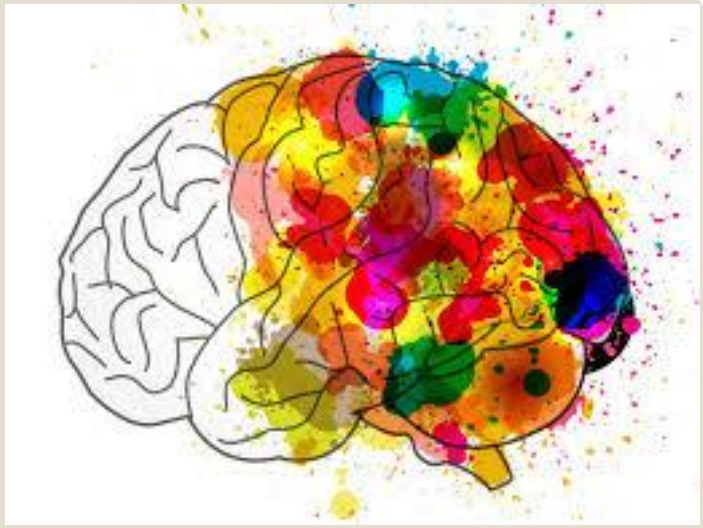
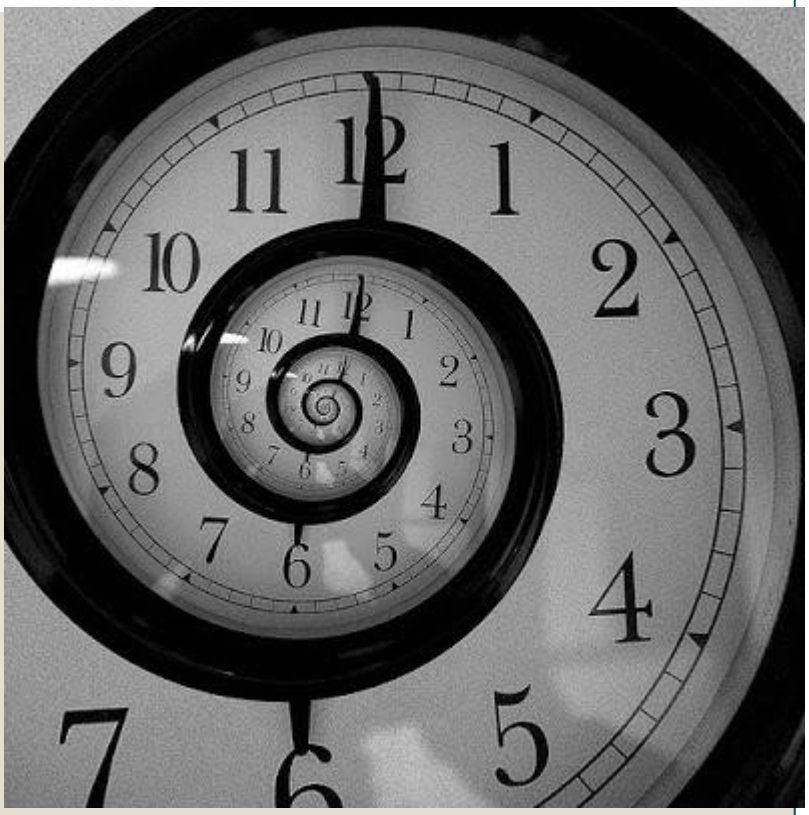
2018 YILINDA NÖROLOJİ ALANINDA NELER OLDU?



ÖZLEM TAŞKAPILIOĞLU



NEUROLOGICAL DISORDERS
public health challenges

World Health Organization

Table 2.4 Number of DALYs for neurological disorders and as percentage of global DALYs projected for 2005, 2015 and 2030

Cause category	2005		2015		2030	
	No. of DALYs (000)	Percentage of total DALYs	No. of DALYs (000)	Percentage of total DALYs	No. of DALYs (000)	Percentage of total DALYs
Epilepsy	7308	0.50	7419	0.50	7442	0.49
Alzheimer and other dementias	11078	0.75	13540	0.91	18394	1.20
Parkinson's disease	1617	0.11	1762	0.12	2015	0.13
Multiple sclerosis	1510	0.10	1586	0.11	1648	0.11
Migraine	7660	0.52	7736	0.52	7596	0.50
Cerebrovascular disease	50785	3.46	53815	3.63	60864	3.99
Poliomyelitis	115	0.01	47	0.00	13	0.00
Tetanus	6423	0.44	4871	0.33	3174	0.21
Meningitis	5337	0.36	3528	0.24	2039	0.13
Japanese encephalitis	561	0.04	304	0.02	150	0.01
Total	**92392**	**6.29**	**94608**	**6.39**	**103335**	**6.77**

disability-adjusted life years (DALYs) (Yeti yitimine ayarlanmış yaşam yılı)

1 DALY: Yaşamdan kaybedilmiş sağlıklı bir yıl

World Health Organization 2006

Table 2.5 DALYs per 100 000 population for neurological disorders globally and by World Bank income category, 2005

Cause category	World (100 000 population)	Income category			
		Low	Lower middle	Upper middle	High
Epilepsy	113.4	158.3	80	139.2	51.3
Alzheimer and other dementias	172	90.7	150.7	166.9	457.3
Parkinson's disease	25.1	15.1	19.7	17.5	70.8
Multiple sclerosis	23.4	20.1	23.3	24.9	32.5
Migraine	118.9	114	106.8	147.1	146.3
Cerebrovascular disease	788.4	662.5	1 061.2	612.2	592
Poliomyelitis	1.8	2.6	1.6	0.9	0.6
Tetanus	99.7	228.6	10.8	1.3	0.1
Meningitis	82.9	143.2	51.2	39.7	10.7
Japanese encephalitis	8.7	13	9	0.4	0.6
Total	**1 434.3**	**1 448.1**	**1 514.3**	**1 150.1**	**1 362.2**

Figure 2.2 DALYs for individual neurological disorders as percentage of total neurological disorders

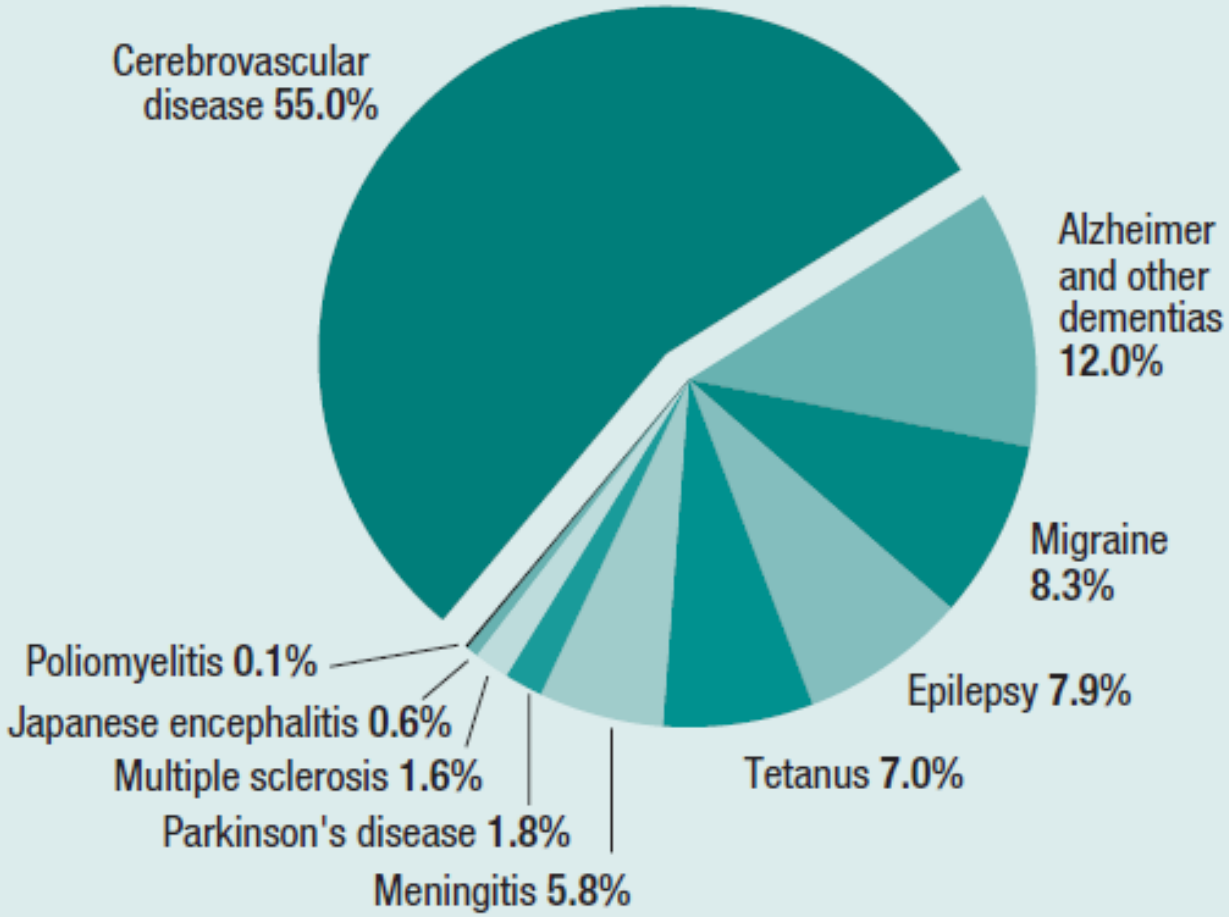


Figure 2.3 Neurological disorders as percentage of total DALYs for 2005, 2015 and 2030 across World Bank income category

