅球中

PER 浓度较高(静脉给药后嗅球/血浆比值分别为 1.266±0.183 和 0.181±0.027)，表明部分药物通过嗅觉途径直接到达大脑。在最大电休克癫痫发作试验中，鼻内给药 PER 保护 60%的小鼠不发生癫痫发作，显著高于口服 PER 后 20%的保护率。在旷场试验和高架迷宫试验中，PER 也表现出抗焦虑作用。埋藏觅食测试未显示嗅觉毒性的迹象。鼻内和口服给药后，在 PER 达到最高浓度时，在旋转试验和旷场试验中发现了神经运动障碍。然而，反复给药后，神经运动表现得到改善。与鼻内给药装置相比，PER 鼻内给药可降低脑内 L-谷氨酸(0.91±0.13 mg/mL vs 0.64±0.12 mg/mL)和一氧化氮(100±15.62% vs 56.62±4.95%)水平，但不影响 GABA 水平。总之，这些结果表明，通过开发的 SMEDDS 鼻内给药 PER 是一种安全且有希望的口服治疗替代方案，这支持了临床研究的设计，以评估 PER 鼻内给药用于治疗癫痫和焦虑等神经系统相关疾病的潜力。

其他药物

1.拉莫三嗪在阿尔茨海默病小鼠模型中挽救神经元改变并防止癫痫引起的记忆衰退

Lamotrigine rescues neuronal alterations and prevents seizure-induced memory decline in an Alzheimer's disease mouse model

Rizzello E, Pimpinella D, Pignataro A, Titta G, Merenda E, Saviana M, Porcheddu GF, Paolantoni C, Malerba F, Giorgi C, Curia G, Middei S, Marchetti C. Lamotrigine rescues neuronal alterations and prevents seizure-induced memory decline in an Alzheimer's disease mouse model. Neurobiol Dis. 2023 Jun 1;181：106106. doi：10.1016/j.nbd.2023.106106. Epub 2023 Mar 29. PMID： 37001613.

Epilepsy is a comorbidity associated with Alzheimer's disease (AD), often starting many years earlier than memory decline. Investigating this association in the early pre-symptomatic stages of AD can unveil new mechanisms of the pathology as well as guide the use of antiepileptic drugs to prevent or delay hyperexcitability-related pathological effects of AD. We investigated the impact of repeated seizures on hippocampal memory and amyloid-β (Aβ) load in pre-symptomatic Tg2576 mice, a transgenic model of AD. Seizure induction caused memory deficits and an increase in oligomeric Aβ42 and fibrillary species selectively in pre-symptomatic transgenic mice, and not in their wildtype littermates. Electrophysiological patch-clamp recordings in ex vivo CA1 pyramidal neurons and immunoblots were carried out to investigate the neuronal alterations associated with the behavioral outcomes of Tg2576 mice. CA1 pyramidal neurons exhibited increased intrinsic excitability and lower hyperpolarization-activated Ih current. CA1 also displayed lower expression of the hyperpolarization-activated cyclic nucleotide-gated HCN1 subunit, a protein already identified as downregulated in the AD human proteome. The antiepileptic drug lamotrigine restored electrophysiological alterations and prevented both memory deficits and the increase in extracellular Aβ induced by seizures. Thus our study provides evidence of pre-symptomatic hippocampal neuronal alterations leading to hyperexcitability and associated with both higher susceptibility to seizures and to AD-specific seizure-induced memory impairment. Our findings also provide a basis for the use of the antiepileptic drug lamotrigine as a way to counteract acceleration of AD induced by seizures in the early phases of the pathology.

癫痫是与阿尔茨海默病（AD）相关的共患病，通常比记忆衰退早许多年。在 AD 症状前的早期阶段研究这种关联可以揭示新的病理机制，并指导使用抗癫痫药物来预防或延缓 AD 与过度兴奋性相关的病理效应。我们研究了反复癫痫发作对有症状前 Tg2576 小鼠(一种 ad 转基因模型)海马记忆和淀粉样 β 蛋白(Aβ)负荷的影响。癫痫发作诱导选择性地在症状前转基因小鼠中引起记忆缺陷和低聚 Aβ42 和纤维种类增加，而在其野生型同窝鼠中没有这种效应。进行离体 CA1 锥体神经元的电生理膜片钳记录和免疫印迹，以研究与 Tg2576 小鼠的行为结果相关的神经元变化。CA1 锥体神经元表现出内源兴奋性增加和较低的超极化激活 Ih 电流。CA1 也显示了超极化激活的环核苷酸门控 HCN1 亚单位的较低表达，这种蛋白已经在 AD 人类蛋白质组中被鉴定为下调。抗癫痫发作药物拉莫三嗪恢复了电生理改变，并防止了记忆缺陷和癫痫发作诱导的细胞外 Aβ 增加。因此，我们的研究提供了导致过度兴奋的症状前海马神经元改变的证据，并与癫痫发作和 AD 特异性癫痫发作诱导的记忆障碍高易感性相关。我们的发现也为抗癫痫发作药物拉莫三嗪的使用提供了基础，作为一种对抗在病理学早期由癫痫发作诱导的 AD 进展的方法。

2.氨己烯酸治疗婴儿癫痫性痉挛综合征的疗效：系统回顾及荟萃分析

Efficacy of vigabatrin in the treatment of infantile epileptic spasms syndrome： A systematic review and meta-analysis

Xu Z, Gong P, Jiao X, Niu Y, Wu Y, Zhang Y, Chang X, Yang Z. Efficacy of vigabatrin in the treatment of infantile epileptic spasms syndrome： A systematic review and meta-analysis. Epilepsia Open. 2023 Jun;8(2)：268-277. doi：10.1002/epi4.12703. Epub 2023 Mar 14. PMID： 36740237; PMCID： PMC10235574.

This systematic review and meta-analysis aimed to evaluate the efficacy of vigabatrin (VGB) in treating infantile epileptic spasms syndrome (IESS). Databases of PubMed, Embase, Web of Science, MEDLINE, and Cochrane Library were systematically searched. All the relevant randomized controlled trials (RCTs) and observational studies (OSs) of VGB for IESS were included and analyzed separately. The primary outcome was the cessation of epileptic spasms (ES). Five RCTs and nine OSs compared the efficacy of VGB vs hormonal monotherapy for IESS. Meta-analysis of the five RCTs showed that hormonal monotherapy was significantly better than VGB monotherapy (OR = 0.37, 95% CI = 0.20-0.67) for patients with new-onset IESS. Meta-analysis of the nine OSs agrees with the result from RCTs (OR = 0.61, 95% CI = 0.43-0.85). VGB was more effective in patients with TSC than in those with other etiologies (five OSs, OR = 5.59, 95% CI = 2.17-14.41). There was no significant difference in the efficiency of VGB combined with hormonal therapy vs hormonal monotherapy for IESS (two RCTs, OR = 0.75, 95% CI = 0.09-6.45). Hormonal monotherapy is better than VGB monotherapy for non-TSC-associated IESS. But for patients with IESS due to TSC, VGB is the first choice. VGB combined with hormone therapy does not definitely increase ES control rates compared with that of hormonal monotherapy.

本系统综述和荟萃分析旨在评估氨己烯酸(VGB)治疗婴儿癫痫痉挛综合征(IESS)的疗效。系统搜索 PubMed、Embase、Web of Science、MEDLINE 和 Cochrane Library 的数据库。纳入 VGB 针对 IESS 的所有相关随机对照试验(RCTs)和观察性研究(OSs),并分别进行分析。主要研究终点是癫痫性痉挛发作的终止。五项 RCT 和九项 OSs 比较了 VGB 和激素单药治疗 IESS 的疗效。五项 RCT 的荟萃分析显示，对于新发 IESS 患者，激素单药疗法明显优于 VGB 单药疗法(OR = 0.37，95% CI = 0.20-0.67)。对 9 个 OSs 的荟萃分析与 RCT 的结果一致(OR = 0.61，95% CI = 0.43-0.85)。VGB 在 TSC 患者中比在其他病因的患者中更有效(5 个 OSs，OR = 5.59，95% CI = 2.17-14.41)。对于 IESS，VGB 联合激素治疗与激素单药治疗的有效率没有显著差异(两个 RCT，OR = 0.75，95% CI = 0.09-6.45)。对于非 TSC 相关的 IESS，激素单药疗法优于 VGB 单药疗法。但对于膀胱移行细胞癌导致的 IESS 患者，VGB 是首选。与激素单药疗法相比，VGB 联合激素疗法并不一定增加 ES 控制率。

3.苯巴比妥治疗超难治性癫痫持续状态(PIRATE)：一项多中心回顾性分析

Phenobarbital in super-refractory status epilepticus (PIRATE)： A retrospective, multicenter analysis

Kunst S, Rojo M, Schmidbauer ML, Pelz JO, Mueller A, Minnerup J, Meyer L, Madžar D, Reindl C, Madlener M, Malter M, Neumann B, Dimitriadis K; IGNITE Study Group. Phenobarbital in super-refractory status epilepticus (PIRATE)： A retrospective, multicenter analysis. Epilepsia. 2023 Jun;64(6)：1482-1492. doi： 10.1111/epi.17608. Epub 2023 Apr 16. PMID： 37021609.

Objective：Super-refractory status epilepticus (SRSE) is an enduring or recurring SE after 24 h or more of general anesthesia. This study aimed to evaluate the efficacy and safety of phenobarbital (PB) for the treatment of SRSE.

Methods：This retrospective, multicenter study included neurointensive care unit (NICU) patients with SRSE treated with PB between September 2015 and September 2020 from six participating centers of the Initiative of German NeuroIntensive Trial Engagement (IGNITE) to evaluate the efficacy and safety of PB treatment for SRSE. The primary outcome measure was seizure termination. In addition, we evaluated maximum reached serum levels, treatment duration, and clinical complications using a multivariate generalized linear model.

Results：Ninety-one patients were included (45.1% female). Seizure termination was achieved in 54 patients (59.3%). Increasing serum levels of PB were associated with successful seizure control (per μg/mL： adjusted odds ratio [adj.OR] = 1.1, 95% confidence interval [CI] 1.0-1.2, p < .01). The median length of treatment in the NICU was 33.7 [23.2-56.6] days across groups. Clinical complications occurred in 89% (n = 81) of patients and included ICU-acquired infections, hypotension requiring catecholamine therapy, and anaphylactic shock. There was no association between clinical complications and treatment outcome or in-hospital mortality. The overall average modified Rankin scale (mRS) at discharge from the NICU was 5 ± 1. Six patients (6.6%) reached mRS ≤3, of whom five were successfully treated with PB. In-hospital mortality was significantly higher in patients in whom seizure control could not be achieved.

Significance： We observed a high rate in attainment of seizure control in patients treated with PB. Success of treatment correlated with higher dosing and serum levels. However, as one would expect in a cohort of critically ill patients with prolonged NICU treatment, the rate of favorable clinical outcome at discharge from the NICU remained extremely low. Further prospective studies evaluating long-term clinical outcome of PB treatment as well as an earlier use of PB at higher doses would be of value.

