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ADHERENCE IS A COMPLEX BEHAVIOR

Consequences of non-adherence to narrow therapeutic index drugs

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Epilepsy

~1% OF WORLD POPULATION

65 million
people worldwide suffer from epilepsy[1]

3.4 million people in the US have epilepsy, with **150,000 new cases** per year[1,2]

1. Mehndiratta MM., Wadhai SA. International Epilepsy Day - A day notified for global public education & awareness. Indian J Med Res. 2015, 141: 143-144.
2. Centers for Disease Control and Prevention website: Epilepsy Data and Statistics | CDC – visited on 2nd September 2022

Narrow therapeutic index drugs

- Have low dose/blood level range of efficacy without toxicity
- Too low a dose: Lack of efficacy; too high a dose: Toxicity
- Antiepileptic drugs (AEDs) = Antiseizure medications (ASMs): A narrow range between too low and too high

- Missing medication may result in uncontrolled disease/seizures, because there is little margin for error i.e., in a patient with epilepsy, missing medications may result in seizure
- With ASMs with short half life, **missing a single dose may result in seizure**[1]

ASM HALF LIFE: SHORT	ASM HALF LIFE: LONGER	ASM HALF LIFE: VERY LONG
Levetiracetam: 7-8 hours	Phenytoin: ~20 h	Zonisamide: ~50-70 h
Lamotrigine: 12 h	Phenobarbital: ~ 24 h	Perampanel: 105 h
Carbamazepine: 12-17 h		Cenobamate: 60 h
Valproic acid: 6-17		
Lacosamide 7-9 h		
Oxcarbazepine: 8-11 h		
Topiramate: 7-9 h		
Brivaracetam: 7-9 h		

1. Cramer JA, Yan T, et. al. Risk of hospitalization among patients with epilepsy using long versus short half-life adjunctive antiepileptic drugs. Epilepsy Behav. 2020; 102:106634

Why does non-adherence with antiseizure medications (ASMs) differ from non-adherence with other medications?

- Seizures are a paroxysmal disorder
- Antiseizure medications prevent spread of brief, spatially confined electrical instability to adjacent brain with longer duration, i.e., a seizure
- Seizure is a sudden loss of control of motor activity or behavior that can result in catastrophic, life changing consequences
  - Loss of awareness, loss of job
  - Car accidents, loss of driving
  - Injury
  - Seizure continuation, i.e., status epilepticus, with high mortality
  - Death – e.g., during seizure or after seizure, with sudden unexplained death in epilepsy, drowning
- Missing a single ASM dose may result in loss of seizure control, seizure and the above consequences

Hovinga CA, Asato MR, et al. Association of non-adherence to antiepileptic drugs and seizures, quality of life, and productivity: survey of patients with epilepsy and physicians. Epilepsy Behav. 2008;13(2):316-22

Non-adherence: Real life experience

- 31 YO W with cryptogenic right temporal lobe epilepsy stating aged 28, with focal to bilateral tonic clonic seizures, normal examination and MRI. Works as an accountant. Meds: Lev 2000 mg/day. No side effects. Forgot to take medication for 2 days> seizure x 2 at work> hospitalization, ICU for 2 days, lost job

- 40 YO M, idiopathic generalized epilepsy with bilateral tonic clonic seizures since 10s, normal examination and MRI. Body builder, works as a personal fitness trainer. Meds: levetiracetam, primidone. No side effects. Serial non-compliance because of disease denial and belief in his strength. 1 am had a bilateral tonic clonic seizure while asleep, fell out of bed, broke his spine, had compression of lumbar spinal cord with paraparesis and urinary and fecal incontinence. 4 months in rehabilitation, with residual paraparesis and impotence

- 36 YO M with focal seizures secondary to (resected) meningioma. Seizure free on carbamazepine and lamotrigine, with mild fatigue. He was religious, did not want to take medications, and believed that “God will take care of me”. Had a tonic clonic seizure while crossing a road, was hit by a car, had traumatic brain injury, memory loss

Brodtkorb E, Samsonsen C, Sund JK, Bråthen G, Helde G, Reimers A. Treatment non-adherence in pseudo-refractory epilepsy. Epilepsy Res. 2016;122:1-6

Incidence and mode of ascertainment of non-adherence with antiseizure medications (ASMs)

ESTIMATES VARY FROM 21-95%

- Different study populations, different definitions of adherence, different methods to measure non-adherence may account for the wide variability

ALL AVAILABLE METHODS TO ASSESS ADHERENCE ARE HAMPERED BY SHORTCOMINGS

- Self-reports are indirect and subjective
- Pill-counts
- Electronic bottle-tops and
- Pharmacy records - are objective, but indirect measures of drug ingestion
- Therapeutic drug monitoring is both direct and objective, but pharmacokinetic and diurnal variability must be taken into account