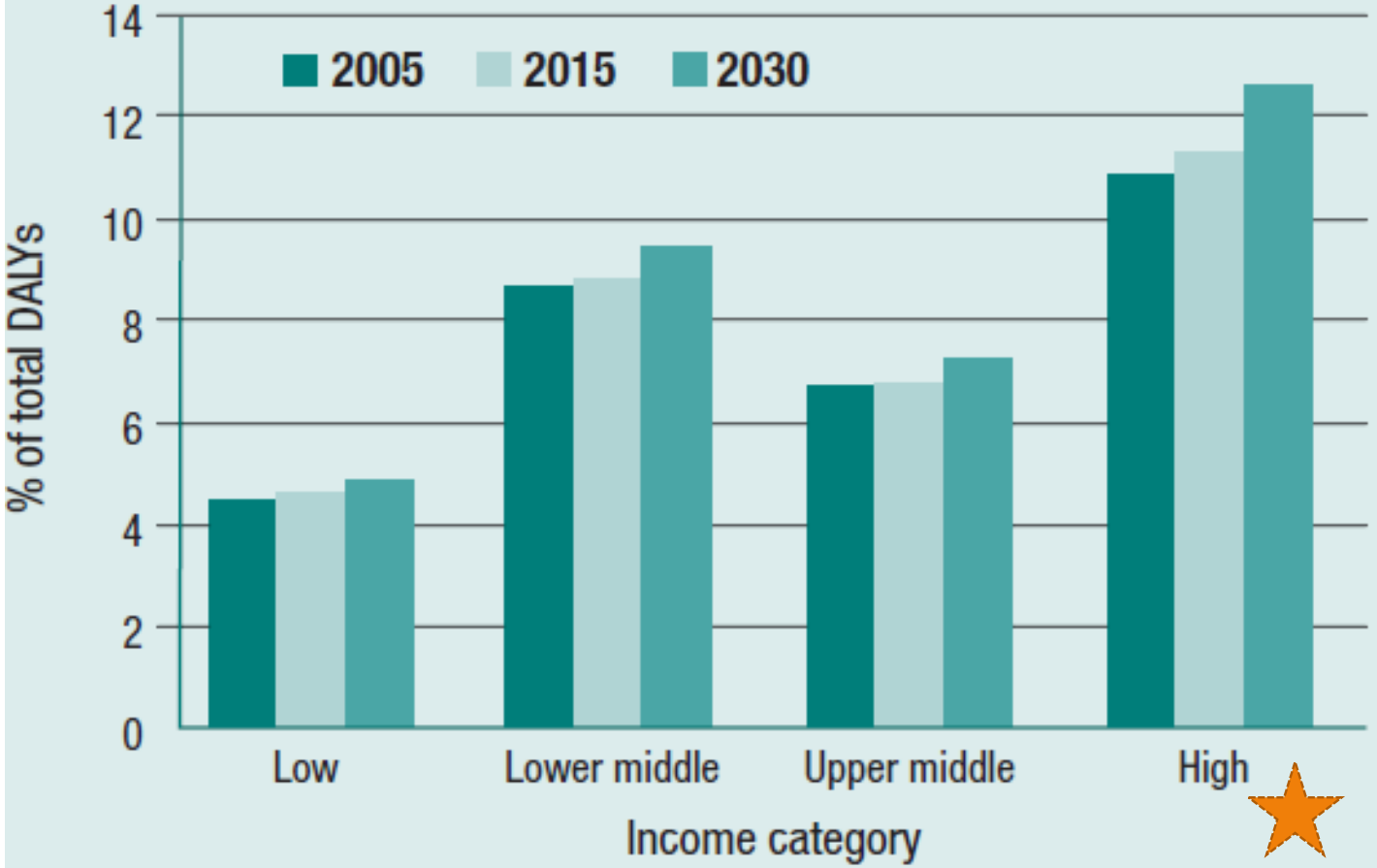


Figure 2.4 DALYs per 100 000 population associated with neurological disorders by WHO region and mortality stratum, 2005

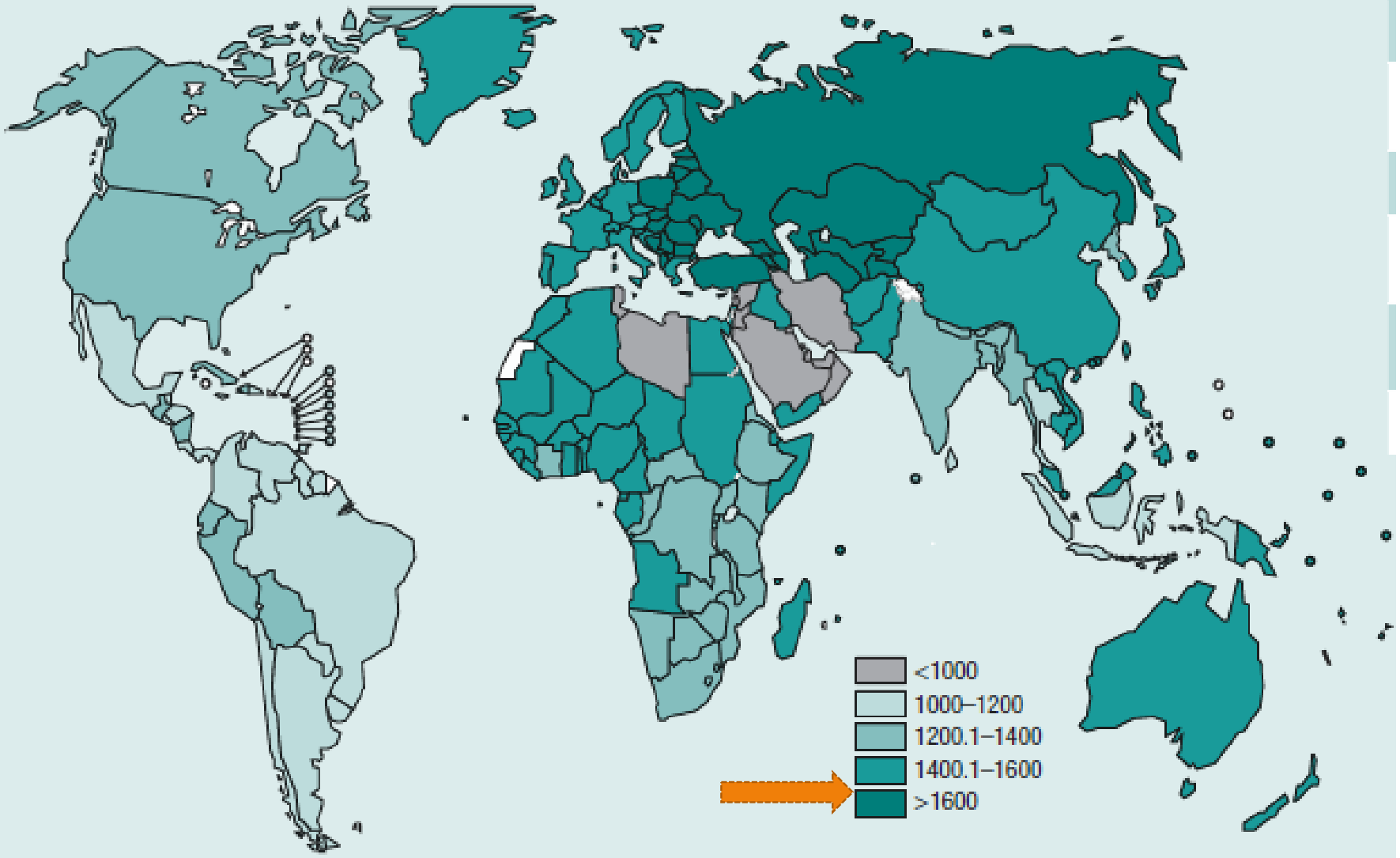
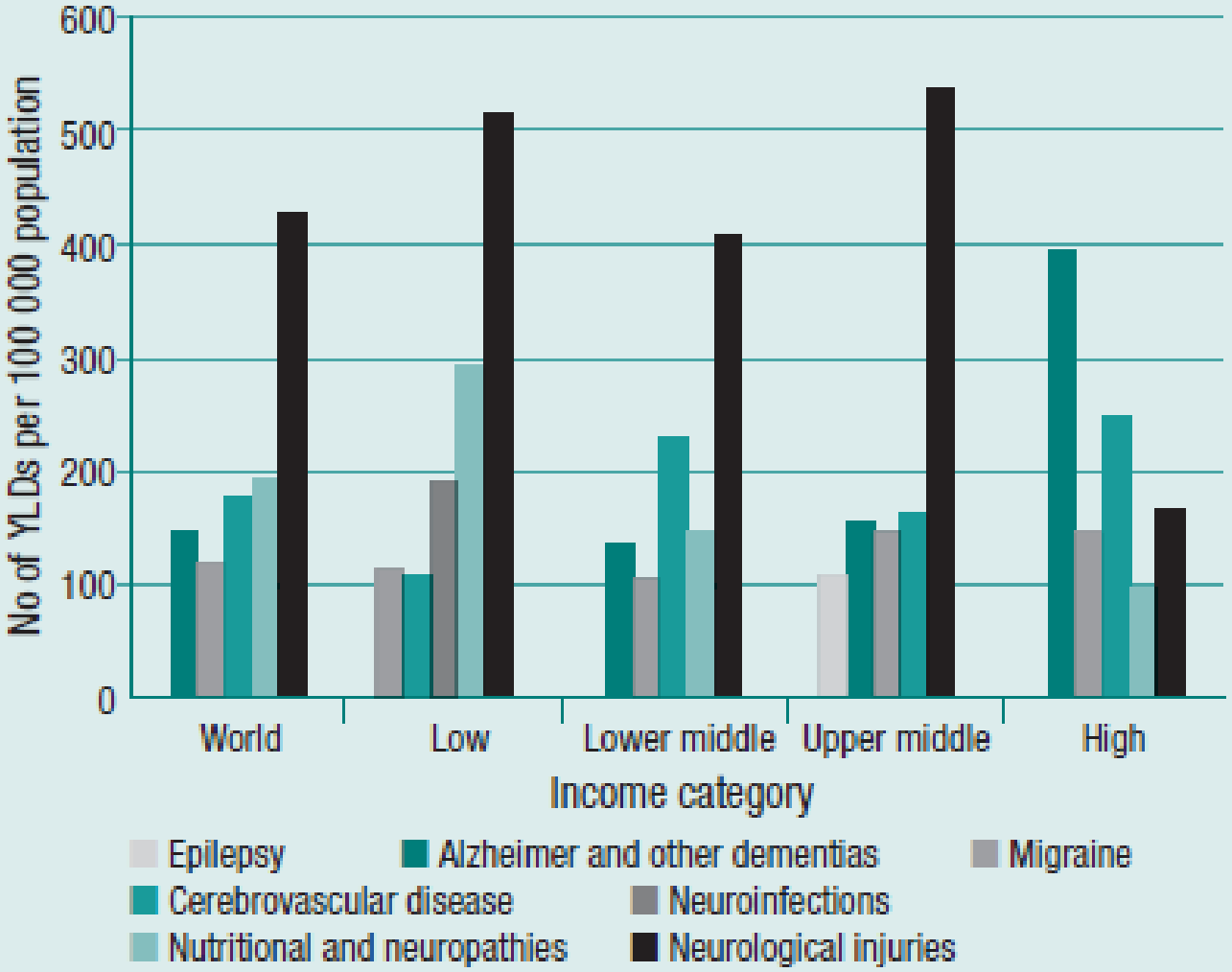


Figure 2.7 Top five causes of YLDs among neurological disorders, by World Bank income category, 2005



years of life lost to disability (YLDs) Yeti yitimi ile geçirilen yıllar

Frequency, associated features, and burden of neurological disorders in older adult inpatients in Brazil: a retrospective cross-sectional study