目的：超难治性癫痫持续状态(SRSE)是使用全麻药物后 24 h 或更长时间内持续或复发的 SE。本研究旨在评价苯巴比妥(PB)治疗 SRSE 的有效性和安全性。

方法：这项回顾性多中心研究纳入了 2015 年 9 月至 2020 年 9 月期间在神经重症监护病房(NICU)接受 PB 治疗的 SRSE 患者，这些患者来自德国神经重症试验管理计划(IGNITE)的六个参与中心，以评估 PB 治疗 SRSE 的疗效和安全性。主要研究终点是癫痫发作终止。此外，我们使用多变量广义线性模型评估最大血清浓度、治疗持续时间和临床并发症。

结果：共纳入 91 例患者(45.1%为女性)。54 例患者(59.3%)癫痫发作终止。血清 PB 水平升高与癫痫发作控制成功相关(每 μg/mL：校正比值比[adj.OR] = 1.1，95%可信区间[CI] 1.0-1.2，p < .01)。各组在 NICU 的平均治疗时间为 33.7 [23.2-56.6]天。89% (n = 81)的患者出现临床并发症，包括 ICU 获得性感染、需要儿茶酚胺治疗的低血压和过敏性休克。临床并发症与治疗结果或住院死亡率之间没有关联。从 NICU 出院时的总体平均改良 Rankin 量表(mRS)为 5±1。6 名患者(6.6%)达到 mRS ≤3，其中 5 名患者成功接受了 PB 治疗。在无法控制癫痫发作的患者中，院内死亡率明显较高。

意义：我们观察到接受 PB 治疗的患者癫痫发作控制率很高。治疗的成功与较高的剂量和血清水平相关。然而，正如长期接受 NICU 治疗的危重患者所预期的那样，从 NICU 出院时的良好临床结果率仍然极低。进一步的前瞻性研究评估 PB 治疗的长期临床结果以及早期使用更高剂量的 PB 将是有价值的。

4.乙酰唑胺治疗谷氨酸缺乏症(G1D)癫痫的简明研究

A concise study of acetazolamide in Glut1 deficiency (G1D) epilepsy

Málaga I, Avila A, Primeaux S, Park JY, Pascual JM. A concise study of acetazolamide in Glut1 deficiency (G1D) epilepsy. Epilepsia. 2023 Jun 19. doi： 10.1111/epi.17684. Epub ahead of print. PMID： 37335529.

Epilepsy constitutes the most common paroxysmal manifestation of glucose transporter type 1 deficiency (G1D) and is generally considered medication-refractory. It can also prove therapeutic diet-resistant. We examined acetazolamide effects in G1D motivated by several longstanding and recent observations： First, the electrographic spike-waves characteristic of absence seizures often resemble those of G1D and, since the 1940s, they have occasionally been successfully treated with acetazolamide, well before G1D was segregated from absence epilepsy as a distinct syndrome. Second, synaptic inhibitory neuron failure characterizes G1D and, in other experimental models, this can be ameliorated by drugs that modify cellular chloride gradient such as acetazolamide. Third, acetazolamide potently stimulates model cell glucose transport in vitro. Seventeen antiepileptic drug or therapeutic diet-refractory individuals with G1D treated with acetazolamide were thus identified via medical record review complemented by worldwide individual survey. Acetazolamide was tolerable and decreased seizures in 76% of them, with 58% of all persons studied experiencing seizure reductions by more than one half, including those who first manifested myoclonic-astatic epilepsy or infantile spams. 88% of individuals with G1D continued taking acetazolamide for over 6 months, indicating sustained tolerability and efficacy. The results provide a novel avenue for the treatment and mechanistic investigation of G1D

癫痫是葡萄糖转运蛋白 1 型缺乏症(G1D)最常见的发作性症状，通常被认为是药物难治性的，同时也被证实对饮食治疗抵抗。我们通过几个长期和近期的观察研究了乙酰唑胺对 G1D 的影响：首先，失神癫痫脑电图的棘慢波特征通常与 G1D 相似，自 20 世纪 40 年代以来，早在 G1D 与失神癫痫作为一种独特的综合征分开之前，失神癫痫偶尔被乙酰唑胺成功治疗。其次，突触抑制性神经元衰竭是 G1D 的特征，在其他实验模型中，可通过改变细胞氯化物梯度的药物(如乙酰唑胺)来改善。第三，乙酰唑胺能有效刺激体外模型细胞葡萄糖转运。通过回顾医疗记录和全球个人调查确定了 17 例药物或饮食难治性 G1D 患者，接受乙酰唑胺治疗。乙酰唑胺可耐受，76%的患者癫痫发作减少，58%的研究对象癫痫发作减少一半以上，包括那些最初表现为肌阵挛性癫痫或婴儿痉挛的患者。88%的 G1D 患者持续服用乙酰唑胺超过 6 个月，显示出持续的耐受性和有效性。该结果为 G1D 的治疗和机理研究提供了新的途径。

临床研究

1.儿童期起病的癫痫患者第二次停用抗癫痫发作药物的预后

Outcomes of the second withdrawal of anti-seizure medication in patients with pediatric-onset epilepsy

Cho J, Kim H, Chae JH, Kim KJ, Lim BC. Outcomes of the second withdrawal of anti-seizure medication in patients with pediatric-onset epilepsy. Epilepsia. 2023 Jun;64(6)：e93-e97. doi： 10.1111/epi.17594. Epub 2023 Apr 7. PMID：36976527.

Withdrawal of anti-seizure medication (ASM) is challenging, especially in patients with recurrent seizures. Only limited evidence exists regarding the success rate and recurrence risk factors after withdrawal of ASM for a second time in patients with pediatric-onset epilepsy. In this observational study, we evaluated 104 patients with recurrent pediatric-onset epilepsy who had ASM withdrawn for a second time. The success rate was 41.3% after the second withdrawal of ASM. The absence of a self-limiting epilepsy syndrome, shorter seizure-free intervals before the second withdrawal of ASM, and relapse during tapering after the initial withdrawal of ASM were negative factors significantly associated with the success of ASM withdrawal for a second time. Even after a second seizure recurrence, all patients eventually became seizure-free after restarting their previous ASM (78.7%) or readjusting the ASM (21.3%). Our findings that 40% of patients with recurrent pediatric-onset epilepsy could achieve long-term seizure freedom and that all patients with a second seizure recurrence remained seizure-free suggest that ASM may be withdrawn for a second time after carefully stratifying clinical risk.

停用抗癫痫发作药物(ASM)是具有挑战性的，尤其是对反复发作的患者。关于儿童期起病患者再次停用 ASM 后成功率和复发风险的证据还很有限。在这项观察性研究中，我们评估了 104 名再次停用 ASM 的复发性儿童癫痫患者。第二次停用 ASM 后成功率为 41.3%。非自限性癫痫综合征、第二次停用 ASM 前无发作间隔时间较短以及初次停用 ASM 后减量期间复发是与第二次停用 ASM 成功显著相关的负相关因素。即使在第二次癫痫复发后，所有患者在重新开始之前的 ASM (78.7%)或重新调整 ASM (21.3%)后，最终都没有再出现癫痫发作。我们的研究发现，40%的儿童癫痫复发患者可以获得长期无发作，并且所有第二次癫痫复发的患者最终仍可达到无发作，这表明在仔细划分临床风险后，可以第二次停用 ASM。

2.成人癫痫术后停用抗癫痫发作药物的预测模型

Predictive models for starting antiseizure medication withdrawal following epilepsy surgery in adults

Ferreira-Atuesta C, de Tisi J, McEvoy AW, Miserocchi A, Khoury J, Yardi R, Vegh DT, Butler J, Lee HJ, Deli-Peri V, Yao Y, Wang FP, Zhang XB, Shakhatreh L, Siriratnam P, Neal A, Sen A, Tristram M, Varghese E, Biney W, Gray WP, Peralta AR, Rainha-Campos A, Gonçalves-Ferreira AJC, Pimentel J, Arias JF, Terman S, Terziev R, Lamberink HJ, Braun KPJ, Otte WM, Rugg-Gunn FJ, Gonzalez W, Bentes C, Hamandi K, O'Brien TJ, Perucca P, Yao C, Burman RJ, Jehi L, Duncan JS, Sander JW, Koepp M, Galovic M. Predictive models for starting antiseizure medication withdrawal following epilepsy surgery in adults. Brain. 2023 Jun 1;146(6)：2389-2398. doi： 10.1093/brain/awac437. PMID： 36415957.

More than half of adults with epilepsy undergoing resective epilepsy surgery achieve long-term seizure freedom and might consider withdrawing antiseizure medications. We aimed to identify predictors of seizure recurrence after

starting postoperative antiseizure medication withdrawal and develop and validate predictive models. We performed an international multicentre observational cohort study in nine tertiary epilepsy referral centres. We included 850 adults who started antiseizure medication withdrawal following resective epilepsy surgery and were free of seizures other than focal non-motor aware seizures before starting antiseizure medication withdrawal. We developed a model predicting recurrent seizures, other than focal non-motor aware seizures, using Cox proportional hazards regression in a derivation cohort (n = 231). Independent predictors of seizure recurrence, other than focal non-motor aware seizures, following the start of antiseizure medication withdrawal were focal non-motor aware seizures after surgery and before withdrawal [adjusted hazard ratio (aHR) 5.5, 95% confidence interval (CI) 2.7-11.1], history of focal to bilateral tonic-clonic seizures before surgery (aHR 1.6, 95% CI 0.9-2.8), time from surgery to the start of antiseizure medication withdrawal (aHR 0.9, 95% CI 0.8-0.9) and number of antiseizure medications at time of surgery (aHR 1.2, 95% CI 0.9-1.6). Model discrimination showed a concordance statistic of 0.67 (95% CI 0.63-0.71) in the external validation cohorts (n = 500). A secondary model predicting recurrence of any seizures (including focal non-motor aware seizures) was developed and validated in a subgroup that did not have focal non-motor aware seizures before withdrawal (n = 639), showing a concordance statistic of 0.68 (95% CI 0.64-0.72). Calibration plots indicated high agreement of predicted and observed outcomes for both models. We show that simple algorithms, available as graphical nomograms and online tools (predictepilepsy.github.io), can provide probabilities of seizure outcomes after starting postoperative antiseizure medication withdrawal. These multicentre-validated models may assist clinicians when discussing antiseizure medication withdrawal after surgery with their patients.

超过一半接受切除性癫痫手术的成年癫痫患者实现了长期无发作，并可考虑停用抗癫痫发作药物。我们旨在确定术后抗癫痫发作药物停药后癫痫复发的预测因素，并开发和验证预测模型。我们在九个三级癫痫转诊中心进行了一项国际多中心观察队列研究。我们纳入了 850 名成年人，他们在癫痫切除术后开始停用抗癫痫发作药物，停药前除局灶性非运动性伴知觉保留性发作外，没有其他类型的发作。我们在一个推导队列(n = 231)中使用 Cox 比例风险回归，开发了一个预测除局灶性非运动性伴知觉保留性发作以外的复发性癫痫发作的模型。除局灶性非运动性伴知觉保留性发作外，抗癫痫发作药物停药后癫痫复发的独立预测因子为手术后和停药前的局灶性非运动性伴知觉保留性发作[调整风险比(aHR) 5.5，95%可信区间(CI) 2.7-11.1]，术前局灶性进展为双侧强直-阵挛发作史(aHR 1.6，95% CI 0.9-2.8)，从手术到开始停药的时间(aHR 0.9，95% CI 0.8-0.9)，手术时抗癫痫发作药物的数量(aHR 1.2, 95% CI 0.9-1.6)。在外部验证队列(n = 500)中，模型区分判别显示一致性统计量为 0.67 (95% CI 0.63-0.71)。开发了预测任何癫痫发作(包括局灶性非运动性伴知觉保留性发作)复发的二级模型，并在戒断前没有局灶性非运动性伴知觉保留性发作的亚组(n = 639)中进行验证，显示一致性统计量为 0.68 (95% CI 为 0.64-0.72)。校准图表明两个模型的预测和观察结果高度一致。我们展示了简单的算法，如图形图和在线工具(predictepilepsy.github.io)，可以提供术后开始停药后癫痫发作结局的概率。这些多中心验证的模型可能有助于临床医生与患者讨论术后抗癫痫发作药物的停用。

3.Lennox-Gastaut 综合征患者添加吡仑帕奈的长期疗效：一项多中心回顾性研究

Long-term effectiveness of add-on perampanel in patients with Lennox-Gastaut syndrome： A multicenter retrospective study

Matricardi S, Cesaroni E, Bonanni P, Foschi N, D Aniello A, Di Gennaro G, Striano P, Cappanera S, Siliquini S, Freri E, Ragona F, Granata T, Deleo F, Villani F, Russo A, Messana T, Siri L, Bagnasco I, Vignoli A, Operto FF, Orsini A,

Bonuccelli A, Papa A, Peruzzi C, Liguori C, Verrotti A, Chiarelli F, Marini C, Lattanzi S. Long-term effectiveness of add-on perampanel in patients with Lennox-Gastaut syndrome： A multicenter retrospective study. Epilepsia. 2023 Jun;64(6)：e98-e104. doi： 10.1111/epi.17601. Epub 2023 Apr 10. PMID： 37000415.