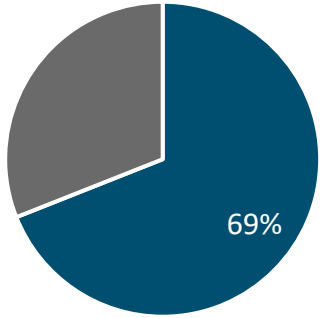
Brodtkorb E, Samsonsen C, Sund JK, Bråthen G, Helde G, Reimers A. Treatment non-adherence in pseudo-refractory epilepsy. Epilepsy Res. 2016;122:1-6

Non-adherence

Missing AED doses is a persistent challenge among children, adolescents, and adults

CHILDREN AND ADOLESCENTS <16 YEARS

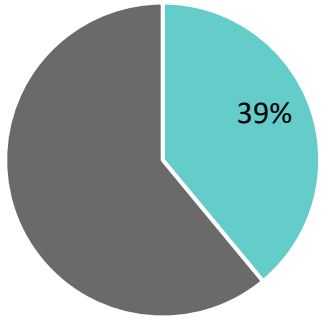
- Population-based study of patients aged <16 years with a diagnosis of epilepsy and receiving AEDs from the Tayside Children's Epilepsy Database in Scotland
- Adherence to AEDs was calculated based on medication dispensing data



Patients with an Adherence Index of <90%[1] (N=320)

ADULTS

- Retrospective analysis of adults in a US managed care population (aged ≥21 years) with a diagnosis of epilepsy (primary or non-primary) or non-febrile convulsions and ≥2 AED prescription claims over the 5-year study period
- AED adherence was calculated based on prescription drug claims



Patients with a Nonadherence medication possession ratio of <80%[2] (N=10,892)

The number one reason for breakthrough seizures is a missed dose
Risk for breakthrough seizures rises when plasma levels fall outside of therapeutic range[3]

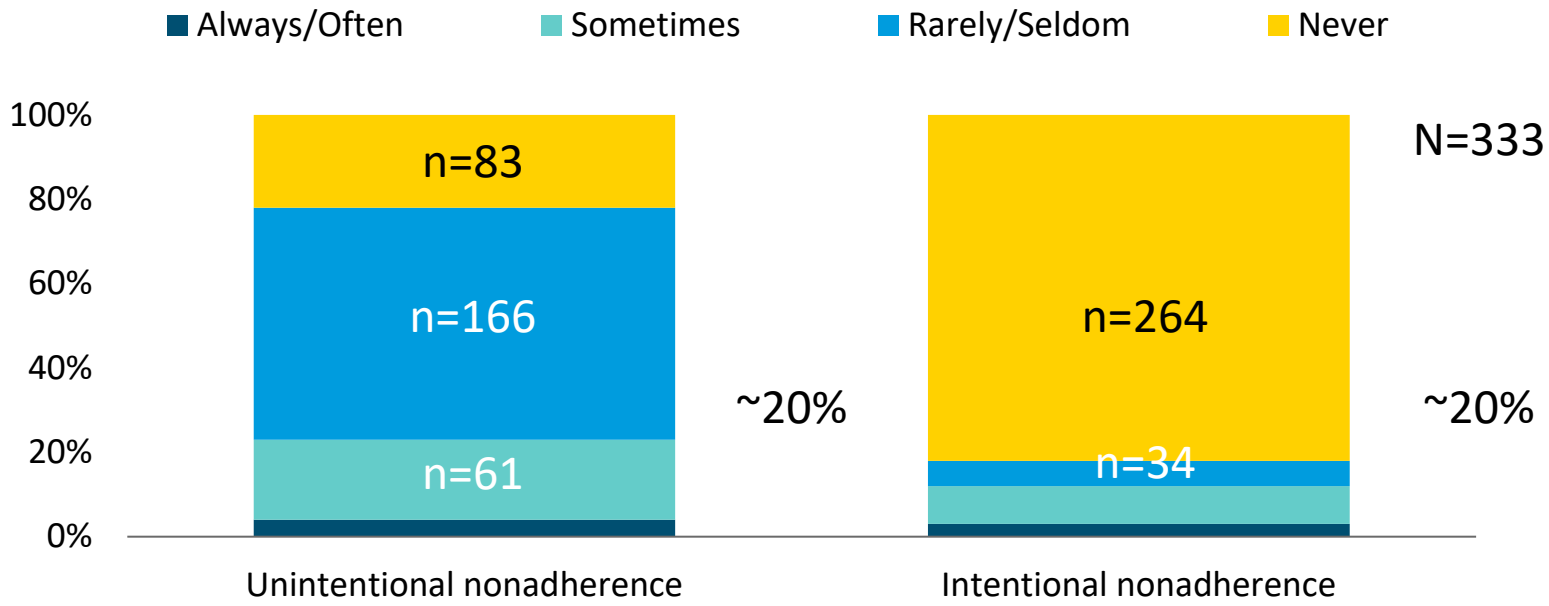
1. Shetty J., Greene SA., et al. Adherence to antiepileptic drugs in children with epilepsy in a Scottish population cohort. Child Neurol. 2016;58:469-474, 2. Davis KL., Candrilli SD., et al. Prevalence and cost of nonadherence with antiepileptic drugs in an adult managed care population. Epilepsia. 2008;49:446-454, 3. Specht U, Elsner H., et al. Postictal serum levels of antiepileptic drugs for detection of noncompliance. Epi Behav. 2003;4:487-495