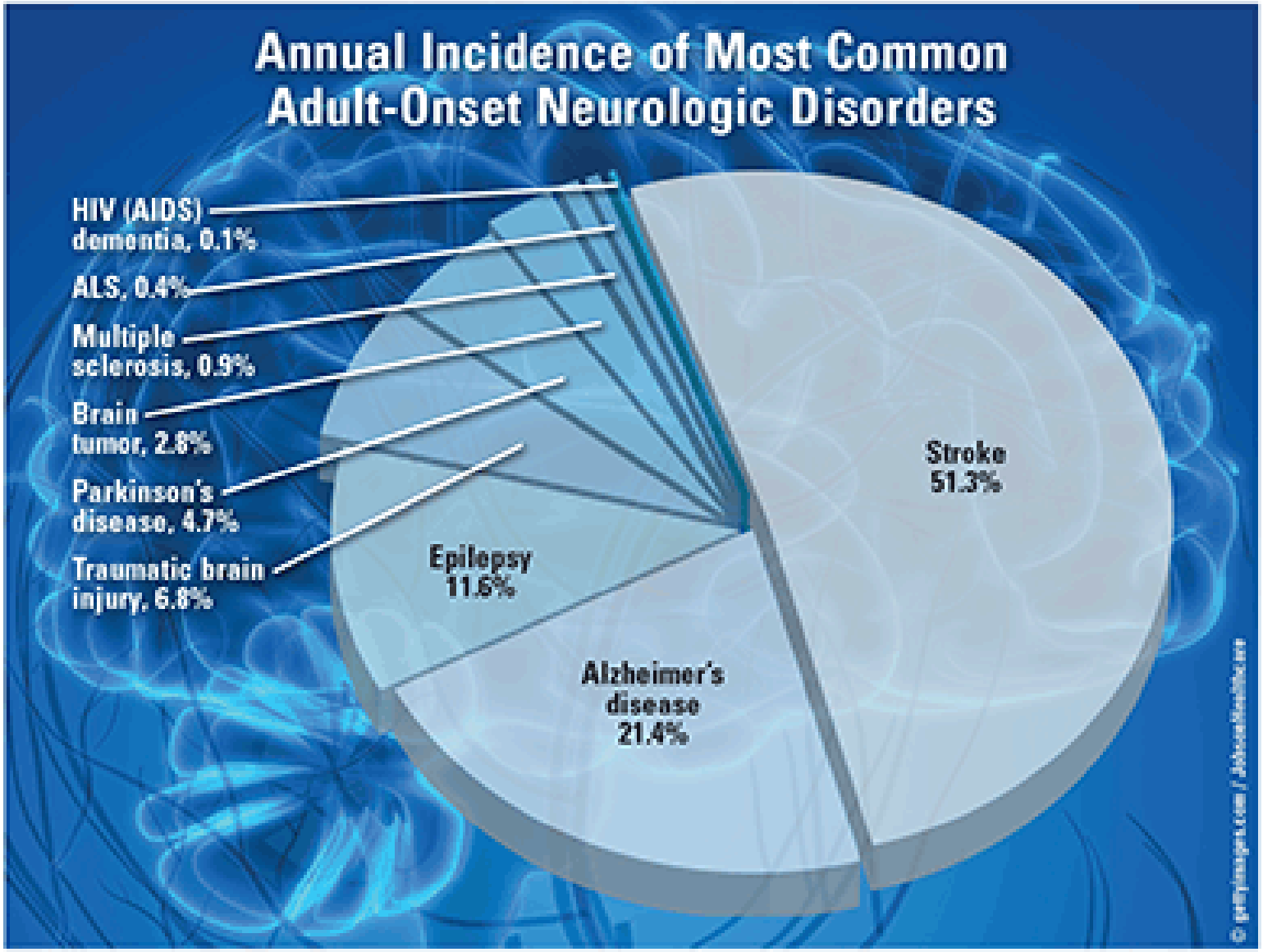
Aroldo Bacellar*, Bruno B. Pedreira, Gersonita Costa and Telma Assis

Table 1 Diagnostic frequency of neurological disorders among older adult inpatients, distributed by sex

Neurological disorder	Men ($n = 363$)	Women ($n = 435$)	Total ($n = 798$)
Cerebrovascular disease	186 (51%)	219 (50%)	405 (51%)
Cognitive disorder	97 (27%)	102 (23%)	199 (25%)
Movement disorder	75 (21%)	65 (15%)	140 (17%)
Epilepsy	62 (17%)	65 (15%)	127 (16%)
Syncope	53 (15%)	69 (16%)	122 (15%)
Headache	42 (12%)	60 (14%)	102 (13%)
Neuromuscular	19 (5%)	36 (8%)	55 (7%)
Toxic & metabolic	7 (2%)	5 (1%)	12 (1%)
CNS infection	3 (0.8%)	2 (0.5%)	5 (0.6%)
Brain injury	0	3 (0.7%)	3 (0.4%)
CNS neoplastic	2 (0.6%)	0	2 (0.3%)
Miscellany	8 (2%)	10 (2%)	18 (2%)
Total	554	636	1190

Abbreviation: *NDs* neurological disorders, *CNS* central nervous system
Note: A total of 350 patients (40%) had more than one neurological disorder (patient neurological multimorbidity)

Bacellar *et al. BMC Health Services Research* (2017) 17:504
DOI 10.1186/s12913-017-2260-x



Incidence and Prevalence of Major Neurologic Disorders, Neurology, 2018

Stroke management — recent advances and residual challenges

Bo Norrving

The past year saw progress in acute treatment of ischaemic stroke, but large inequalities in stroke services were revealed, warranting strategical initiatives to improve treatment access. Reclassification of stroke as a disease of the nervous system in the WHO International Classification of Diseases 11th revision is likely to help such initiatives.

Key advances

- Trials have confirmed that thrombectomy beyond 6 h and up to 24 h since stroke onset substantially benefits patients with large vessel occlusion and salvageable brain tissue[1,2].
- A mismatch of MRI findings in patients with wake-up stroke was shown to identify patients whose stroke onset was probably <4.5 h earlier and who could benefit from thrombolysis[3].
- Substantial inequalities in stroke services between and within countries were revealed; in Europe, research priorities and targets in stroke between 2018 and 2030 have been set[8].
- In the newly released WHO International Classification of Diseases 11th revision, stroke and all cerebrovascular diseases are placed under Diseases of the Nervous System with definitions for global use of the different codes[10].

DAWN VE DEFUSE-3 çalışmaları

- Büyük damar tıkanması ve kurtarılabilir beyin dokusu olan seçilmiş inme olgularında, standart 6 saatlik tedavi penceresini 24 saate uzatıp trombektomi yapmak mümkün.
  - DAWN : Klinik ve enfarkt alanı uyumsuzluğu
    DEFUSE-3: BT veya MR uyumsuzluğuna göre
  - İstenen sonuç için tedavi edilmesi gereken hasta sayısı: 2
  - Penumbranın varlığının pek çok olguda görüntüleme ile ortaya konması gerekli. Bu da daha fazla olgunun inme merkezlerine başvurması ve gözden geçirilmesi demek
  - Amerika ve Kanada Tedavi Kılavuzlarına girdi

- 3 büyük ölçekli çalışma sonuçları:
  - Aspirin, primer strok korumasında etkisiz
  - Sadece kanama riskini arttırıyor
- Trombektomi, beyin görüntüleme yöntemlerine göre seçilmiş olgularda 24 saate dek etkin uygulanabilir
- WAKE-UP strok çalışması:
  - Başlangıcı bilinmeyen inme olgularında, görüntüleme sonuçlarına göre ilk 4.5 saatinde olduğu düşünülenlerde tromboliz yapılabilir

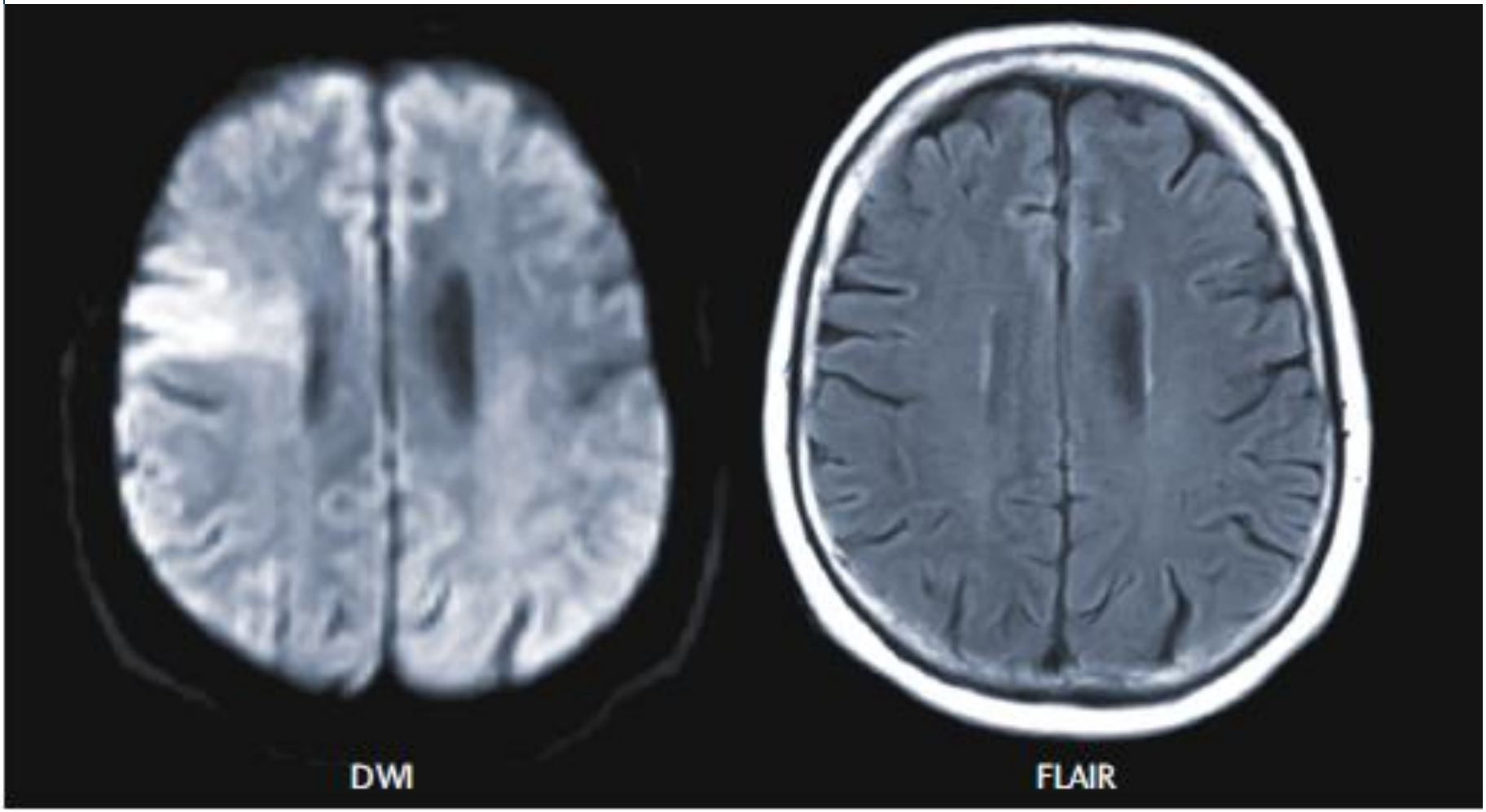


Fig. 1 | **The imaging mismatch between diffusion-weighted imaging (DWI) and fluid attenuation inversion recovery (FLAIR) imaging that indicated a probable benefit of thrombolysis in the WAKE-UP trial.** Image courtesy of Götz Thomalla, University Medical Center Hamburg-Eppendorf, Germany.