This retrospective study assessed long-term effectiveness of add-on perampanel (PER) in patients with Lennox-Gastaut syndrome (LGS). Outcomes included time to PER failure and time to seizure relapse in responders. PER failure was defined as either discontinuation of PER or initiation of another treatment. Seizure relapse in responders was defined as occurrence of a seizure in seizure-free patients and increase of at least 50% in average monthly seizure frequency for those who were responders. Eighty-seven patients were included. Treatment failure occurred in 52 (59.8%) subjects at a median time of 12 months. Treatment failure was due to lack of efficacy in 27 (52.0%) patients, lack of tolerability in 14 (27.0%), and both reasons in 11 (21.0%). A slower titration was associated with a lower risk of PER failure compared to faster titration schedules, and the occurrence of adverse events increased the risk of treatment failure. Thirty-six patients (41.4%) were responders during a median follow-up of 11 months. Seizure relapse occurred in 13 of 36 (36.1%) patients after a median time of 21 months. The overall rate of seizure responders was 23 of 87 (26.4%) at the end of follow-up. This study provides real-world evidence on the effectiveness of PER as adjunctive treatment in LGS patients.

这项回顾性研究评估了在 Lennox-Gastaut 综合征(LGS)患者中添加吡仑帕奈 (PER)的长期疗效。结果包括应答者失效的时间和癫痫复发的时间。PER 失败被定义为停用 PER 或开始另一种治疗。应答者癫痫复发被定义为无发作患者出现癫痫再发，应答者平均每月发作频率增加至少 50%。87 名患者被纳入研究。52 名(59.8%)受试者治疗失败，中位时间为 12 个月。治疗失败是因为 27 例(52.0%)患者缺乏疗效，14 例(27.0%)患者缺乏耐受性，11 例(21.0%)患者两种原因都有。与快速滴定方案相比，慢速滴定与较低的 PER 失败风险相关，并且不良事件的发生增加了治疗失败的风险。36 名患者(41.4%)在中位数为 11 个月的随访中有应答。36 例患者中有 13 例(36.1%)在中位时间 21 个月后癫痫复发。随访结束时，87 名患者中有 23 名(26.4%)癫痫发作出现应答。这项研究为 PER 用于 LGS 患者添加治疗的有效性提供了现实世界的证据。

4.使用拉莫三嗪和其他调节钠通道抗癫痫发作药物的癫痫患者突然意外死亡的风险

Risk of sudden unexpected death in epilepsy (SUDEP) with lamotrigine and other sodium channel-modulating antiseizure medications

Nightscales R, Barnard S, Laze J, Chen Z, Tao G, Auvrez C, Sivathamboo S, Cook MJ, Kwan P, Friedman D, Berkovic SF, D'Souza W, Perucca P, Devinsky O, O'Brien TJ. Risk of sudden unexpected death in epilepsy (SUDEP) with lamotrigine and other sodium channel-modulating antiseizure medications. Epilepsia Open. 2023 Jun;8(2)：334-345. doi：10.1002/epi4.12693. Epub 2023 Feb 15. PMID： 36648376; PMCID： PMC10235563.

Objective： In vitro data prompted U.S Food and Drug Administration warnings that lamotrigine, a common sodium channel modulating anti-seizure medication (NaM-ASM), could increase the risk of sudden death in patients with structural or ischaemic cardiac disease, however, its implications for Sudden Unexpected Death in Epilepsy (SUDEP) are unclear.

Methods： This retrospective, nested case-control study identified 101 sudden unexpected death in epilepsy (SUDEP) cases and 199 living epilepsy controls from Epilepsy Monitoring Units (EMUs) in Australia and the USA. Differences in

proportions of lamotrigine and NaM-ASM use were compared between cases and controls at the time of admission, and survival analyses from the time of admission up to 16 years were conducted. Multivariable logistic regression and survival analyses compared each ASM subgroup adjusting for SUDEP risk factors.

Results： Proportions of cases and controls prescribed lamotrigine (P = 0.166), one NaM-ASM (P = 0.80), or ≥2NaM-ASMs (P = 0.447) at EMU admission were not significantly different. Patients taking lamotrigine (adjusted hazard ratio [aHR] = 0.56; P = 0.054), one NaM-ASM (aHR = 0.8; P = 0.588) or ≥2 NaM-ASMs (aHR = 0.49; P = 0.139) at EMU admission were not at increased SUDEP risk up to 16 years following admission. Active tonic-clonic seizures at EMU admission associated with >2-fold SUDEP risk, irrespective of lamotrigine (aHR = 2.24; P = 0.031) or NaM-ASM use (aHR = 2.25; P = 0.029). Sensitivity analyses accounting for incomplete ASM data at follow-up suggest undetected changes to ASM use are unlikely to alter our results.

Significance： This study provides additional evidence that lamotrigine and other NaM-ASMs are unlikely to be associated with an increased long-term risk of SUDEP, up to 16 years post-EMU admission.

目的：体外研究数据促使美国食品药品监督管理局对拉莫三嗪提出警告，这是一种常见的调节钠通道的抗癫痫发作药物(NaM-ASM),可能增加结构性或缺血性心脏病患者的猝死风险，然而，其对癫痫猝死(SUDEP)的影响尚不清楚。

方法：这项回顾性、巢式病例对照研究确定了来自澳大利亚和美国癫痫监测单位的 101 例癫痫猝死(SUDEP)病例和 199 例存活癫痫对照。在入院时，比较病例组和对照组之间拉莫三嗪和 NaM-ASM 使用比例的差异，并进行从入院时到 16 年的生存分析。多变量逻辑回归和生存分析比较校正每个 ASM 亚组的 SUDEP 危险因素。

结果： 病例组和对照组在 EMU 入院时服用拉莫三嗪(P = 0.166)、1 种 NaM-ASM (P = 0.80)或≥2 种 NaM-ASMs (P = 0.447)方面无显著差异。服用拉莫三嗪 (校正风险比[aHR]= 0.56；P = 0.054)、一种 NaM-ASM(aHR = 0.8；P = 0.588)或≥2 种 NaM-ASMs(aHR = 0.49； P = 0.139) 的患者在入院后 16 年的 SUDEP 风险没有增加。在不考虑使用拉莫三嗪或 NaM-ASM 的情况下，EMU 入院时的活动性强直-阵挛发作与> 2 倍 SUDEP 风险相关(aHR = 2.24，P = 0.031)(aHR = 2.25， P = 0.029)。考虑到随访时 ASM 数据不完整的敏感性分析表明，未检测到的 ASM 使用变化不太可能改变我们的结果。

意义：这项研究提供了额外的证据，表明拉莫三嗪和其他 NaM-ASMs 不太可能与 EMU 入院后 16 年发生 SUDEP 的长期风险增加相关。

5.癫痫患者抗癫痫发作药物停药讨论与决定的频率和相关因素：一项多中心回顾性图表回顾

Frequency of and factors associated with antiseizure medication discontinuation discussions and decisions in patients with epilepsy： A multicenter retrospective chart review

Terman SW, Slinger G, Koek A, Skvarce J, Springer MV, Ziobro JM, Burke JF, Otte WM, Thijs RD, Braun KPJ. Frequency of and factors associated with antiseizure medication discontinuation discussions and decisions in patients with

epilepsy： A multicenter retrospective chart review. Epilepsia Open. 2023 Jun;8(2)： 371-385. doi： 10.1002/epi4.12695. Epub 2023 Feb 14. PMID： 36693718; PMCID： PMC10235583.

Objective： Guidelines suggest considering antiseizure medication (ASM) discontinuation in patients with epilepsy who become seizure-free. Little is known about how discontinuation decisions are being made in practice. We measured the frequency of, and factors associated with, discussions and decisions surrounding ASM discontinuation.

Methods： We performed a multicenter retrospective cohort study at the University of Michigan (UM) and two Dutch centers： Wilhelmina Children's Hospital (WCH) and Stichting Epilepsie Instellingen Nederland (SEIN). We screened all children and adults with outpatient epilepsy visits in January 2015 and included those with at least one visit during the subsequent 2 years where they were seizure-free for at least one year. We recorded whether charts documented (1) a discussion with the patient about possible ASM discontinuation and (2) any planned attempt to discontinue at least one ASM. We conducted multilevel logistic regressions to determine factors associated with each outcome.

Results： We included 1058 visits from 463 patients. Of all patients who were seizure-free at least one year, 248/463 (53%) had documentation of any discussion and 98/463 (21%) planned to discontinue at least one ASM. Corresponding frequencies for patients who were seizure-free at least 2 years were 184/285 (65%) and 74/285 (26%). The probability of discussing or discontinuing increased with longer duration of seizure freedom. Still, even for patients who were 10 years seizure-free, our models predicated that in only 49% of visits was a discontinuation discussion documented, and in only 16% of visits was it decided to discontinue all ASMs. Provider-to-provider variation explained 18% of variation in whether patients discontinued any ASM.

Significance： Only approximately half of patients with prolonged seizure freedom had a documented discussion about ASM discontinuation. Discontinuation was fairly rare even among low-risk patients. Future work should further explore barriers to and facilitators of counseling and discontinuation attempts.

目的：指南建议在无发作的癫痫患者中考虑停用抗癫痫发作药物(ASM)。在实践中，人们对如何作出停药决定知之甚少。我们评测了围绕停用 ASM 的讨论和决策的频率及其相关因素。

方法：我们在密歇根大学(UM)和两个荷兰中心：威廉敏娜儿童医院(WCH)和荷兰癫痫治疗中心(SEIN)进行了一项多中心回顾性队列研究。我们筛选了 2015 年 1 月癫痫门诊就诊的所有儿童和成人，并包括在随后的 2 年内至少就诊一次且至少一年无癫痫发作的儿童和成人。我们记录图表中是否记录了(1)与患者关于可能停用 ASM 的讨论和(2)任何计划停止至少一种 ASM 的尝试。我们进行了多水平逻辑回归来确定与每个结果相关的因素。

结果：我们纳入了 463 例患者的 1058 次就诊。在所有至少一年无癫痫发作的患者中，248/463(53%)有任何讨论的记录，98/463(21%)至少一次计划停用 ASM。至少 2 年无癫痫发作的患者对应频率分别为 184/285(65%)和 74/285(26%)。讨论或停止治疗的可能性随着无发作持续时间的延长而增加。尽管如此，即使对于 10 年无癫痫发作的患者，我们的模型预测，只有 49%的就诊记录中有停药讨论，只有 16%的就诊决定停药。提供者之间的差异解释了 18%的患者是否停止任何 ASM 的差异。

意义：只有约一半长时间无发作的患者有关于 ASM 停药的讨论记录。即使在低风险患者中，停药也是相当罕见的。未来的工作应进一步探讨咨询的障碍并促进停药尝试。

6.抗癫痫发作药物停药风险评估和建议：美国神经病学学会和 EpiCARE 成员的调查

Antiseizure medication withdrawal risk estimation and recommendations： A survey of American Academy of Neurology and EpiCARE members

Terman SW, van Griethuysen R, Rheaume CE, Slinger G, Haque AS, Smith SN, Kerr WT, van Asch C, Otte WM, Ferreira-Atuesta C, Galovic M, Burke JF, Braun KPJ. Antiseizure medication withdrawal risk estimation and recommendations： A survey of American Academy of Neurology and EpiCARE members. Epilepsia Open. 2023 Jun;8(2)：386-398. doi： 10.1002/epi4.12696. Epub 2023 Feb 14. PMID： 36721311; PMCID：PMC10235556.