İnme ve Patent Foramen Ovale (PFO)

- Daha önce PFO kapatılmasının sekonder inmeyi önlemede açık etkisini göstermeyen çalışmalar:
  - CLOSURE I
  - PC trial
  - RESPECT short-term
  - «Amplatzer PFO occluder» cihazının kullanıldığı alt grup analizleri
- Son dönemde sonlanan iki çalışma:
  - CLOSE: PFO kapatılan her 20 hasta için 5 yılda 1 özürlülük bırakan inmenin engellendiği gösterildi.
  - REDUCE:PFO kapatılan her 28 hasta için 2 yılda 1 olguda inme engelleniyordu.

İnme ve PFO

Büyük PFO'su olan **<60 yaş** olgularda PFO'nu kapatılmasının **etkin**liğini pek çok çalışma gösterdi.

Ancak aterosklerozu olanlarda **yapılmaması** önerilmekte

>60 yaş olgularda işe yarayıp yaramadığı **bilinmiyor**

Cryptogenic Stroke and Patent Foramen Ovale. *J Am Coll Cardiol* 2018;71:1035-1043

ESUS
(kaynağı bulunamamış embolik inme çalışması)

Rivaroksaban ve dabigatran

inme tekrarını önlemede aspirine üstün değil

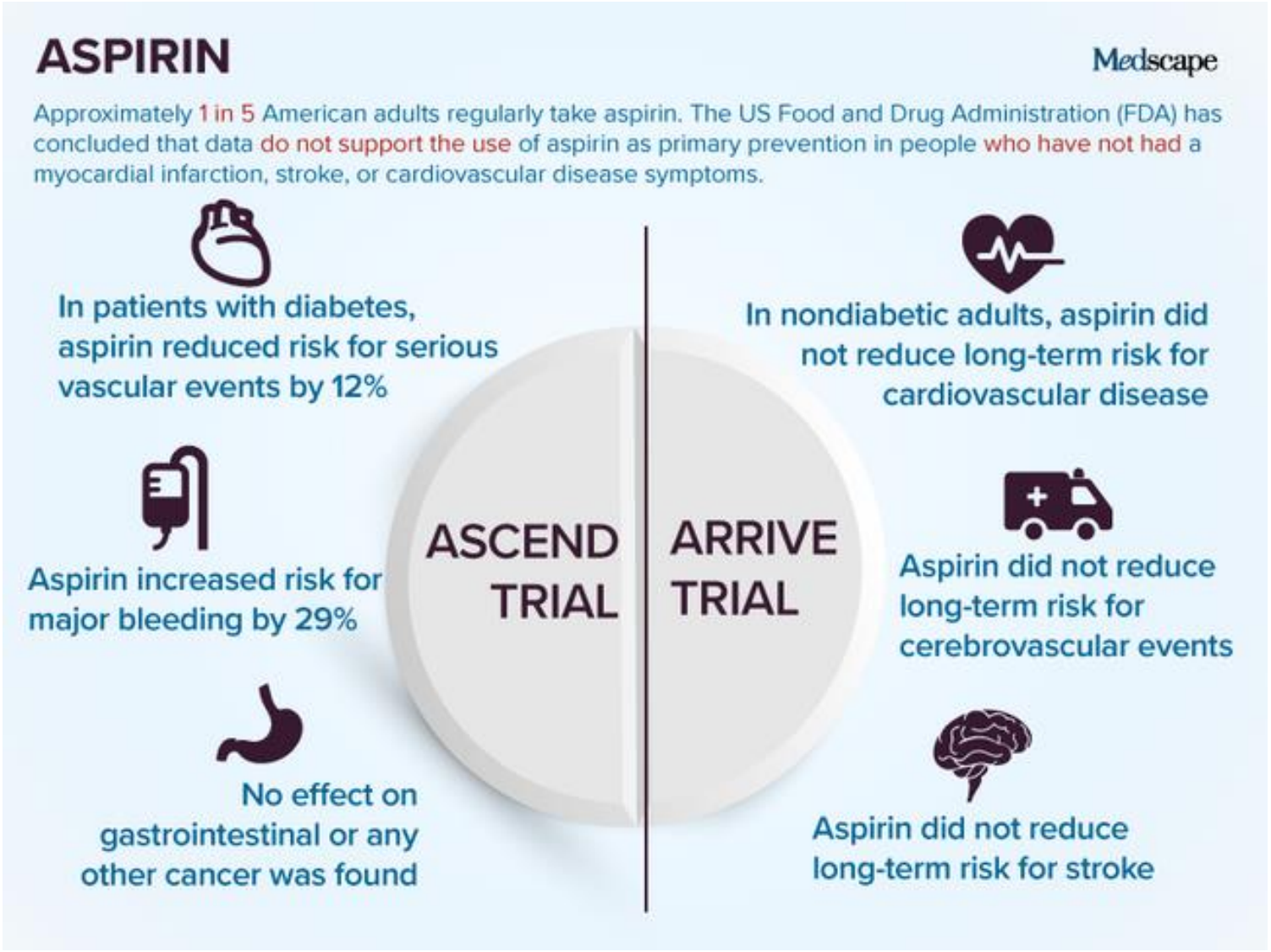
ESUS çalışmasındaki kriptojenik inme olgularında;

Rivaroksabanın kanama riskinin aspirinden fazla dabigatranınkine benzer

European Society of Cardiology 2018 Kongresi'nde iki çalışma sonucu:

- ASCEND (**A S**tudy of **C**ardiovascular **E**vents i**N D**iabetes)
  - DM olgularında 100mg/gün Aspirin ile KVH gelişimine etki ve yan etki profili çalışıldı

- ARRIVE (**A R**andomized T**ri**al of Induction **V**ersus **E**xpectant Management)
  - Orta düzey KVH riski taşıyanlarda aspirinin ilk vasküler olayın yaşanma riskini azaltması çalışıldı


ASPIRIN
Medscape
Approximately 1 in 5 American adults regularly take aspirin. The US Food and Drug Administration (FDA) has concluded that data do not support the use of aspirin as primary prevention in people who have not had a myocardial infarction, stroke, or cardiovascular disease symptoms.
In patients with diabetes, aspirin reduced risk for serious vascular events by 12%
In nondiabetic adults, aspirin did not reduce long-term risk for cardiovascular disease
Aspirin increased risk for major bleeding by 29%
ASCEND TRIAL
ARRIVE TRIAL
Aspirin did not reduce long-term risk for cerebrovascular events
No effect on gastrointestinal or any other cancer was found
Aspirin did not reduce long-term risk for stroke

Bad news and good news in AD, and how to reconcile them

David S. Knopman

2018 saw the failure of several large clinical trials that were based on the premise that reduction of amyloid-β levels is an effective treatment for symptomatic Alzheimer disease. Yet, over the same time period, good news also emerged about the diagnostic value of tau PET imaging.

Credit: Philip Patenall/ Springer Nature Limited

Key advances

- Failures of anti-amyloid-β (Aβ) antibodies have highlighted gaps in understanding their dosing and the timing of their usage in the Alzheimer disease (AD) spectrum[1,2].
- The human clinical trials of BACE1 inhibitors cast doubt on this therapeutic approach but might provide valuable insights into the normal cellular and synaptic functions of Aβ and its precursor[6].
- Tau PET imaging shows excellent specificity and expected sensitivity for clinically diagnosed dementia with elevated Aβ[8].
- A new research framework offers researchers a common language for describing the Aβ, tau and neurodegeneration patterns of patients along the entire cognitive spectrum of AD[10].

AD tedavisinde tüm ilaç çalışmaları başarısız oldu

Neden? Hastalık muhtemelen hasta **ilk bilişsel bozukluk** semptomu ile doktor karşısına gitmeden **20-30 yıl önce** başlıyor

ŞU ANDA **SADECE YAŞAM TARZI DEĞİŞİMLERİ**

DEMANS GELİŞİMİNİ ÖNLEMEDE ETKİN

Sağlıklı beslenme

Düzenli egzersiz

Vasküler risk faktörlerinin tedavisi

Teamwork aids management and raises new issues in epilepsy

Dong Zhou

Publications on epilepsy in 2018 have shed light on the aetiology and management of the condition and raised new questions. Translation from mechanisms to clinical practice, driven by cooperation among multiple fields, will be crucial to further advances.

Credit: Image courtesy of T. En, Chengdu, China.

Key advances

- A longitudinal observational cohort study in newly diagnosed patients with epilepsy revealed that long-term outcomes have not improved with the introduction of new antiepileptic drug (AED) regimens[1].
- Mossy cells — key neurons in the hippocampal excitatory circuit — emerged as promising targets for new epilepsy treatments[5].
- A randomized trial of stereotactic radiosurgery (SRS) versus anterior temporal lobectomy in patients with mesial temporal lobe epilepsy indicated that SRS is a viable alternative to open surgery in selected patients[6].
- Advanced gene sequencing strategies that can detect parental mosaicism should allow more accurate genetic counselling of parents who have offspring with epileptic encephalopathies apparently caused by de novo mutations[8].
- An epidemiological study found that the incidence of sudden unexpected death in epilepsy (SUDEP) in children was comparable to that in adults, suggesting that SUDEP in the paediatric population is more common than previously thought[10].

FEBRUARY 2019 | VOLUME 15

www.nature.com/nrneurol

Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study.

- İngiltere, Avustralya, Çin
- N: 1795, Gözlemsel Çalışma
- Yeni tanı epilepsi hastalarında etkinlik yeni antiepileptik ilaçlar sonrası değişmedi, ödediğimiz ücret arttı.

Chen, Z. et al. *JAMA Neurol.* **75**, 279–286 (2018).

Hipokampusta Dentat Girustaki «Mossy Cells-Tırmanıcı Hücreler»

- Lokal kök hücrelerin yeni nöron oluşturmasını kontrolünde görevli
- Bu durum normal öğrenme ve bellek, stres yanıtı ve duygu durumunun düzenlenmesinde önemli

DOI: 10.1016/j.neuron.2018.07.010

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Radiosurgery versus open surgery for mesial temporal lobe epilepsy: The randomized, controlled ROSE trial

Objective: To compare stereotactic radiosurgery (SRS) versus anterior temporal lobectomy (ATL) for patients with pharmacoresistant unilateral mesial temporal lobe epilepsy (MTLE).

Methods: This randomized, single-blinded, controlled trial recruited adults eligible for open surgery among 14 centers in the USA, UK, and India. Treatment was either SRS at 24 Gy to the 50% isodose targeting mesial structures, or standardized ATL. Outcomes were seizure remission (absence of disabling seizures between 25 and 36 months), verbal memory (VM), and quality of life (QOL) at 36-month follow-up.

Results: A total of 58 patients (31 in SRS, 27 in ATL) were treated. Sixteen (52%) SRS and 21 (78%) ATL patients achieved seizure remission (difference

Significance: These data suggest that ATL has an advantage over SRS in terms of proportion of seizure remission, and both SRS and ATL appear to have effectiveness and reasonable safety as treatments for MTLE. SRS is an alternative to ATL for patients with contraindications for or with reluctance to undergo open surgery.

Barbaro, N. M. et al. *Epilepsia* **59**, 1198–1207 (2018).