Objective： Choosing candidates for antiseizure medication (ASM) withdrawal in well-controlled epilepsy is challenging. We evaluated (a) the correlation between neurologists' seizure risk estimation ("clinician predictions") vs calculated predictions, (b) how viewing calculated predictions influenced recommendations, and (c) barriers to using risk calculation.

Methods：We asked US and European neurologists to predict 2-year seizure risk after ASM withdrawal for hypothetical vignettes. We compared ASM withdrawal recommendations before vs after viewing calculated predictions, using generalized linear models.

Results：Three-hundred and forty-six neurologists responded. There was moderate correlation between clinician and calculated predictions (Spearman coefficient 0.42). Clinician predictions varied widely, for example, predictions ranged 5%-100% for a 2-year seizure-free adult without epileptiform abnormalities. Mean clinician predictions exceeded calculated predictions for vignettes with epileptiform abnormalities (eg, childhood absence epilepsy：clinician 65%, 95% confidence interval [CI] 57%-74%; calculated 46%) and surgical vignettes (eg, focal cortical dysplasia 6-month seizure-free mean clinician 56%, 95% CI 52%-60%; calculated 28%). Clinicians overestimated the influence of epileptiform EEG findings on withdrawal risk (26%, 95% CI 24%-28%) compared with calculators (14%, 95% 13%-14%). Viewing calculated predictions slightly reduced willingness to withdraw (-0.8/10 change, 95% CI -1.0 to -0.7), particularly for vignettes without epileptiform abnormalities. The greatest barrier to calculator use was doubting its accuracy (44%).

Significance：Clinicians overestimated the influence of abnormal EEGs particularly for low-risk patients and overestimated risk and the influence of seizure-free duration for surgical patients, compared with calculators. These data may question widespread ordering of EEGs or time-based seizure-free thresholds for surgical patients. Viewing calculated predictions reduced willingness to withdraw particularly without epileptiform abnormalities

目的：在控制良好的癫痫患者中，抗癫痫发作药物(ASM)停药的选择具有挑战性。我们评估了(a)神经科医生的癫痫发作风险估计(“临床医生预测”)与计算预测之间的相关性，(b)查看计算预测如何影响建议，以及(c)使用风险计算的障碍。

方法：我们要求美国和欧洲的神经科医生预测 ASM 停药后 2 年的癫痫发作风险。我们使用广义线性模型比较了在查看计算预测之前和之后的 ASM 停药建议。

结果：346 名神经科医生回应。临床医生与计算预测之间存在中度相关性(Spearman 系数 0.42)。临床医生的预测差异很大，例如对于 2 年无发作无癫痫样放电的成人患者，其预测范围为 5%-100%。对于有癫痫样放电的患者，临床医生的平均预测要高于计算预测(如儿童失神癫痫：临床医生预测为 65%，95%可信区间[CI] 57%-74%;计算预测为 46%)；对于手术患者(如局灶性皮质发育不良 6 个月无癫痫发作，临床医生预测平均为 56%，95% CI 52%-60%;计算预测为 28%)。与计算预测相比，临床医生高估了癫痫样 EEG 结果对停药风险的影响(26%，95% CI 24%-28%) (14%， 95% CI 13%-14%)。计算预测结果轻度降低了停药意愿(-0.8/10 变化，95% CI -1.0 至-0.7)，特别是对于没有癫痫样放电的患者。使用计算公式的最大障碍是怀疑它的准确性(44%)。

意义：与计算预测相比，临床医生高估了异常脑电图的影响，特别是对低风险患者，高估了无发作持续时间对手术患者的影响。这些数据可能对脑电图的广泛应用或手术患者基于时间的无发作阈值产生质疑。计算预测降低了停药意愿，特别是在没有癫痫样放电的情况下。

7.基于多电极阵列记录的实时电磁刺激对幼年大鼠海马癫痫样活动的调节作用

Modulatory effects of real-time electromagnetic stimulation on epileptiform activity in juvenile rat hippocampus based on multi-electrode array recordings

Dong L, Song LL, Zhao WJ, Zhao L, Tian L, Zheng Y. Modulatory effects of real-time electromagnetic stimulation on epileptiform activity in juvenile rat hippocampus based on multi-electrode array recordings. Brain Res Bull. 2023 Jun 15;198：27-35. doi： 10.1016/j.brainresbull.2023.04.006. Epub 2023 Apr 19. PMID： 37084982.

Electromagnetic stimulation (EMS) has proven to be useful for the focal suppression of epileptiform activity (EFA) in the hippocampus. There is a critical period during EFA for achieving the transition from brief interictal discharges (IIDs) to prolonged ictal discharges (IDs), and it is unknown whether EMS can modulate this transition. Therefore, this study aimed to evaluate the intensity- and time-dependent effect of EMS on the transition of EFA. A juvenile rat EFA model was constructed by perfusing magnesium-free artificial cerebrospinal fluid (aCSF) on brain slices, and the induced EFA was recorded using a micro-electrode array (MEA) platform. After a stable EFA event was recorded for some time, real-time pulsed magnetic stimulation with low and high peak-to-peak input magnetic field intensities was carried out. A 5-min intervention with real-time magnetic fields with low intensity was found to reduce the amplitude of IDs (ID events still existed), whereas a 5-min intervention with real-time magnetic fields with high input voltages completely suppressed IDs. Short-time magnetic fields (9 s and 1 min) with high or low input intensity had no effect on EFA. Real-time magnetic fields can block the normal EFA process from IIDs to IDs (i.e., a complete EFA cycle) and this suppression effect is dependent on input intensities and intervention duration. The experimental findings further indicate that magnetic stimulation may be chosen as an alternative antiepileptic therapy.

电磁刺激(EMS)已被证明可用于抑制海马局灶性癫痫样活动(EFA)。在 EFA 过程中，有一个从短暂间歇放电(IIDs)过渡到长程间歇放电(IDs)的关键时期，EMS 能否调节这种过渡尚不清楚。因此，本研究旨在评估 EMS 对 EFA 转变的强度和时间依赖效应。采用无镁人工脑脊液(aCSF)灌注于脑片构建幼龄大鼠 EFA 模型，采用微电极阵列

(MEA)平台记录诱导的 EFA。记录到一段时间的稳定 EFA 事件后，分别进行低和高强度的峰-峰输入磁场实时脉冲磁刺激。研究发现，低强度实时磁场干预 5 分钟可降低 ID 的幅度(ID 事件仍然存在)，而高输入电压实时磁场干预 5 分钟可完全抑制 ID。高强度或低强度的短时磁场(9 s 和 1 min)对 EFA 没有影响。实时磁场可以阻断从 IIDs 到 IDs 的正常 EFA 过程(即一个完整的 EFA 周期)，这种抑制效果取决于输入强度和干预持续时间。实验结果进一步表明，磁刺激可以作为一种替代的抗癫痫治疗方法。

8.成人患者耐药性癫痫的危险因素

Risk factors for drug-resistant epilepsy in adult patients

Lagger I, Garino E, Martinez O, Knorre E, Ernst G, Burgueño AL. Risk factors for drug-resistant epilepsy in adult patients. Med Clin (Barc). 2023 Jun 23;160(12)：547-550. English, Spanish. doi： 10.1016/j.medcli.2023.03.006. Epub 2023 Apr 10. PMID： 37045668.

Introduction： Drug-resistant epilepsy occurs in about 30% of epilepsy patients. It has been suggested that etiology or seizure type would increase the risk of pharmacoresistance. This study aims to compare the characteristics of patients with drug-sensitive epilepsy with patients with drug-resistant epilepsy to identify risk factors.

Patient and methods：A multicentric cohort study was conducted between 2019 and 2022. We included patients >18 years-old with epilepsy but excluded psychogenic non-epileptic seizures and less than 2 years of follow-up.

Results：We included 128 patients, of whom 46 had drug-resistance epilepsy, and 82 responding to medication. Both groups showed similar characteristics. Febrile seizures (OR： 7.25), focal epilepsy (OR： 2.4), focal seizures with loss of consciousness (OR： 2.36), structural etiology (OR： 2.2) and abnormal MRI (OR： 4.6) were significant risk factors for drug-resistance epilepsy.

Conclusion：Following other studies, we observed that factors such as epilepsy type, seizure type, structural etiology, abnormal MRI, and febrile seizure increased the risk for drug-resistance epilepsy, in our population.

简介：大约 30%的癫痫患者会出现耐药性癫痫。有研究表明，病因或癫痫发作类型会增加耐药风险。本研究旨在比较药物敏感性癫痫患者与耐药性癫痫患者的特点，以确定危险因素。

患者和方法：在 2019 年至 2022 年间进行了一项多中心队列研究。我们纳入了 18 岁以上的癫痫患者，排除了心因性非痫性发作和随访时间少于 2 年的患者。

结果：我们纳入了 128 名患者，其中 46 名患有耐药性癫痫，82 名对药物有应答。两组都表现出相似的特征。热性惊厥（OR：7.25）、局灶性癫痫（OR：2.4）、局灶性癫痫伴意识丧失（OR：2.36）、结构性病因（OR：2.2）和 MRI 异常（OR：4.6）是耐药性癫痫的重要危险因素。

结论：继其他研究之后，我们观察到癫痫类型、癫痫发作类型、结构性病因、MRI 异常和热性惊厥等因素增加了我们人群中耐药性癫痫的风险。

9.拉莫三嗪治疗患者心律失常事件的调查：FAERS 分析

Investigation of Cardiac Arrhythmia Events in Patients Treated with Lamotrigine： FAERS Analysis

Aboukaoud M, Wilf-Yarkoni A, Maor E. Investigation of Cardiac Arrhythmia Events in Patients Treated with Lamotrigine： FAERS Analysis. Epilepsia. 2023 Jun 23. doi： 10.1111/epi.17696. Epub ahead of print. PMID：37350356.

Abstract

Objectives：In October 2020 and March 2021, the Federal Drug Agency classified lamotrigine as class IB antiarrhythmic, announcing an increased risk of heart rhythm problems. We sought to investigate the nature of the arrhythmia signal with lamotrigine use compared to anticonvulsants with sodium and non-sodium blocking mechanisms.

Methods：This retrospective pharmacovigilance case-non-case study used disproportionality analysis to detect signals of adverse reaction of interest reported with lamotrigine to the FDA adverse event reporting system between 1998 and 2022. Our regression model adjusted for interacting concomitant medications. Sensitivity analyses included stratifying by indication and publication date.

Results：Overall, 2917 cases of heart rhythm problems with anticonvulsants were analyzed (1557 female [58.4%] and 1109 male [41.6%]). The mean age was 43±19, the groups did not differ significantly by age. Forty cases [7.91%] in the epileptic indication included more than one concomitant medications that influence cardiac conduction. The disproportionality signal for cardiac arrest did not differ for lamotrigine compared with other anti-convulsants, [adj.ROR, 0.88; 95%CI, 0.59-1.29] in the epileptic indication. A significantly lower reporting risk for bradyarrhythmia was identified with lamotrigine users in the epileptic population, [adj.ROR, 0.45; 95%CI, 0.29-0.68]. The psychiatric indication demonstrated a six-fold reporting risk for cardiac arrest compared to the epileptic indication. Concomitant medications that affect cardiac conduction, as well as reports on overdose and suicide attempts were significant variables in psychiatric patients, [ROR, 2.45; 95%CI, 2.21-2.71], and [ROR, 1.44; 95%CI, 1.34-1.55] respectively.

Significance：Our results do not support a significant difference in the reporting risk for cardiac arrest, syncope, tachy- and bradyarrhythmia with lamotrigine in the epileptic indication. Signals of cardiac arrest in lamotrigine could be explained by confounding factors in the psychiatric indication, such as greater concomitant use of medications with cardiac adverse events, and greater reports on overdose and suicide attempts. We recommend that patients with polypharmacy undergo clinical and electrocardiographic monitoring. We illustrate the importance of examining signals for seperate indications.

目标：2020 年 10 月和 2021 年 3 月，联邦药品管理局将拉莫三嗪列为 IB 类致心律失常药，宣布心律问题的风险增加。我们试图研究使用拉莫三嗪时的心律失常倾向的性质，并与使用钠通道和非钠通道阻滞机制的抗惊厥药物进行比较。

方法：这项回顾性药物安全病例-非病例研究使用歧化分析来检测 1998 年至 2022 年间向 FDA 不良事件报告系统报告的拉莫三嗪相关不良反应倾向。我们的回归模型针对相互作用的合并用药进行了调整。敏感性分析包括按适应证和发表日期进行分层。

结果：总共分析了 2917 例抗惊厥药物引起的心律失常，其中女性 1557 例(58.4%)，男性 1109 例(41.6%)。平均年龄 43±19 岁，两组年龄差异无统计学意义。40 例(7.91%)患者服用一种以上影响心脏传导的药物。拉莫三嗪与其他抗惊厥药相比，心脏骤停的歧化倾向没有差异，[adj.ROR, 0.88; 95%CI, 0.59-1.29]。癫痫人群中使用拉莫三嗪的缓慢性心律失常报告风险显著降低[adj.ROR, 0.45; 95%CI, 0.29-0.68]。与癫痫患者相比，精神病患者显示心脏骤停的报告风险为六倍。影响心脏传导的合用药物，以及过量用药和自杀企图的报告是精神病人的重要变量[ROR, 2.45;95%CI, 2.21-2.71]， [ROR, 1.44;95%CI, 1.34-1.55]。

意义：我们的研究结果不支持拉莫三嗪在癫痫患者中心脏骤停、晕厥、心动过速和缓慢性心律失常的报告风险有显著差异。拉莫三嗪的心脏骤停倾向可以通过精神病患者中的混杂因素来解释，例如与心脏不良事件同时使用的药物较多，过量使用和企图自杀的报告较多。我们建议使用多种药物的患者接受临床和心电图监测。我们说明了对个体患者进行心律失常检查的重要性。

10.普瑞巴林作为脊柱手术后急性术后疼痛的有效治疗无主要副作用：一项前瞻性、随机对照、双盲试验方案

Pregabalin as an effective treatment for acute postoperative pain following spinal surgery without major side effects：protocol for a prospective, randomized controlled, double-blinded trial

Park KH, Chung NS, Chung HW, Kim TY, Lee HD. Pregabalin as an effective treatment for acute postoperative pain following spinal surgery without major side effects： protocol for a prospective, randomized controlled, double-blinded trial. Trials. 2023 Jun 22;24(1)：422. doi： 10.1186/s13063-023-07438-2. PMID： 37349841; PMCID： PMC10286380.

Abstract

Background： Patients experience considerable postoperative pain after spinal surgery. As the spine is located at the centre of the body and supports body weight, severe postoperative pain hinders upper body elevation and gait which can lead to various complications, including pulmonary deterioration and pressure sores. It is important to effectively control postoperative pain to prevent such complications. Gabapentinoids are widely used as preemptive multimodal analgesia, but their effects and side effects are dose-dependent. This study was designed to examine the efficacy and side effects of varying doses of postoperative pregabalin for the treatment of postoperative pain after spinal surgery.

Methods： This is a prospective, randomized controlled, double-blind study. A total of 132 participants will be randomly assigned to the placebo (n = 33) group or to the pregabalin 25 mg (n = 33), 50 mg (n = 33), or 75 mg (n = 33) groups. Each participant will be administered placebo or pregabalin once prior to surgery and every 12 h after surgery for 72 h. The primary outcome will be the visual analogue scale pain score, total dose of administered intravenous patient-controlled analgesia, and frequency of rescue analgesic administered for 72 h from arrival to the general ward after surgery, subdivided into four periods： 1-6 h, 6-24 h, 24-48 h, and 48-72 h. The secondary outcomes will be the incidence and frequency of nausea and vomiting due to intravenous patient-controlled

analgesia. Safety will be assessed by monitoring the occurrence of side effects such as sedation, dizziness, headache, visual disturbance, and swelling.

Discussion：Pregabalin is already widely used as preemptive analgesia and, unlike nonsteroidal anti-inflammatory drugs, is not associated with a risk of nonunion after spinal surgery. A recent meta-analysis demonstrated the analgesic efficacy and opioid-sparing effect of gabapentinoids with significantly decreased risks of nausea, vomiting, and pruritus. This study will provide evidence for the optimal dosage of pregabalin for the treatment of postoperative pain after spinal surgery.

背景：脊柱手术后患者会经历相当严重的术后疼痛。由于脊柱位于身体的中心，支撑身体的重量，严重的术后疼痛阻碍了上半身的抬高和活动，这可能导致各种并发症，包括肺部疾病恶化和压疮。有效控制术后疼痛是防止此类并发症发生的关键。加巴喷丁类药物已广泛用于术前多模式镇痛，其作用和副作用是具有剂量依赖性的。本研究旨在研究不同剂量普瑞巴林治疗脊柱术后疼痛的疗效和副作用。

方法：这是一项前瞻性、随机对照、双盲研究。总共 132 名参与者将被随机分配到安慰剂组 (n = 33) 或普瑞巴林 25 mg (n = 33)、50 mg (n = 33) 或 75 mg (n = 33) 组。每个参与者将在术前和术后每 12 小时服用一次安慰剂或普瑞巴林，持续 72 小时。主要终点是视觉模拟量表疼痛评分、静脉自控镇痛药总量以及术后到达普通病房后 72 小时内给予抢救性镇痛药的频率，分为四个阶段：1-6 小时、 6-24 小时、24-48 小时和 48-72 小时。次要终点是静脉自控镇痛药引起的恶心和呕吐的发生率和频率。安全性将通过监测副作用的发生来评估，如镇静、头晕、头痛、视力障碍和水肿。

讨论：普瑞巴林已广泛用作术前镇痛药，与非甾体类抗炎药不同，普瑞巴林与脊柱手术后骨折不愈合风险无关。最近的一项荟萃分析表明，加巴喷丁类药物的镇痛效果和阿片类药物保留作用可显著降低恶心、呕吐和瘙痒的风险。本研究将为普瑞巴林治疗脊柱术后疼痛的最佳剂量提供依据。

11.围产期卒中足月婴儿常伴发癫痫发作，并在出院时服用抗癫痫发作药物

Term-born infants with a perinatal stroke frequently had seizures and were prescribed anti-seizure medication at discharge

Barsch Bergqvist A, Simatou E, Skiöld B, Mitha A, Bolk J. Term-born infants with a perinatal stroke frequently had seizures and were prescribed anti-seizure medication at discharge. Acta Paediatr. 2023 Jun 26. doi：10.1111/apa.16890. Epub ahead of print. PMID： 37365777.

Abstract

Aim：We investigated the prevalence of seizures in term-born infants with a perinatal stroke in Swedish neonatal wards, assessed the antiseizure medication prescribed and determined the accuracy of diagnostic codes.

Methods：This cross-sectional study used data from the Swedish Neonatal Quality Register. The cases were infants born at ≥37 weeks in 2009-2018 and admitted to a neonatal ward in Stockholm County with a stroke diagnosis, confirmed by their medical chart. The controls were all Swedish infants born during those years.

Results：There were 76 infants with a confirmed perinatal stroke： 51 ischaemic and 25 haemorrhagic. Seizures were documented in 66/76 (87%) of infants with a stroke and 0.2% of controls. Antiseizure medication was administered to 64/66 (97%) infants with a stroke and seizures. In 60 cases the drugs administered were specified, with phenobarbital used in 59/60 cases (98%). More than one drug was administered to 25/60 (42%) infants and 31/60 (52%) were discharged with antiseizure medication. The positive predictive value for the stroke diagnostic codes was 80.5% (95% CI 76.5-84.5).

Conclusion：Seizures were common in infants with a perinatal stroke. More than one antiseizure drug was often required and many infants were on antiseizure medication at discharge, against Swedish recommendations.

目的：我们调查了瑞典新生儿病房中患有围产期卒中的足月婴儿癫痫发作的患病率，评估了抗癫痫发作药物的处方，并确定了诊断代码的准确性。

方法：这项横断面研究使用了来自瑞典新生儿质量登记的数据。这些病例是 2009 年至 2018 年出生的≥37 周的婴儿，入住斯德哥尔摩县新生儿病房，经病历证实被诊断为卒中。对照组都是当年出生的瑞典婴儿。

结果：76 名婴儿确诊为围产期卒中：51 名缺血性卒中，25 名出血性卒中。66/76 (87%) 的卒中婴儿和 0.2% 的对照婴儿中记录有癫痫发作。对 64/66(97%)卒中合并癫痫患儿给予抗癫痫发作药物治疗。在 60 例中指定了给药药物，59/60 例(98%)使用苯巴比妥。25/60(42%)的婴儿服用一种以上药物，31/60(52%)的婴儿出院时服用抗癫痫发作药物。脑卒中诊断代码阳性预测值为 80.5% (95% CI 为 76.5-84.5)。

结论：癫痫发作在围产期卒中婴儿中很常见。通常需要使用不止一种抗癫痫发作药物，许多婴儿在出院时正在服用抗癫痫发作药物，这违反了瑞典的推荐建议。

生酮饮食

1.生酮饮食减轻伴有 ATAD3A 变异的 Harel-Yoon 综合征的难治性癫痫：1 例病例报道及文献回顾

Ketogenic Diet Attenuates Refractory Epilepsy of Harel-Yoon Syndrome With ATAD3A Variants： A Case Report and Review of Literature

Chen Y, Rong S, Luo H, Huang B, Hu F, Chen M, Li C. Ketogenic Diet Attenuates Refractory Epilepsy of Harel-Yoon Syndrome With ATAD3A Variants： A Case Report and Review of Literature. Pediatr Neurol. 2023 Jun;143：79-83. doi：10.1016/j.pediatrneurol.2023.03.003. Epub 2023 Mar 9. PMID： 37031571.

Background：Harel-Yoon syndrome is a disease caused by variants in the ATAD3A gene, which manifest as global developmental delay, hypotonia, intellectual disability, and axonal neuropathy. The aim of this study is to summarize the clinical and gene mutation characteristics of a child with refractory epilepsy caused by ATAD3A gene mutation.

Methods：The whole-exome sequencing combined with copy number variation analysis could help to understand the genetic diversity and underlying disease mechanisms in ATAD3A gene mutation.

Results：We report a Chinese boy with Harel-Yoon syndrome presenting with refractory epilepsy, hypotonia, global developmental delay, and congenital cataract through whole-exome sequencing. Genetic analysis showed a missense mutation, c.251T>C(p.Thr84Met) in the ATAD3A gene (NM_001170535.1). Further copy number variation analysis identified a novel heterozygous deletion on chromosome1p36.33, which spans ATAD3A exon 1 and 2 regions. Multiple antiepileptic drugs failed to control his seizures. Eventually, seizure was controlled through ketogenic diet (KD).

Conclusion：Our case shows the potential diagnostic role of whole-exome sequencing in Harel-Yoon syndrome and expands the ATAD3A gene mutation spectrum. Multiple antiepileptic drugs failed to control refractory epilepsy in Harel-Yoon syndrome. The KD therapy may be effective for patients with refractory epilepsy who carry the ATAD3A variants.