Parental Mosaicism in "De Novo" Epileptic Encephalopathies

De novo disease-causing variants have been increasingly recognized in apparently sporadic, severe neurologic disorders in children, including developmental and epileptic encephalopathies[1] and autism.[2] Geneticists indicate that the risk of recurrence of these disorders in families with one affected child is approximately 1%; this accounts for the fact that one parent may have gonadal mosaicism.[2] In families with an affected child, the actual risk of recurrence may be as high as 50%.

Myers, C. T. et al. *N. Engl. J. Med.* **378**,1646–1648 (2018).

We tested somatic tissue (blood or saliva) obtained from the parents in the remaining 120 families to infer gonadal mosaicism; of these, 10 parents (8.3%; 95% confidence interval, 3.4 to 13.3) had mosaicism for their child's pathogenic variant (6 fathers and 4 mothers; minor allele frequency, 1.4 to 30.6%; mean, 12.9%; median, 9.4%) (Table 1). The minor allele frequency was well below that traditionally detected by means of Sanger sequencing in 8 of these 10 parents. In the saliva and blood samples obtained from 8 of the 10 parents with mosaicism (Table 1), the mutant allele had a similar frequency. Pathogenic variants occurred in eight genes. These genes included *SCN1A* in 3 of 40 families with apparently de novo *SCN1A* mutations; these findings showing that approximately 10% of children with an apparently de novo SCN1A variant had a parent with mosaicism replicated those of another study.[5] In addition, one variant occurred in each of the following genes: *SCN8A*, *GNB1*, *SLC6A1*, *DNM1*, *KCNT1*, *CACNA1A*, and *KCNQ2*. Owing to the small sample size, we were unable to determine whether certain genes, such as those encoding ion channels, were more prone to mosaicism.

Myers, C. T. et al. *N. Engl. J. Med.* **378**,1646–1648 (2018).

In 13 of 120 families, a second child had seizures or a neurodevelopmental abnormality. In 5 of these 13 families, the affected sibling had a phenotype concordant with that of the proband and shared the proband's mutation. However, parental mosaicism was detected in only 3 of these 5 families (these 3 families were captured in the 10 in which we observed parental mosaicism). Mosaicism in a parent of the other 2 families may have been below the level of detection by means of single-molecule molecular inversion probes or confined to gonadal tissue (which we did not test). If so, we have underestimated the true frequency of mosaicism in the parents. Conversely, only 1 of 8 siblings with a milder (discordant) phenotype carried their sibling's mutation; mosaicism was detected in their father. Targeted high-coverage testing of parents who have a child with a developmental and epileptic encephalopathy due to an apparently de novo mutation may be helpful in counseling parents regarding the risk of recurrence.

A parental history of seizures was associated with an increased likelihood of parental mosaicism ($P = 0.03$ by Fisher's exact test). Of the 16 parents who had a history of seizures, 4 had mosaicism and 12 did not; however, only 6 of 104 families with unaffected parents carried a variant that was also present, in a mosaic pattern, in either the mother or father (Table 1, and Fig. S1 in the Supplementary Appendix). The level of mosaicism correlated broadly with the severity of disease in the 4 affected parents who were found to have mosaicism.

Myers, C. T. et al. *N. Engl. J. Med.* **378**,1646–1648 (2018).

New therapeutic developments for Parkinson disease

Günther Deuschl and Rob M. A. de Bie

In 2018, developments in Parkinson disease (PD) research yielded improved diagnostic criteria and provided evidence for the effects of some treatments, both old and new. These developments enrich the treatment options available for PD and are likely to change important guideline recommendations.

Key advances

- The new diagnostic criteria for Parkinson disease (PD) yield high diagnostic specificity, but modest sensitivity[2].
- Although many drugs have failed to protect against disease progression in trials, exenatide is a promising new candidate[5].
- Subcutaneous infusion of apomorphine, a dopamine agonist, shortens the off-time of patients with advanced PD according to a confirmatory double-blind study[6].
- A secondary analysis of a trial testing deep brain stimulation of the subthalamic nucleus against the best available medical treatment has shown that it improves impulse control disorders[8].
- Pulsed focused ultrasound lesioning, an invasive procedure without incision, was successfully used in the subthalamic nucleus as a treatment of PD with motor response fluctuations[10].

Movement disorder society criteria for clinically established early Parkinson's disease.

1. All duration components from the original criteria (eg, falls within the first 3 years, absent nonmotor PD despite 5 years duration, etc.) were removed.
2. Criteria that can only be applied with long-duration disease were removed (eg, absence of progression over 5 years).
3. All red flags were now defined as absolute exclusion criteria (this optimizes specificity and also allows a simple exclusion criteria checklist for clinical trials). This implies that supportive criteria are no longer required to counterbalance a red flag, so supportive criteria are not included in the early-PD category. Note also that 2 of the supportive criteria required levodopa treatment (ie, dramatic levodopa response and dyskinesia) and thus do not apply to de novo PD and that hyposmia remains in the criteria as 1 of the markers that can document nonmotor parkinsonism (see criterion 15, Fig. 1).

ABSTRACT: Background: In 2015, the International Parkinson and Movement Disorder Society published clinical diagnostic criteria for Parkinson's disease (PD). Although recent validation studies suggest high accuracy, one unmet need is for highly specific criteria for clinical trials in early/de novo PD.
Objectives: The objective of this study was to generate and test a PD diagnostic criteria termed "clinically established early PD."
Methods: We modified the Movement Disorder Society criteria to increase specificity for early PD by removing all disease duration components and changing red flags to absolute exclusions. We then estimated the sensitivity/specificity of clinically established early PD criteria in patients with disease duration <5 years, selected from a 626-patient validation study.
Results: After documentation of parkinsonism, 18 individual exclusion criteria are assessed that preclude the diagnosis of "clinically established early PD." Among 212 PD and 152 non-PD patients, the estimated specificity was 95.4%, with 69.8% sensitivity.
Conclusions: We describe high-specificity criteria for de novo PD, which are freely available for use in clinical trials. © 2018 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; diagnosis; criteria

Berg, D. et al. *Mov. Disord.* **33**, 1643–1646 (2018).

These criteria are designed specifically for studies of early PD (duration < 5 years) in which specificity needs to be optimized. The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least 1 of rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the International Parkinson and Movement Disorders Society–Unified Parkinson Disease Rating Scale. Once parkinsonism has been diagnosed, documentation of any of these features rules out the diagnosis of clinically established early PD.

Parkinsonizm = Bradikinezi +
İstirahat tremoru ve/veya Rijidite

PH varlığını dışlayıcı durumların olmadığının gösterilmesi

Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo- controlled trial.

Background—Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has neuroprotective effects in preclinical models of Parkinson's disease. We investigated whether these effects would be apparent in a clinical trial.

Methods—In this single-centre, randomised, double-blind, placebo-controlled trial, patients with moderate Parkinson's disease were randomly assigned (1:1) to receive subcutaneous injections of exenatide 2 mg or placebo once weekly for 48 weeks in addition to their regular medication, followed by a 12-week washout period. Eligible patients were aged 25–75 years, had idiopathic Parkinson's disease as measured by Queen Square Brain Bank criteria, were on dopaminergic treatment with wearing-off effects, and were at Hoehn and Yahr stage 2·5 or less when on treatment. Randomisation was by web-based randomisation with a two strata block design according to disease severity. Patients and investigators were masked to treatment allocation. The primary outcome was the adjusted difference in the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor subscale (part 3) in the practically defined off-medication state at 60 weeks. All efficacy analyses were based on a modified intention-to-treat principle, which included all patients who completed any post-randomisation follow-up assessments. The study is registered at ClinicalTrials.gov (NCT01971242) and is

Athauda, D. et al. *Lancet* **390**, 1664–1675 (2017)

GLP-1 RESEPTÖR AGONİSTİ

- Glukogani inhibe eder. Gastrik boşalmayı yavaşlatır.
- Exedine-4'ün sentetik formu: Exenatide
- Kemirgenlerde PH modelinde KBB'ni geçer
- Nöroprotektif ve nörorestoratif etkisi (+)
- Tip 2 DM'te kullanılan dozda kullanılır; GLP-1 reseptörlerine etki edip motor performans, davranış, öğrenme ve belleğe olumlu etkileri var.

Findings—Between June 18, 2014, and March 13, 2015, 62 patients were enrolled and randomly assigned, 32 to exenatide and 30 to placebo. Our primary analysis included 31 patients in the exenatide group and 29 patients in the placebo group. At 60 weeks, off-medication scores on part 3 of the MDS-UPDRS had improved by 1·0 points (95% CI −2·6 to 0·7) in the exenatide group and worsened by 2·1 points (−0·6 to 4·8) in the placebo group, an adjusted mean difference of −3·5 points (−6·7 to −0·3; p=0·0318). Injection site reactions and gastrointestinal symptoms were common adverse events in both groups. Six serious adverse events occurred in the exenatide group and two in the placebo group, although none in either group were judged to be related to the study interventions.

Interpretation—Exenatide had positive effects on practically defined off-medication motor scores in Parkinson's disease, which were sustained beyond the period of exposure. Whether exenatide affects the underlying disease pathophysiology or simply induces long-lasting symptomatic effects is uncertain. Exenatide represents a major new avenue for investigation in Parkinson's disease, and effects on everyday symptoms should be examined in longer-term trials.

Funding—Michael J Fox Foundation for Parkinson's Research.

Athauda, D. et al. *Lancet* **390**, 1664–1675 (2017).

İleri dönem PD tanılı olgularda prospektif, plasebo kontrollü, sc apomorfin ilk çalışma

- Plasebodan etkindi

- GİS'in PH patofizyolojisinde önemli rolü olabileceğine dair pek çok çalışma oluştu.
- Enflamatuvar bağırak hastalığı olanlarda haha fazla PH prevalansı olması bir örnek
- Apandiksin rolü olabilir.

Behavioural outcomes of subthalamic stimulation and medical therapy versus medical therapy alone for Parkinson's disease with early motor complications (**EARLYSTIM trial**): secondary analysis of an open- label randomised trial

- EARLYSTIM (PD'de derin beyin stimulasyonu) çalışması alt grup analizleri

- DBS sadece PD motor semptomlarında düzelme yapmıyor aynı zamanda davranışsal semptomlar ve duygu durumunda da düzelme yapıyor.

Lhommee, E. et al. *Lancet Neurol.* **17**, 223–231 (2018)

Focused ultrasound subthalamotomy in patients with asymmetric Parkinson's disease: a pilot study.

- MR önderliğinde odaklanılan USG ile kafatasını açmadan derin beyin yapılarında fokal lezyonlar oluşturulabilir.
- Odaklanılmış ultrason ile PH'da unilateral subtalamatominin ilk etkinlik ve güvenlik verileri araştırıldı.
- İspanya, asimetrik PH olan 10 hasta
- 6 aylık sonuçlar
- Güvenilir bir şekilde asimetrik PH'da motor özelliklerde düzelme saptandı. Daha büyük çaplı araştırmalar gerekli

Martinez- Fernandez, R. et al. *Lancet Neurol.* **17**, 54–63 (2018)

Targeting progression in multiple sclerosis — an update

Maria A. Rocca and Massimo Filippi

In 2018, the distinguishing pathological features of white matter lesions in patients with progressive multiple sclerosis (MS) were refined, and serological and MRI biomarkers of clinical worsening and evolution to progressive MS were identified. We also saw therapeutic advances in progressive MS with the emergence of new neuroprotective strategies and putative markers of neurodegeneration.