背景：Harel-Yoon 综合征是一种由 ATAD3A 基因变异引起的疾病，表现为全面发育迟缓、肌张力减低、智力残疾和轴索神经病。本研究的目的是总结一例由 ATAD3A 基因突变引起的难治性癫痫患儿的临床和基因突变特点。

方法：全外显子测序结合拷贝数变异分析有助于了解 ATAD3A 基因突变的遗传多样性和致病机制。

结果：我们通过全外显子组测序报告了一例患有 Harel-Yoon 综合征的中国男孩，表现为难治性癫痫、肌张力减低、全面发育迟缓和先天性白内障。遗传分析显示 ATAD3A 基因(NM_001170535.1)存在一个错义突变，c.2T>C(p.Thr84Met)。进一步的拷贝数变异分析确定了染色体 1p36.33 上一个新的杂合缺失，它跨越了 ATAD3A 外显子 1 和 2 区域。多种抗癫痫药物都未能控制发作。最终，通过生酮饮食(KD)控制了癫痫发作。

结论：我们的病例显示了全外显子组测序在 Harel-Yoon 综合征中的潜在诊断作用，并扩展了 ATAD3A 基因突变谱。多种抗癫痫药物未能控制 Harel-Yoon 综合征中的难治性癫痫。KD 疗法可能对携带 ATAD3A 变异的难治性癫痫患者有效。

2.间歇性与持续性生酮饮食：对癫痫发作、肠道微生物及线粒体代谢的影响。

Intermittent versus continuous ketogenic diet： impact on seizures, gut microbiota and mitochondrial metabolism

Shearer J, Scantlebury MH, Rho JM, Tompkins TA, Mu C. Intermittent versus continuous ketogenic diet： impact on seizures, gut microbiota and mitochondrial metabolism. Epilepsia. 2023 Jun 19. doi： 10.1111/epi.17688. Epub ahead of print. PMID： 37335622.

We have previously shown that the ketogenic diet (KD) is effective in reducing the seizures associated with infantile spasms syndrome (ISS) and that this benefit is related to alterations in the gut microbiota. However, it remains unclear whether the efficacy of the KD persists after switching to a normal diet. Employing a neonatal rat model of ISS, we tested the hypothesis that the impact of the KD would diminish when switched to a normal diet. Following epilepsy induction, neonatal rats were divided into two groups： continuous KD for 6 days; and a group fed with KD for 3 days, then a normal diet for 3 days. Spasms frequency, mitochondrial bioenergetics in the hippocampus, and fecal microbiota were evaluated as major readouts. We found that the antiepileptic effect of KD was reversible, as evidenced by the increased spasms frequency in rats that were switched from the KD to a normal diet. The spasms frequency was inversely correlated with mitochondrial bioenergetic function and a set of gut microbes, including Streptococcus thermophilus and Streptococcus azizii. These findings suggest that the antiepileptic and metabolic benefits of the KD decline rapidly in concert with gut microbial alterations in the ISS model.

我们之前已经证明生酮饮食(KD)在减少与婴儿癫痫性痉挛综合征(ISS)相关的癫痫发作方面是有效的，而且这种益处与肠道微生物群的改变有关。然而，目前尚不清楚 KD 在转换为正常饮食后是否仍然有效。采用 ISS 的新生大鼠模型，我们验证了 KD 的影响会在切换到正常饮食时减少的假设。诱导癫痫后，新生大鼠被分为两组：连续 KD 治疗 6 d;1 组先饲喂 KD 3 d，再饲喂正常饲粮 3 d。以痉挛频率、海马线粒体生物能量学及粪便微生物群为主要评估参数。我们发现 KD 的抗癫痫作用是可逆的，从 KD 转换为正常饮食的大鼠痉挛频率增加证明了这一点。痉挛频率与线粒体生物能量及肠道微生物群(包括嗜热链球菌和阿齐兹链球菌)呈负相关。这些发现表明，在 ISS 模型中，KD 的抗癫痫和代谢益处随着肠道微生物的改变而迅速下降。

3.生酮饮食在新生儿耐药癫痫：疗效和副作用——一个单中心的实验

Ketogenic Diet in Neonates with Drug-Resistant Epilepsy： Efficacy and Side Effects-A Single Center's Initial Experience

Falsaperla R, Sortino V, Collotta AD, Privitera GF, Palmeri A, Mauceri L, Ruggieri M. Ketogenic Diet in Neonates with Drug-Resistant Epilepsy： Efficacy and Side Effects-A Single Center's Initial Experience. Neuropediatrics. 2023 Jun 15. doi： 10.1055/s-0043-1769505. Epub ahead of print. PMID： 37321250.

Background：For patients with pharmacoresistant epilepsy, a therapeutic option is ketogenic diet. Currently, data on young infants are scarce, particularly during hospitalization in the neonatal intensive care unit (NICU).

Objective：The aim of the present study was to evaluate the short-term (3-month) efficacy and side effects of ketogenic diet in infants with "drugs-resistant" epilepsy treated during NICU stay.

Methods：This retrospective study included infants aged under 2 months started on ketogenic diet during NICU hospitalization to treat drug-resistant epilepsy from April 2018 to November 2022.

Results：Thirteen term-born infants were included, three (23.1%) of whom were excluded because they did not respond to the ketogenic diet. Finally, we included 10 infants. Six (60%) patients took three antiepileptics before starting the ketogenic diet, while four (40%) took more drugs. Diet had a good response in four (40%) patients. In four patients, the ketogenic diet was suspended because of the onset of serious side effects. The emetic levels of sodium, potassium, and chlorine, pH, and onset of diarrhea, constipation, and gastroesophageal reflux showed significant differences. Ketonuria was higher and blood pH lower in the group that took more than three drugs than in the group taking fewer than three drugs.

Conclusion：The ketogenic diet is efficacious and safe in infants, but the early and aggressive management of adverse reactions is important to improve the safety and effectiveness of the ketogenic treatment.

背景：生酮饮食是耐药性癫痫患者的一种治疗选择。目前关于低月龄婴儿的数据很少，尤其是在新生儿重症监护病房(NICU)住院期间。

目的：本研究的目的是评价 NICU 住院期间“耐药”性癫痫患儿生酮饮食短期(3 个月)的疗效和不良反应。

方法：回顾性研究 2018 年 4 月至 2022 年 11 月在 NICU 住院治疗耐药性癫痫期间开始采用生酮饮食治疗的 2 个月以下婴幼儿。

结果：13 名足月婴儿被纳入，其中 3 名(23.1%)被排除，因为他们对生酮饮食没有应答。最后，我们纳入了 10 个婴儿。6 名(60%)患者在开始生酮饮食前服用了 3 种抗癫痫药物，而 4 名(40%)患者服用了更多药物。四名(40%)患者对饮食的应答良好。在 4 例患者中，生酮饮食因出现严重的副作用而暂停。呕吐时钠、钾、氯水平、pH 值、腹泻、便秘、胃食管反流的发生均存在显著性差异。与服用少于三种药物的患儿组相比，服用三种以上药物患儿组的酮尿症比例更高，血液 pH 值更低。

结论：生酮饮食对婴幼儿是安全有效的，但早期积极处理不良反应对提高生酮治疗的安全性和有效性至关重要。

4.饮食炎症特性介导癫痫对中至重度抑郁症的影响：NHANES 2013-2018 的结果。

Inflammatory properties of diet mediate the effect of epilepsy on moderate to severe depression： Results from NHANES 2013-2018

Ding R, Han Z, Gui J, Xie L, Yang J, Yang X, Huang D, Luo H, Han W, Jiang L. Inflammatory properties of diet mediate the effect of epilepsy on moderate to severe depression： Results from NHANES 2013-2018. J Affect Disord. 2023 Jun 15;331：175-183. doi： 10.1016/j.jad.2023.03.054. Epub 2023 Mar 21. PMID： 36948467.

Background：Depression is a major public health problem, and epilepsy and a high-inflammatory diet are important causes of depression. We aimed to explore the level of dietary inflammation in epileptic patients and its relationship with moderate to severe depression (MSD).

Methods：This cross-sectional study included 12,788 participants aged 20-80 years from the NHANES database from 2013 to 2018. Depressive symptoms were evaluated using the nine-item Patient Health Questionnaire (PHQ-9), and epilepsy was diagnosed based on the use of antiepileptic drugs within the previous 30 days. Dietary inflammatory index (DII) scores and energy-adjusted DII (E-DII) scores were calculated based on dietary recalls of the past 24 h, and average DII (ADII) and energy-adjusted ADII (E-ADII) were calculated based on two 24-hour dietary recalls.

Results：The DII, E-DII, and ADII scores and prevalence of MSD were significantly increased in epileptic patients compared with non-epilepsy subjects. The E-ADII score (P = 0.078) was weakly associated with comorbid MSD in patients with epilepsy. Mediation models showed that dietary inflammation scores mediated 2.31 % to 12.25 % of epilepsy-related MSD. In stratified analysis, an increased prevalence of MSD was present in the Quartile 2 subgroup based on DII and E-ADII scores and in the Quartile 3 subgroup of epileptic patients based on DII, E-DII, and ADII scores.

Conclusions： Epileptics consume more proinflammatory foods and nutrients than control subjects. MSD in patients with epilepsy is associated with their high inflammatory diet. Suggesting an urgent need for rational dietary management in the epileptic population.

背景：抑郁症是一个重要的公共卫生问题，癫痫和高炎症性饮食是抑郁症的重要原因。我们的目的是探讨癫痫患者的饮食炎症水平及其与中重度抑郁症(MSD)的关系。

方法：这项横断面研究包括 2013 年至 2018 年 NHANES 数据库中年龄 20-80 岁的 12,788 名受试者。采用 9 项患者健康问卷(PHQ-9)评估抑郁症状，根据过去 30 天内抗癫痫药物的使用情况诊断癫痫。根据过去 24 小时的饮食回顾计算膳食炎症指数(DII)评分和能量-校正 DII (E-DII)评分，并根据两次 24 小时的饮食回顾计算平均 DII (ADII)和能量-校正 DII (E-ADII)。

结果：与非癫痫患者相比，癫痫患者的 DII、E-DII 和 ADII 评分和 MSD 患病率显著增加。E-ADII 评分(P = 0.078)与癫痫患者共病 MSD 相关性较弱。中介模型显示，饮食炎症评分介导了 2.31%至 12.25%的癫痫相关 MSD。在分层分析中，基于 DII 和 E-ADII 评分的四分位 2 亚组和基于 DII、E-DII 和 ADII 评分的四分位 3 亚组癫痫患者的 MSD 患病率增加。

结论：癫痫患者比对照组摄入更多的促炎食物和营养物质。癫痫患者的 MSD 与高炎症性饮食有关。建议癫痫患者迫切需要进行合理的饮食管理。

药物相关基因研究

1.鉴定基因标记作为预测患者对抗癫痫发作药物反应标记的初步研究

A pilot study on identifying gene signatures as markers for predicting patient response to antiseizure medications

Duan Y, Kang L, He Y, Li M, Li T, Wen Z, Chen L. A pilot study on identifying gene signatures as markers for predicting patient response to antiseizure medications. Neurol Sci. 2023 Jun;44(6)：2137-2148. doi：10.1007/s10072-023-06605-2. Epub 2023 Jan 20. PMID： 36658410.

The majority of the biomarkers were associated with the diagnosis of epilepsy and few of them can be applied to predict the response to antiseizure medications (ASMs). In this study, we identified 26 significantly up-regulated genes and 32 down-regulated genes by comparing the gene expression profiles of patients with epilepsy that responded to valproate with those without applying any ASM. The results of gene set enrichment analysis indicated that the ferroptosis pathway was significantly impacted (p = 0.0087) in patients who responded to valproate. Interestingly, the gene NCOA4 in this pathway exhibited significantly different expression levels between the two groups, indicating that NCOA4 could serve as a potential biomarker to better understand the mechanism of valproate resistance. In addition, six up-regulated genes SF3A2, HMGN2, PABPN1, SSBP3, EFTUD2, and CREB3L2 as well as six down-regulated genes ZFP36L1, ACRC, SUB1, CALM2, TLK1, and STX2 also showed significantly different expression patterns between the two groups. Moreover, based on the gene expression profiles of the patients with the treatment of valproate, carbamazepine, and phenytoin, we proposed a strategy for predicting the response to the ASMs by using the Connectivity Map scoring method. Our findings could be helpful for better understanding the mechanisms of drug resistance of ASMs and improving the clinical treatment of epilepsy.