Key advances

- A pathological study showed that substantial white matter lesion activity, in the form of mixed active–inactive, smouldering and slowly expanding lesions, persists and correlates with disease severity in patients with long-standing progressive multiple sclerosis (MS)[1].
- Levels of serum neurofilament light chain, a marker of neuroaxonal damage, were found to be higher in progressive MS than in relapsing MS, to correlate with current and future clinical disability, and to predict accelerated brain and spinal cord atrophy[4].
- In patients with relapse-onset MS, a high cortical lesion count at disease onset predicted conversion to secondary progressive MS[5], and in patients with primary progressive MS, baseline grey matter damage was predictive of clinical worsening after 15 years[6].
- Integration of MRI measures into the clinical evaluation of patients with MS would allow earlier prognostication of long-term clinical outcomes[6], leading to possible improvements in treatment decision-making and optimization of overall costs.
- In a phase II trial in patients with progressive MS, ibudilast treatment was associated with slower progression of brain atrophy but also had some adverse effects[10]; this study provides the impetus for future trials of neuroprotection in progressive MS.

MS’te 2018

- Nörofilament ve tau proteini, MSlilerde beyin atrofisini tahmin edebilecek belirteçler olabilir.
- Sigaranın hem MS hem de MS tedavi edici ajanları üzerinde olumsuz etkisi var.
- Siponimodun SPMSte olumlu etkilerinin gösteren ilk çalışma yayınlandı.
- Juvenil pediatrik MS’te ilk randomize ilaç çalışmasında fingolimodun beta interferona üstünlüğü gösterildi.

Getting closer to a cure for migraine

Cristina Tassorelli and Roberto De Icco

In the past few years the scientific community has witnessed a prodigious surge in research activity, publication of data and progress in understanding the mechanistic components of migraine. This renaissance is the result of efforts initiated decades ago that are finally being translated into benefits for individuals affected by this disease.

Key advances

- Trials have demonstrated that monoclonal antibodies that target calcitonin gene-related peptide 1 induce marked improvements (>75%) among a small but meaningful proportion of patients with chronic migraine[1] or episodic migraine[2].
- Noninvasive vagal nerve stimulation delivered with two short-duration stimulations at the neck level has proved effective in the treatment of migraine attacks: one-third of patients achieved pain-free status at 2 h (REF.[4]).
- Preclinical data support the idea that pituitary adenylate cyclase-activating polypeptide and its G-protein-coupled receptors are viable targets for new migraine treatments[8].
- Intriguing findings obtained in a migraine-specific animal model point to another potential pathway implicated in migraine pain: inhibition of acid-sensing ion channels prevents cephalic allodynia[10].

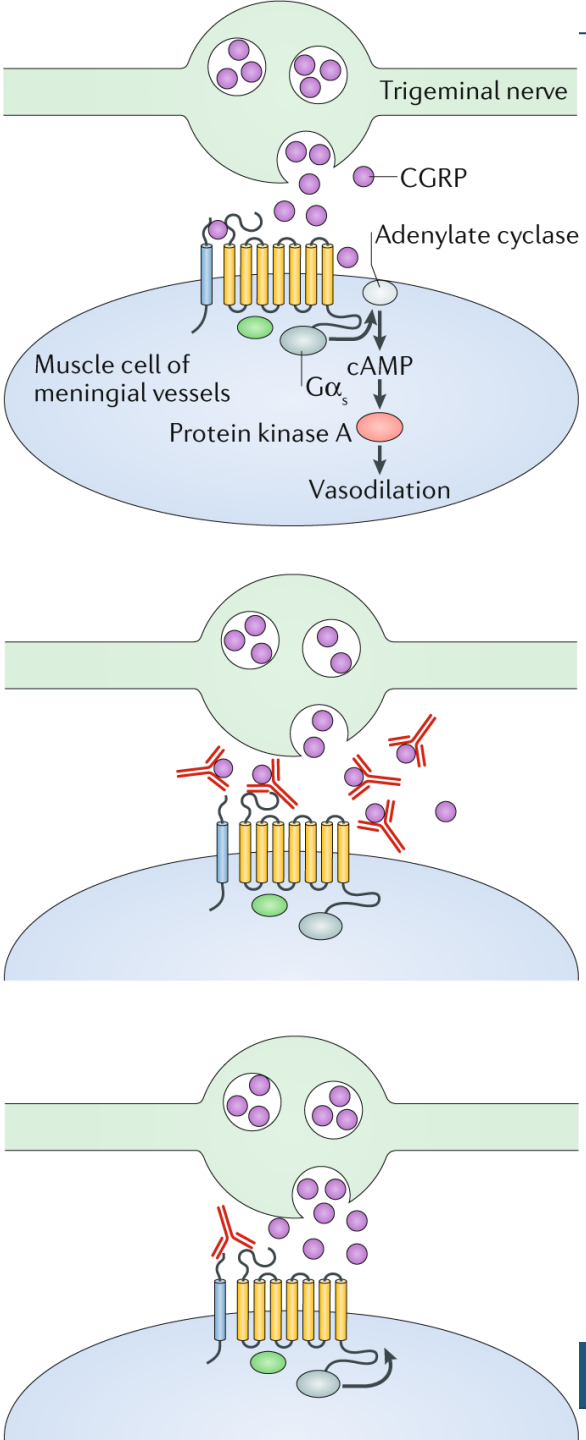


Fig. 1 | **Mechanism of action of monoclonal antibodies that target calcitonin gene-related peptide 1.** Normal binding of calcitonin gene-related peptide 1 (CGRP) to its receptor (top) can be blocked by antibodies that target the peptide itself (middle; galcanezumab, fremanezumab and eptinezumab) or that target the receptor (bottom; erenumab).

- Migrenin varlığı, tüm vasküler hastalıklar için risk faktörüdür.
- Absolü risk çok düşük AMA MİGRENLİ BİREYLERDE VASKÜLER RİSK FAKTÖRLERİ TANINMALI VE TEDAVİ EDİLMELİ
- Migren profilaksisinde yeni tedavi yaklaşımlarında CGRP veya CGRP reseptörlerine karşı etkili monoklonal antikorlar kullanılıyor. Şu anki diğer tedavi seçeneklerine etkinlik olarak üstün ama yan etki profillerine dikkat. Daha pahalı.

- AHS 2018 toplantısından 3 çalışma sonucu:
  - Kronik migren ve kognitif bozulma ilintili
    - TPM kullanımı, duygudurum bozukluğundan bağımsız tek başına risk faktörü
  - Rimegepant (CGRP) Faz III çalışması
    - Tedavi alan olguların %20si (plasebo %12) 2. saatte ağrısız; %88'i fotofobisiz (plasebo %25) idi.
  - Kronik migrenin önlenmesinde:
    - Fremanezumab (CRPG antagonisti) >TPM
    - Onabotulİnumtoksİn A> TPM

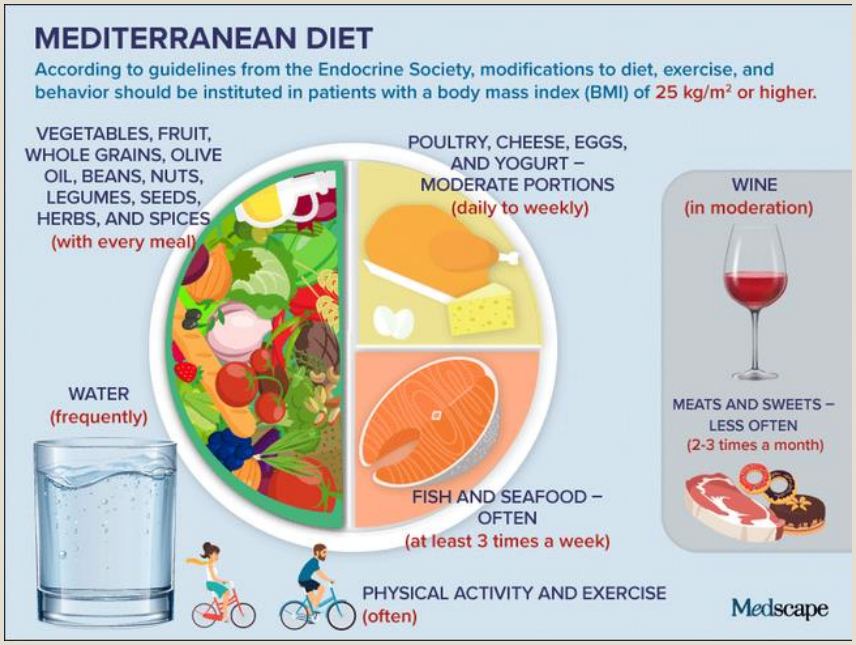
Huzursuz Bacaklar Sendromu

- 13 yeni riskli gen tanımlandı
- 6 eski tanımlanmış gen doğrulandı
- MEIS1 en güçlü genetik risk faktörü

- Mayo Proceedings
  - İhtiyaç duyulan opioid dozları diğer hastalıklardan daha az; yaşam kalitesini düzenleyebilir.
- Neurology dergisindeki çalışma:
  - RLS + K, KVH nedeniyle mortalite daha fazla ve bu durum, sadece eşlik eden KVS ilintili değil

AKDENİZ DİYETİ

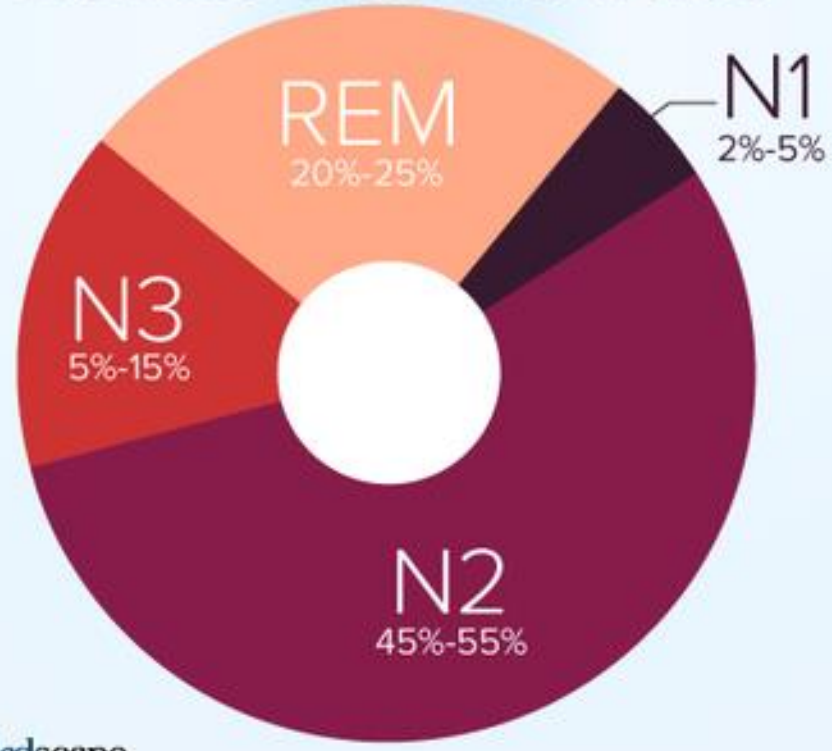
- DASH ve Akdeniz diyeti benzer
  - Meyve, sebze, whole grains, lean proteins, moderate alcohol intake
  - HT ve DM için en iyi beslenme şekilleri
  - Pekçok kalp damar hastalığı ve bazı kanser tiplerinin oluşumunu engelleyebilir



SLEEP

Normal sleep is divided into non–rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep is further divided into progressively deeper stages of sleep: stage N1, stage N2, and stage N3. Memory consolidation is thought to require both NREM and REM sleep.

PERCENTAGE OF TIME SPENT IN SLEEP STAGES



Medscape

TIPS FOR QUALITY SLEEP

SET A SCHEDULE
(SLEEP AND WAKE AT THE SAME TIME EACH DAY)

EXERCISE
(20-30 MINUTES A DAY, NO LATER THAN A FEW HOURS BEFORE SLEEP)

AVOID CAFFEINE, NICOTINE, AND ALCOHOL
(ESPECIALLY LATE IN THE DAY)

RELAX BEFORE BED
(CREATE A RELAXING ROUTINE)

DEDICATE A ROOM TO SLEEP
(AVOID BRIGHT LIGHTS, SOUND, AND TV/COMPUTER/PHONE)

DON'T LIE IN BED AWAKE
(IF YOU CAN'T SLEEP, DO SOMETHING ELSE BEFORE RETURNING TO BED)

2018'DE UYKUDA NELER OLDU?

- Hastalık Kontrol ve Korunma Merkezleri'nin (Centers for Disease Control and Prevention=CDC) önerisi:
  - **18-60 yaş uyku süresi ≥ 7saat/gece**
- Yeni çalışmalar: Fazla uyku gerekli değil
  - **≥ 8saat/gece uyuyanlarda ani ölüm ve KVH gelişim riski (+)**
  - Uyku süresi — Herhangi bir nedenle ölüm risk
    - ≥ 9saat/gece — %14
    - ≥ 10saat/gece — %30
    - ≥ 11saat/gece — %47

KTS

- CDC’nin Mart 2018 uyarısı:
  - “Hint keneviri-Marijuana işleyenler, KTS gelişimi açısından dikkatli olmalı”
  - Özellikle kanabis yapraklarının koparılması gibi elle budama yapanlarda sık
  - Pekçok alanda çalışanlarda görülüyor

DEHB Tedavisinde Yenilik

- Jornay PM® isimli metilfenidat içeren ilaç
- DEHB için FDA tarafınca onaylandı.
  - ≥ 6 yaş çocuklarda sabah semptomlarıNI engellemek için
  - 18:30-21:30 arasında uyku öncesi verilmeli

2018 FDA drug approvals

The FDA approved a record 59 drugs last year, but the commercial potential of these drugs is lacklustre.

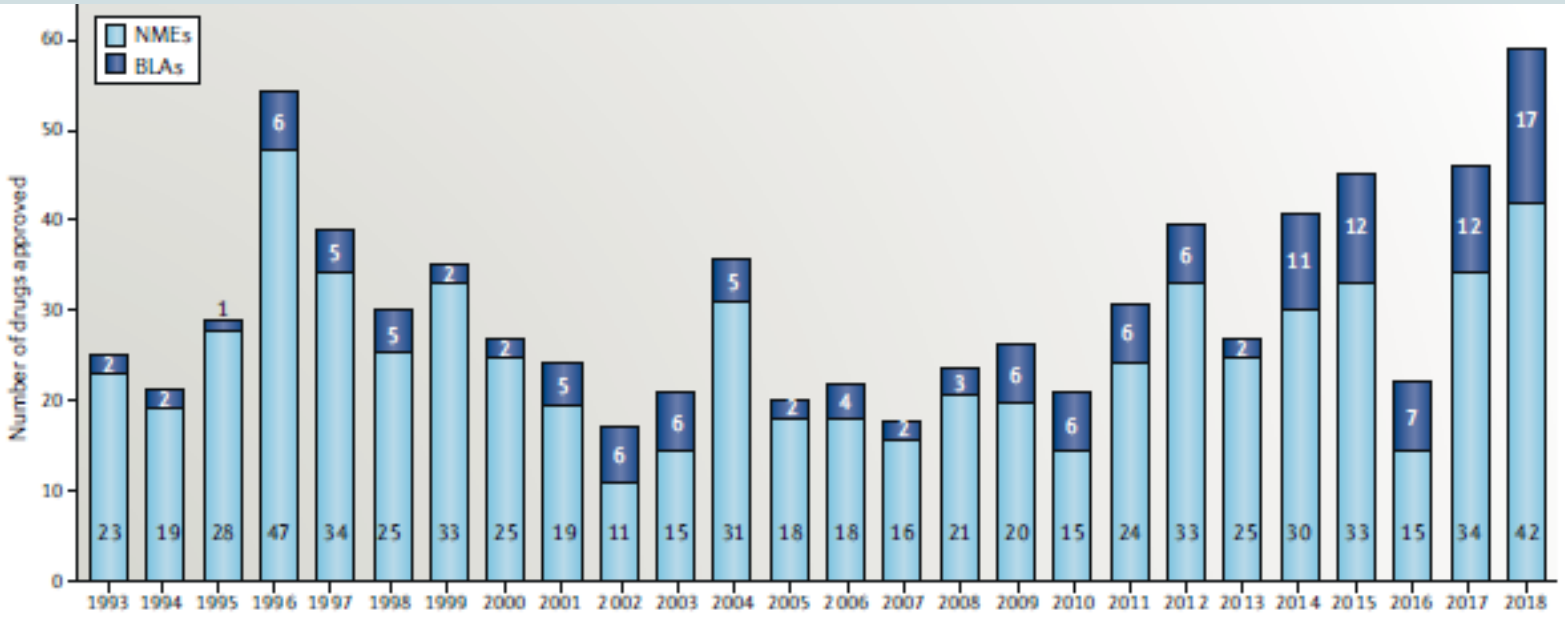


Fig. 1 | **Novel FDA approvals since 1993.** Annual numbers of new molecular entities (NMEs) and biologics license applications (BLAs) approved by the Center for Drug Evaluation and Research (CDER). See Table 1 for new approvals in 2018. Approvals of products such as vaccines by the Center for Biologics Evaluation and Research (CBER) are not included in this drug count (see Table 2). Source: Drugs@FDA.

NMEs: New Molecular Entities BLAs: Biologics License Applications

Table 1 | **CDER approvals in 2018**

Drug (brand name)	Sponsor	Properties	Indication	Review type
Lutetium Lu 177 dotatate (Lutathera)	Advanced Accelerator Applications/Novartis	Somatostatin receptor-targeted radiopharmaceutical	GEP-NETs	P, O
Bictegravir, emtricitabine and tenofovir alafenamide (Biktarvy)	Gilead Sciences	HIV-1 integrase inhibitor and HIV-1 nucleoside/nucleotide reverse transcriptase inhibitors	HIV	P
Tezacaftor and ivacaftor (Symdeko)	Vertex Pharmaceuticals	CFTR corrector and CFTR potentiator	Cystic fibrosis	P, O, B
Apalutamide (Erleada)	Johnson & Johnson	Androgen receptor inhibitor	Prostate cancer	P
Ibalizumab (Trogarzo)[a]	TaiMed Biologics/ Theratechnologies	CD4 antibody	HIV	P, O, B
Tildrakizumab (Ilumya)[a]	Sun Pharma	IL-23 antibody	Plaque psoriasis	S
Fostamatinib (Tavalisse)	Rigel Pharmaceuticals	SYK inhibitor	Immune thrombocytopenic purpura	S, O
Burosumab (Crysvita)[a]	Ultragenyx Pharmaceutical/Kyowa Hakko Kirin	FGF23 antibody	X-linked hypophosphataemia	P, O, B
Palonosetron and fosnetupitant (Akynzeo IV)	Helsinn Group	5-HT_3 receptor antagonist and NK_1 receptor antagonist	Chemotherapy-induced emesis	S
Lofexidine (Lucemyra)	US WorldMeds	α_2-adrenoceptor agonist	Opioid withdrawal	P
Erenumab (Aimovig)[a]	Amgen/Novartis	CGRP receptor antibody	Migraine	S
Sodium zirconium cyclosilicate (Lokelma)	AstraZeneca	Potassium binder	Hyperkalaemia	S
Avatrombopag (Doptelet)	Dova Pharmaceuticals	Thrombopoietin receptor agonist	Thrombocytopenia	P
Pegvaliase (Palynziq)[a]	BioMarin Pharmaceutical	PAL replacement therapy	Phenylketonuria	P, O
Baricitinib (Olumiant)	Incyte/Eli Lilly	JAK inhibitor	Rheumatoid arthritis	S
Moxidectin (NA)	Medicines Development for Global Health	Antihelmintic GABA receptor and glutamate channel modulator	River blindness	P, O
Cannabidiol (Epidiolex)	GW Pharmaceuticals	Cannabinoid	Dravet syndrome and Lennox–Gastaut syndrome	P, O

Plazomicin (Zemdri)	Achaogen	Aminoglycoside antibacterial	Urinary tract infections	P
Binimetinib (Mektovi)	Array BioPharma	MEK inhibitor	BRAF-mutated melanoma	S, O
Encorafenib (Braftovi)	Array BioPharma	BRAF inhibitor	BRAF-mutated melanoma	S, O
Tecovirimat (TPOXX)	SIGA Technologies	Viral p37 protein inhibitor	Smallpox	P, O
Ivosidenib (Tibsovo)	Agios Pharmaceuticals	IDH1 inhibitor	IDH1-mutated AML	P, O
Tafenoquine (Krintafel)	Medicines for Malaria Venture/GlaxoSmithKline	8-Aminoquinoline antimalarial	*Plasmodium vivax* malaria	P, O, B
Elagolix sodium (Orilissa)	AbbVie	GnRH receptor antagonist	Pain associated with endometriosis	P
Fish oil triglycerides (Omegaven)	Fresenius	Mixture of fatty acids	Parenteral nutrition-associated cholestasis	P, O
Lusutrombopag (Mulpleta)	Shionogi	Thrombopoietin receptor agonist	Thrombocytopenia	P
Mogamulizumab (Poteligeo)[a]	Kyowa Hakko Kirin	CCR4 antibody	Mycosis fungoides and Sézary syndrome	P, O, B
Patisiran (Onpattro)	Alnylam Pharmaceuticals	TTR-directed small interfering RNA	Hereditary TTR-mediated amyloidosis	P, O, B
Segesterone acetate and ethinyl estradiol vaginal system (Annovera)	TherapeuticsMD	Progestin and estrogen combined hormonal contraceptive	Female contraception	S
Migalastat (Galafold)	Amicus Therapeutics	α-galactosidase regulator	Fabry disease	P, O, A