大多数生物标志物与癫痫的诊断相关，其中很少可以用于预测对抗癫痫发作药物(ASMs)的反应。在这项研究中，我们通过比较对丙戊酸钠有反应的癫痫患者和没有应用任何 ASM 的癫痫患者的基因表达谱，确定了 26 个显著上调的基因和 32 个下调的基因。基因集富集分析的结果表明，在对丙戊酸钠有反应的患者中，铁死亡通路受到显著影响(p = 0.0087)。有趣的是，该途径中的基因 NCOA4 在两组之间表现出显著不同的表达水平，这表明 NCOA4 可以作为一种潜在的生物标志物，以更好地了解丙戊酸钠耐药的机制。此外，六个上调基因 SF3A2、HMGN2、PABPN1、SSBP3、EFTUD2 和 CREB3L2 以及六个下调基因 ZFP36L1、ACRC、SUB1、CALM2、TLK1 和 STX2 在两组之间也显示出明显不同的表达模式。基于接受丙戊酸钠、卡马西平和苯妥英治疗患者的基因表达谱，我们提出了一种使用连接地图评分方法预测对 ASMs 反应的策略。我们的研究结果将有助于更好地理解 ASMs 的耐药机制和提高癫痫的临床治疗水平。

2.癫痫队列的风险性 HLA 变异：全基因组测序在临床实践中多方面应用的获益

Risk-conferring HLA variants in an epilepsy cohort： benefits of multifaceted use of whole genome sequencing in clinical practice

Vakrinou A, Bellampalli R, Gulcebi MI, Martins Custodio H, Research Consortium GE, Balestrini S, Sisodiya SM. Risk-conferring HLA variants in an epilepsy cohort： benefits of multifaceted use of whole genome sequencing in

clinical practice. J Neurol Neurosurg Psychiatry. 2023 Jun 26：jnnp-2023-331419. doi： 10.1136/jnnp-2023-331419. Epub ahead of print. PMID： 37364985.

Abstract

Background：Whole genome sequencing is increasingly used in healthcare, particularly for diagnostics. However, its clinically multifaceted potential for individually customised diagnostic and therapeutic care remains largely unexploited. We used existing whole genome sequencing data to screen for pharmacogenomic risk factors related to antiseizure medication-induced cutaneous adverse drug reactions (cADRs), such as human leucocyte antigen HLA-B*15：02, HLA-A*31：01 variants.

Methods：Genotyping results, generated from the Genomics England UK 100 000 Genomes Project primarily for identification of disease-causing variants, were used to additionally screen for relevant HLA variants and other pharmacogenomic variants. Medical records were retrospectively reviewed for clinical and cADR phenotypes for HLA variant carriers. Descriptive statistics and the χ2 test were used to analyse phenotype/genotype data for HLA carriers and compare frequencies of additional pharmacogenomic variants between HLA carriers with and without cADRs, respectively.

Results：1043 people with epilepsy were included. Four HLA-B*15：02 and 86 HLA-A*31：01 carriers were identified. One out of the four identified HLA-B*15：02 carriers had suffered antiseizure medication-induced cADRs; the point prevalence of cADRs was 16.9% for HLA-A*31：01 carriers of European origin (n=46) and 14.4% for HLA-A*31：01 carriers irrespective of ancestry (n=83).

Conclusions：Comprehensive utilisation of genetic data spreads beyond the search for causal variants alone and can be extended to additional clinical benefits such as identifying pharmacogenomic biomarkers, which can guide pharmacotherapy for genetically-susceptible individuals.

背景：全基因组测序越来越多地应用于医疗保健领域，特别是诊断领域。然而，其在个性化定制诊断和治疗护理方面的临床多方面潜力仍未得到充分利用。我们利用现有的全基因组测序数据来筛选与抗惊厥药物引起的皮肤药物不良反应（cADRs）相关的药物基因组风险因素，例如人类白细胞抗原 HLA-B*15：02 、HLA-A*31： 01 变异。

方法：基因分型结果来自英国基因组学 10 万人基因组计划，主要用于鉴定致病变异，用于额外筛选相关的 HLA 变异和其他药物基因组变异。回顾性审查 HLA 变异携带者的临床和 cADR 表型的医疗记录。采用描述性统计和 χ2 检验对 HLA 携带者的表型/基因型数据进行分析，并比较有和无 cADRs 的 HLA 携带者之间额外药物基因组变异的频率。

结果：纳入了 1043 名癫痫患者。鉴定出 4 名 HLA-B*15：02 和 86 名 HLA-A*31：01 携带者。四分之一的 HLA-B*15：02 携带者患有抗癫痫药物引起的 cADR；欧洲血统的 HLA-A*31：01 携带者 (n=46)的 cADR 点患病率为 16.9% ，其他血统的 HLA-A*31：01 携带者 (n=83) 的 cADR 点患病率为 14.4%。

结论：遗传数据的综合利用不仅局限于寻找因果变异，还可扩展到其他临床获益，例如识别药物基因组生物标志物，可指导遗传易感个体的药物治疗。

机制研究

1.Nav1.7 拮抗剂的结构定位

Structural mapping of Nav1.7 antagonists

Wu Q, Huang J, Fan X, Wang K, Jin X, Huang G, Li J, Pan X, Yan N. Structural mapping of Nav1.7 antagonists. Nat Commun. 2023 Jun 3;14(1)：3224. doi： 10.1038/s41467-023-38942-3. PMID： 37270609; PMCID： PMC10239435.

Voltage-gated sodium (Nav) channels are targeted by a number of widely used and investigational drugs for the treatment of epilepsy, arrhythmia, pain, and other disorders. Despite recent advances in structural elucidation of Nav channels, the binding mode of most Nav-targeting drugs remains unknown. Here we report high-resolution cryo-EM structures of human Nav1.7 treated with drugs and lead compounds with representative chemical backbones at resolutions of 2.6-3.2 Å. A binding site beneath the intracellular gate (site BIG) accommodates carbamazepine, bupivacaine, and lacosamide. Unexpectedly, a second molecule of lacosamide plugs into the selectivity filter from the central cavity. Fenestrations are popular sites for various state-dependent drugs. We show that vinpocetine, a synthetic derivative of a vinca alkaloid, and hardwickiic acid, a natural product with antinociceptive effect, bind to the III-IV fenestration, while, an analgesic candidate, penetrates the IV-I fenestration of the pore domain. Our results permit building a 3D structural map for known drug-binding sites on Nav channels summarized from the present and previous structures.

电压门控钠(Nav)通道是许多广泛使用和正在研究的癫痫、心律失常、疼痛和其他疾病的治疗药物靶点。尽管最近在 Nav 通道的结构解析方面取得了进展，但大多数 Nav 靶向药物的结合模式仍然未知。在这里，我们报告了用具有代表性化学骨架的药物和先导化合物处理过的人类 Nav1.7 的高分辨率低温电镜结构，分辨率为 2.6-3.2 Å。胞内门下方的结合位点(BIG 位点)容纳卡马西平、布比卡因和拉考沙胺。出乎意料的是，第二个拉考沙胺分子从中央孔插入选择性过滤器。孔是各种状态依赖性药物的常见结合位点。我们发现长春花生物碱的合成衍生物长春花碱和具有抗痛感作用的天然产物硬柳酸(hardwickiic acid)结合到 III-IV 孔，而维克三嗪(vixotrigine)，一种镇痛药物，穿透孔域的 IV-I 孔。我们的研究结果可以建立一个三维结构图，从现有和以前的结构中总结出 Nav 通道上已知的药物结合位点。

2.酪蛋白激酶 2 通过调节离子通道影响癫痫： 一个潜在的机制

Casein kinase 2 affects epilepsy by regulating ion channels： a potential mechanism

Liu Y, Xia D, Zhong L, Chen L, Zhang L, Ai M, Mei R, Pang R. Casein kinase 2 affects epilepsy by regulating ion channels：a potential mechanism. CNS Neurol Disord Drug Targets. 2023 Jun 22. doi： 10.2174/1871527322666230622124618. Epub ahead of print. PMID： 37350003.

Abstract

Epilepsy, characterized by recurrent seizures and abnormal brain discharges, is the third most common chronic disorder of the Central Nervous System (CNS). Although significant progress has been made in the research on

antiepileptic drugs (AEDs), approximately one-third of patients with epilepsy are refractory to these drugs. Thus, research on the pathogenesis of epilepsy is ongoing to find more effective treatments. Many pathological mechanisms are involved in epilepsy, including neuronal apoptosis, mossy fiber sprouting, neuroinflammation, and dysfunction of neuronal ion channels, leading to abnormal neuronal excitatory networks in the brain. CK2 (Casein kinase 2), which plays a critical role in modulating neuronal excitability and synaptic transmission, has been shown to be associated with epilepsy. However, there is limited research on the mechanisms involved. Recent studies have suggested that CK2 is involved in regulating the function of neuronal ion channels by directly phosphorylating them or their binding partners. Therefore, in this review, we will summarize recent research advances regarding the potential role of CK2 regulating ion channels in epilepsy, aiming to provide more evidence for future studies.

癫痫是中枢神经系统（CNS）的第三大最常见的慢性疾病，以反复发作和异常的脑部放电为特征。尽管抗癫痫药物（AEDs）的研究取得了重大进展，但约三分之一的癫痫患者对这些药物是耐药性的。因此，对癫痫发病机制的研究正在进行中，以寻找更有效的治疗方法。癫痫涉及多种病理机制，包括神经元凋亡、苔藓纤维芽生、神经炎症、神经元离子通道功能障碍等，导致脑内神经元兴奋性网络异常。CK2（酪蛋白激酶 2）在调节神经元兴奋性和突触传递中起着关键作用，已被证明与癫痫有关。然而，对其相关机制的研究还有限。最近的研究表明，CK2 通过直接磷酸化神经元离子通道或其结合配体，参与调节它们的功能。因此，本文将对近年来 CK2 调节离子通道在癫痫中潜在作用的研究进展进行综述，为今后的研究提供更多的依据。

新药

1.枫香树脂精油作为抗癫痫药物的分子模型、神经行为学特征及毒性评估

In silico molecular modeling, neuro-behavioral profile, and toxicity assessment of the essential oil of Ferula gummosa Boiss. as an anti-seizure agent

Bashiri-Nahnjeh M, Sarihi A, Ebadi A, Dastan D, Mohammadi M. In silico molecular modeling, neuro-behavioral profile, and toxicity assessment of the essential oil of Ferula gummosa Boiss. as an anti-seizure agent. J Ethnopharmacol. 2023 Jun 12;309：116347. doi： 10.1016/j.jep.2023.116347. Epub 2023 Mar 7. PMID： 36894108.

Abstract

Ethnopharmacological relevance：Ferula gummosa Boiss., known in Persian as "Baridje," belongs to the Apiaceae family. All parts of this plant, especially the root, contain galbanum. Galbanum, the oleo-gum resin of F. gummosa, is one of the essential traditional herbal medicines in Iran, which is used as a tonic for epilepsy and chorea, memory enhancement, gastrointestinal diseases, and wound healing.

Aim of the study：We investigated the toxicity, anticonvulsant effects, and molecular modeling of the essential oil (EO) distilled from the oleo-gum resin of F. gummosa.

Materials and methods：Gas chromatography-mass spectrometry was used to identify the EO components. The cytotoxicity of EO on HepG2 cell lines was assessed by the MTT method. Male mice were arranged as follows：negative control groups (sunflower oil (10 ml/kg, i.p.) or saline (10 ml/kg, p.o.)), EO groups (0.5, 1, 1.5, and 2.5 ml/kg, p.o.), and positive control groups (ethosuximide (150 mg/kg, p.o.) or diazepam (1.0 or 2 mg/kg, i.p.)). The motor coordination and neurotoxicity of EO were studied using the rota-rod test. Open-field, novel object recognition, and passive avoidance learning tests were used to investigate the effect of EO on locomotor activity and memory function. An acute pentylenetetrazole-induced seizure model was utilized to evaluate the anticonvulsant properties of the EO. The interaction of the EO main components with the GABAA receptor was investigated by coarse-grained molecular dynamics simulations.