Drug (brand name)	Sponsor	Properties	Indication	Review type
Stiripentol (Diacomit)	Biocodex	GABA reuptake inhibitor	Dravet syndrome	P, O
Cenegermin (Oxervate)[a]	Dompé	Recombinant NGF	Neurotrophic keratitis	P, O, B
Lanadelumab (Takhzyro)[a]	Dyax/Shire	Kallikrein antibody	Hereditary angioedema	P, O, B
Eravacycline (Xerava)	Tetraphase Pharmaceuticals	Tetracycline antibiotic	Complicated intra-abdominal infections	P
Doravirine (Pifeltro)	Merck & Co.	NNRTI	HIV	S
Moxetumomab pasudotox (Lumoxiti)[a]	AstraZeneca	CD22-directed antibody–drug conjugate	Hairy cell leukaemia	P, O
Fremanezumab (Ajovy)[a]	Teva	CGRP antibody	Migraine	P
Duvelisib (Copiktra)	Verastem	PI3K inhibitor	CLL, FL and SLL	P, O, A
Galcanezumab (Emgality)[a]	Eli Lilly	CGRP antibody	Migraine	S
Dacomitinib (Vizimpro)	Pfizer	EGFR inhibitor	EGFR-mutated NSCLC	P, O
Cemiplimab (Libtayo)[a]	Regeneron/Sanofi	PD1 antibody	CSCC	P, B
Sarecycline (Seysara)	Allergan	Tetracycline antibiotic	Severe acne vulgaris	S
Omadacycline (Nuzyra)	Paratek Pharmaceuticals	Tetracycline antibiotic	CABP and ABSSSI	P
Elapegademase (Revcovi)[a]	Leadiant Biosciences	Recombinant adenosine deaminase	ADA-SCID	P, O
Inotersen (Tegsedi)	Ionis Pharmaceuticals	TTR-directed antisense oligonucleotide	Hereditary TTR-mediated amyloidosis	P, O
Talazoparib (Talzenna)	Pfizer	PARP inhibitor	BRCA-mutated HER2-negative breast cancer	P
Baloxavir marboxil (Xofluza)	Shionogi/Roche	Polymerase acidic endonuclease inhibitor	Acute uncomplicated influenza	P
Lorlatinib (Lorbrena)	Pfizer	ALK and ROS1 inhibitor	ALK-positive NSCLC	P, O, B, A
Revefenacin (Yupelri)	Theravance Biopharma/ Mylan	Long-acting muscarinic receptor antagonist	COPD	S
Rifamycin (Aemcolo)	Cosmo Technologies	Ansamycin antibacterial	Travellers' diarrhoea	P
Emapalumab (Gamifant)[a]	Novimmune	Interferon-γ-blocking antibody	Primary haemophagocytic lymphohistiocytosis	P, O, B
Glasdegib (Daurismo)	Pfizer	Hedgehog pathway inhibitor	AML	P, O
Larotrectinib (Vitrakvi)	Loxo Oncology/Bayer	TRKA, TRKB and TRKC inhibitor	NTRK-positive solid cancers	P, O, B, A
Gilteritinib (Xospata)	Astellas	FLT3 inhibitor	FLT3-positive AML	P, O, B
Amifampridine (Firdapse)	Catalyst Pharmaceuticals	Potassium channel blocker	Lambert–Eaton myasthenic syndrome	P, O
Prucalopride (Motegrity)	Shire/Takeda	5-HT_4 receptor agonist	Chronic idiopathic constipation	S
Calaspargase pegol (Asparlas)[a]	Servier	Asparagine specific enzyme	ALL	S, O
Ravulizumab (Ultomiris)[a]	Alexion	Complement inhibitor	Paroxysmal nocturnal haemoglobinuria	S, O
Tagraxofusp (Elzonris)[a]	Stemline Therapeutics	IL-3 and diphtheria toxin fusion protein	Blastic plasmacytoid dendritic cell neoplasm	P, O, B

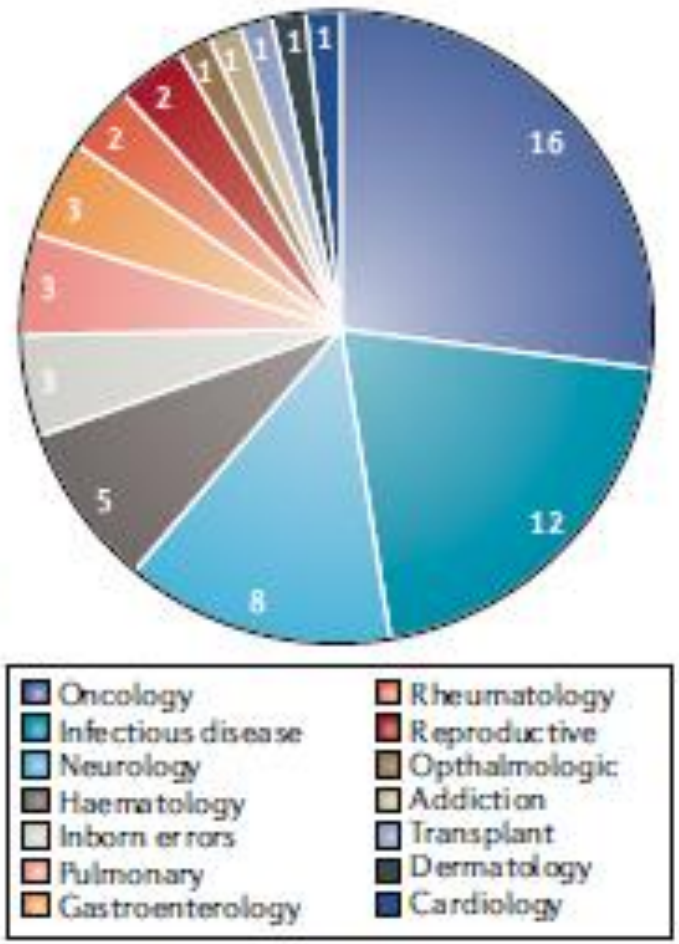


Fig. 3 | **CDER approvals by therapeutic area in 2018.** Source: *Nature Reviews Drug Discovery*.

Table 3 | **Selected Complete Response Letters and Refuse to File letters in 2018**

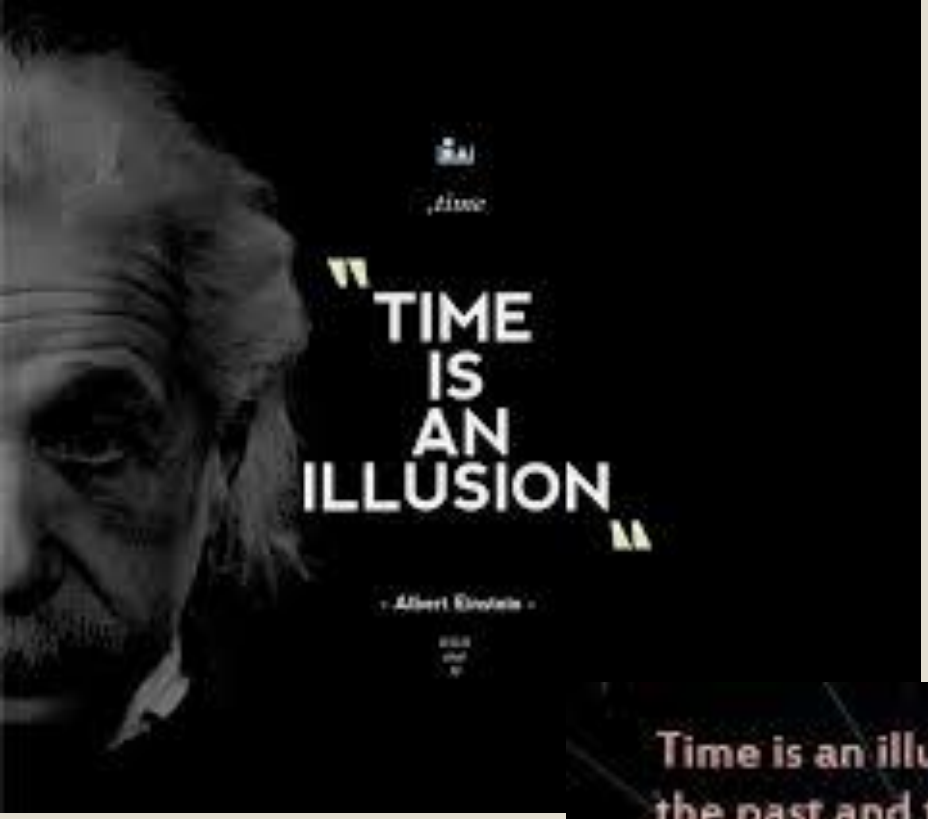
Drug name	Sponsor	Properties	Indication	Status
Ozanimod	Celgene	$S1P_1$ and $S1P_5$ receptor modulator	Multiple sclerosis	Resubmission expected
Volanesorsen	Akcea Therapeutics/Ionis Pharmaceuticals	Apolipoprotein CIII antisense	Dyslipidaemia and hypercholesterolaemia	Resubmission expected
Oliceridine	Trevena	Biased opioid agonist	Acute pain	Undisclosed
Stannsoporfin	Mallinckrodt	Haem oxygenase inhibitor	Hyperbilirubinaemia	Undisclosed

Source: BioMedTracker

Table 4 | **Selected potential approvals for new drugs in 2019**

Drug name	Sponsor	Properties	Indication	Expected PDUFA date
Sacituzumab govitecan[a]	Immunomedics	Anti-TROP2 antibody–drug conjugate	Breast cancer	January
Cladribine	Merck KGaA	Purine nucleoside analogue	Multiple sclerosis	January (third review)
Caplacizumab	Sanofi	Anti-vWF nanobody	Thrombotic thrombocytopenic purpura	February
Esketamine[a]	Johnson & Johnson	Fast-acting antidepressant	Major depressive disorder	March
Brexanolone[a]	SAGE Therapeutics	$GABA_A$ receptor modulator	Postpartum depression	March
Siponimod	Novartis	S1P receptor modulator	Multiple sclerosis	March
Risankizumab[b]	AbbVie	IL-23 antibody	Psoriasis	April
Quizartinib[a]	Daiichi Sankyo	FLT3 inhibitor	Acute myelogenous leukaemia	May
Onasemnogene abeparvovec[a,b]	Novartis	Gene therapy	Spinal muscular atrophy	May
AR101[a,b]	Aimmune Therapeutics	Peanut flour	Peanut allergies	August
Erdafitinib[a]	Johnson & Johnson	Pan-FGFR inhibitor	Bladder cancer	September
Upadacitinib[a,b]	AbbVie	JAK1 inhibitor	Rheumatoid arthritis	December
Romosozumab	Amgen	Sclerostin antibody	Osteoporosis and osteopenia	2019 (second review)

- Siponimod (Mayzent)
  - 27 Mart 2019 FDA onayı
  - KİS, RRMS ve SPMS aktif hastalık
  - SPMS'te ilk oral ilaç
- Kladribin (Mavenclad)
  - 29 Mart 2019 FDA onayı
  - RRMS ve ataklı SPMS (Ataklı MS)


"TIME
IS
AN
ILLUSION"
- Albert Einstein -


Time is an illusion. Time only exists when we think about the past and the future. Time doesn't exist in the present here and now. - Marina Abramovic
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