Results：β-pinene, sabinene, α-pinene, and ρ-cymene were the main components of EO. The IC50 of the EO at 24, 48, and 72 h was found to be 59.90, 12.96, and 3.93 µl/ml, respectively. No adverse effects were observed in memory, motor coordination, and locomotor activity in mice treated with EO. Administration of EO (1, 1.5, and 2.5 ml/kg) improved survival rates in mice receiving pentylenetetrazole (PTZ; to induce an epileptic seizure). Sabinene was able to bind to the binding site of benzodiazepines at the GABAA receptor.

Conclusions：Acute treatment with the EO of F. gummosa caused antiepileptic effects and could effectively increase the survival rate in PTZ-treated mice with no significant toxicity.

民族药理学相关：Ferula gummosa Boiss 在波斯语中被称为“Baridje”，属于伞形科。这种植物的所有部分，尤其是根部，都含有白松香。枫香油胶树脂白松香是伊朗重要的传统草药之一，被用作治疗癫痫及舞蹈病、增强记忆、胃肠道疾病、促进伤口愈合。

目的：研究从枫香油胶树脂中提取的精油(EO)的毒性、抗惊厥作用及分子模型。

材料与方法：采用气相色谱-质谱法对其进行鉴定。采用 MTT 法评价 EO 对 HepG2 细胞株的细胞毒性。雄性小鼠分为阴性对照组(葵花籽油(10 ml/kg, 1 次)或生理盐水(10 ml/kg, 1 次)，EO 组(0.5、1、1.5、2.5 ml/kg, 1 次)，阳性对照组(乙氧亚胺(150 mg/kg, 1 次)或地西泮(1.0、2 mg/kg, 1 次)。采用旋转杆(rota-rod)试验研究 EO 对运动协调性的影响和神经毒性。采用旷场、新物体识别和被动回避学习测试来研究 EO 对运动活动和记忆功能的影响。采用急性戊四唑诱发癫痫模型，评价其抗惊厥作用。通过粗粒度分子动力学模拟研究 EO 主要组分与 GABAA 受体的相互作用。

结果：β-蒎烯、桧烯、α-蒎烯和 ρ-甲基异丙基苯是 EO 的主要成分。在 24、48 和 72 h 时，EO 的 IC50 分别为 59.90、12.96 和 3.93 μl/ml。在小鼠的记忆、运动协调和运动活动方面未观察到不良反应。给予 EO(1,1.5 和 2.5 ml/kg)可提高接受戊四唑(PTZ;诱导癫痫发作)小鼠的存活率。桧烯能与 GABAA 受体上苯二氮卓类药物的结合位点结合。

结论：枫香油胶树脂具有抗癫痫作用，可有效提高 PTZ 处置小鼠的存活率，且无明显毒性。

2.反应性 A1 星形胶质细胞靶向核酸纳米抗癫痫药物下调腺苷激酶逆转内源性抗癫痫通路

Reactive A1 Astrocyte-Targeted Nucleic Acid Nanoantiepileptic Drug Downregulating Adenosine Kinase to Rescue Endogenous Antiepileptic Pathway

Zhu J, Qiu W, Wei F, Wang Y, Wang Q, Ma W, Xiong H, Cui Y, Li X, Xu R, Lin Y. Reactive A1 Astrocyte-Targeted Nucleic Acid Nanoantiepileptic Drug Downregulating Adenosine Kinase to Rescue Endogenous Antiepileptic Pathway. ACS Appl Mater Interfaces. 2023 Jun 19. doi： 10.1021/acsami.3c03455. Epub ahead of print. PMID： 37334941.

Abstract： Resistance to traditional antiepileptic drugs is a major challenge in chronic epilepsy treatment. MicroRNA-based gene therapy is a promising alternative but has demonstrated limited efficacy due to poor blood-brain barrier permeability, cellular uptake, and targeting efficiency. Adenosine is an endogenous antiseizure agent deficient in the epileptic brain due to elevated adenosine kinase (ADK) activity in reactive A1 astrocytes. We designed a nucleic acid nanoantiepileptic drug (tFNA-ADKASO@AS1) based on a tetrahedral framework nucleic acid (tFNA), carrying an antisense oligonucleotide targeting ADK (ADKASO) and A1 astrocyte-targeted peptide (AS1). This tFNAADKASO@AS1 construct effectively reduced brain ADK, increased brain adenosine, mitigated aberrant mossy fiber sprouting, and reduced the recurrent spontaneous epileptic spike frequency in a mouse model of chronic temporal lobe epilepsy. Further, the treatment did not induce any neurotoxicity or major organ damage. This work provides proof-of-concept for a novel antiepileptic drug delivery strategy and for endogenous adenosine as a promising target for gene-based modulation

摘要：传统抗癫痫药物的耐药性是慢性癫痫治疗的主要挑战。基于 MicroRNA 的基因治疗是一种很有前途的替代方法，但由于血脑屏障渗透性差、细胞摄取和靶向效率低，其疗效有限。腺苷是一种内源性抗癫痫药，由于反应性 A1 星形胶质细胞中腺苷激酶(ADK)活性升高，癫痫患者脑中缺乏腺苷。我们设计了一种基于四面体构架

核酸(tFNA)的核酸纳米抗癫痫药物(tFNA-ADKASO@AS1)，该药物携带靶向 ADK（ADKASO)和 A1 星形细胞靶向肽(AS1)的反义寡核苷酸。在慢性颞叶癫痫小鼠模型中，这种 tFNAADKASO@AS1 结构有效降低脑 ADK，增加了脑腺苷，减轻苔藓纤维的异常芽生，并降低复发性自发癫痫样棘波的频率。此外，该治疗未导致任何神经毒性或重要器官损伤。这项工作为新型抗癫痫药物递送策略和内源性腺苷作为基因调控的希望靶点提供了概念验证。

药物副作用

1.加巴喷丁致心房颤动一例病例报告

Atrial fibrillation induced by gabapentin： a case report

Park SH, Hunter K, Berry H, Martins YC. Atrial fibrillation induced by gabapentin： a case report. J Med Case Rep. 2023 Jun 9;17(1)：236. doi： 10.1186/s13256-023-03975-1. PMID： 37291648; PMCID： PMC10251649.

Background：Gabapentin is commonly prescribed for the treatment of neuropathic pain, restless leg syndrome, and partial-onset seizures. Although the most frequent side effects of gabapentin are associated with the central nervous system, gabapentin can also affect the cardiovascular system. Case reports and observational studies have showed that gabapentin can be associated with increased risk of atrial fibrillation. However, all the evidence is concentrated in patients older than 65 years old with comorbidities that predispose them to the development of arrhythmias.

Case presentation：We describe a case of an African American male in his 20s that presented to our chronic pain clinic with lumbar radiculitis and developed atrial fibrillation 4 days after being started on gabapentin. Laboratory workup did not show significant abnormalities, including normal complete blood count, comprehensive metabolic panel, toxicology screen, and thyroid-stimulating hormone. Transthoracic and transesophageal echocardiography showed a patent foramen ovale with right-to-left shunt. The patient was initially treated with diltiazem for heart rate control and apixaban. Direct current cardioversion with successful conversion to sinus rhythm was performed 24 hours after admission. The patient was then discharged on apixaban and diltiazem. Apixaban was changed to low-dose aspirin 1 month after discharge.

Conclusion：With rapidly increasing usage of gabapentin for approved and off-label indications, it is important to identify unintended adverse effects of this drug as they are considered safe alternatives to opioids. New-onset atrial fibrillation could be induced by gabapentin in young individuals.

背景：加巴喷丁常用于神经性疼痛、不宁腿综合征和局灶性起源癫痫发作的治疗。尽管加巴喷丁最常见的副作用与中枢神经系统有关，但加巴喷丁也会影响心血管系统。病例报告和观察性研究表明，加巴喷丁可能与房颤风险增加有关。然而，所有的证据都集中在 65 岁以上有合并症的患者身上，这些合并症使他们易患心律失常。

病例介绍：我们描述了一个 20 多岁的非洲裔美国男性病例，因腰椎脊神经根炎就诊于我们的慢性疼痛门诊，在开始服用加巴喷丁 4 天后出现房颤。实验室检查未发现明显异常，包括全血细胞计数、综合代谢组、毒理学筛查和促甲状腺激素均正常。经胸及经食道超声心动图显示卵圆孔未闭伴右至左分流。患者最初使用地尔硫卓控制心率和阿哌沙班治疗。入院 24 小时后进行了直流电复律，并成功转复为窦性心律。患者出院后给予阿哌沙班和地尔硫卓治疗。阿哌沙班在出院 1 个月后改为小剂量阿司匹林。

结论：随着加巴喷丁在批准适应证和说明书外适应证中的使用迅速增加，确定这种药物的意外不良反应非常重要，因为它们被认为是阿片类药物的安全替代品。加巴喷丁可诱发年轻人新发心房颤动。

药物监测

1.提高癫痫患者抗癫痫药物耐受性：药学服务的影响

Improving antiepileptic drug tolerability among patients living with epilepsy： the impact of pharmaceutical care services.

Eshiet UI, Ubaka C, Igboeli N. Improving antiepileptic drug tolerability among patients living with epilepsy： the impact of pharmaceutical care services. Psychol Health Med. 2023 Jun 12 ： 1-11. doi ： 10.1080/13548506.2023.2224040. Epub ahead of print. PMID： 37309133.

Therapeutic management of epilepsy is usually long term; thus, patient tolerability of prescribed antiepileptic drugs should be a major consideration as it affects compliance to therapy. The aim of this study was to determine the impact of pharmaceutical care services on antiepileptic drug tolerability among patients living with epilepsy. This study was an open, randomized, controlled, longitudinal and two-arm parallel prospective study with a 6-month patient follow-up period. Patients were recruited from the neurology and medical out-patient clinics of two selected epilepsy referral centres. Recruited patients were randomized into one of the two study groups： pharmaceutical care (PC) or usual care (UC) groups. Patients in the UC group received the usual care provided in the hospitals, while patients in the PC group received PC services in addition to the usual care provided in the hospitals. The impact of PC on patient tolerability of antiepileptic drugs was evaluated using a patient judged antiepileptic drug tolerabiltity scale. The evaluation was done at baseline (pre-intervention), 3 months and 6 months post-intervention. Patients in the PC group had a significantly lower antiepileptic drug tolerability score than those of the UC group at 3 months and 6 months - (Pre-intervention： 0.97 versus 1.13; t = -1.081; p = 0.281), (3 months： 1.13 versus 0.71; t = 3.084; p = 0.001), (6 months： 1.00 versus 0.60; t = 3.083; p = 0.001), indicating a significant improvement in the tolerability of antiepileptic drugs among those in the PC group over time. Pharmaceutical care interventions that included education and counseling services significantly improved tolerability of antiepileptic drugs among patients living with epilepsy.

癫痫的治疗管理通常是长期的。因此，患者对处方抗癫痫药物的耐受性应该是一个主要考虑因素，因为它会影响治疗的依从性。本研究的目的是确定药学服务对癫痫患者抗癫痫药物耐受性的影响。本研究是一项开放、随机、对照、纵向、双臂平行前瞻性研究，患者随访期为 6 个月。患者是从两个选定的癫痫转诊中心的神经科和内科门诊招募的。招募的患者被随机分为两组：药学护理组(PC)或常规护理组(UC)。UC 组患者接受医院提供的常规护理，而 PC 组患者在医院提供的常规护理之外接受 PC 服务。采用患者判断抗癫痫药物耐受性量表评价 PC 对患者抗癫痫药物耐受性的影响。评估分别在基线(干预前)、干预后 3 个月和 6 个月进行。在 3 个月和 6 个月时，PC 组患者的抗癫痫药物耐受性评分明显低于 UC 组(干预前：0.97 对 1.13;T = -1.081;P = 0.281)，(3 个月：1.13 vs 0.71;T = 3.084;P = 0.001)，(6 个月：1.00 vs 0.60;T = 3.083;p = 0.001)，表明随着时间的推移，PC 组抗癫痫药物耐受性有显著改善。包括教育和咨询服务在内的药物保健干预措施显著提高了癫痫患者对抗癫痫药物的耐受性。