Incidence of non-adherence in epilepsy

NON-REFRACTORY EPILEPSY

- 40% unintentional non-adherence
- 30% intentional non-adherence[1]

REFRACTORY EPILEPSY



- One in five rarely, sometimes, or often **consciously decide** not to take the AED as scheduled
- One-five sometimes or often **forget** to take the AEDs as scheduled

1. Henning O, Johannessen Landmark C, Nakken KO, Lossius MI. Nonadherence to treatment regimens in epilepsy from the patient's perspective and predisposing factors: Differences between intentional and unintentional lack of adherence. Epilepsia. 2019;60(5):e58-e62, 2. Henning O, Lossius MI, Lima M, et al. Refractory epilepsy and nonadherence to drug treatment. Epilepsia Open. 2019;4(4):618-623

Risks for non-adherence

PATIENT RELATED

- Young age
- Depression
- Male
- Dementia
- Poor medication self-administration management
- Disease denial

MEDICATION-RELATED

- Side effects
- Dosing regimen: > 2x/day
- Mono vs polytherapy: > 3 ASMs
- Lack of efficacy

SOCIOECONOMIC

- Drug cost
- Drug availability
- Low socioeconomic status
- Living alone

SUPPORT

- Healthcare provider/relationship
- Personal/home

OTHER

- Personal beliefs
- Alternative medicine
- Circumstances: Travel, illness
- Forgetting
- Stigmatization

May differ in different countries/societies/ages

Commonest cause: Simple forgetting

Henning O, Lossius MI, Lima M, et al. Refractory epilepsy and nonadherence to drug treatment. Epilepsia Open. 2019;4(4):618-623.

Mendorf S, Prell T, Schönenberg A. Detecting Reasons for Nonadherence to Medication in Adults with Epilepsy: A Review of Self-Report Measures and Key Predictors. J Clin Med. 2022;11(15):4308

Risks for non-adherence: Ethiopia

N=292

65.4% of epilepsy patients were nonadherent

The commonest cause of nonadherence was forgetfulness (49%), followed by inability to get medicine (29%) and safety concern (24%)

The majority (78%) of the patients had high belief in medication necessity while 44% had high concern about the potential side effects of their medications

39% of the patients had a negative belief toward their medications

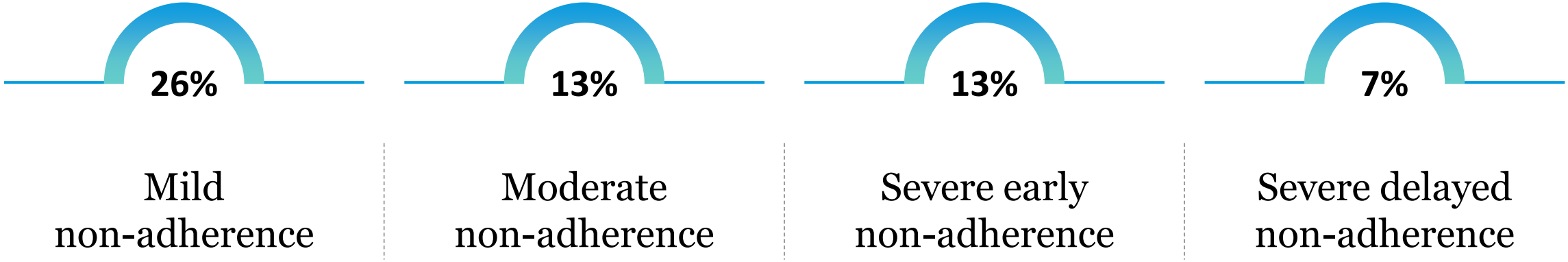
Comorbidity, seizure in the last 3 months, low medication necessity, high medication concern belief, and negative medication belief were predictors of medication non-adherence

Niriayo YL, Mamo A, Gidey K, Demoz GT. Medication Belief and Adherence among Patients with Epilepsy. Behav Neurol. 2019;2019:2806341

Risks for non-adherence: Children

University of Cinncinatti
124 children aged **2-12** with newly diagnosed epilepsy
Objective adherence measures using electronic monitors

58% had persistent non-adherence during the first 6 months of therapy



Adherence pattern for most patients was established in the first month of therapy

Socioeconomic status was the sole predictor

Modi AC, Rausch JR, Glauser TA. Patterns of nonadherence to antiepileptic drug therapy in children with newly diagnosed epilepsy. JAMA. 2011;305(16):1669-1676.

Consequence of ASM non-adherence

Seizures!

N=661, postal survey

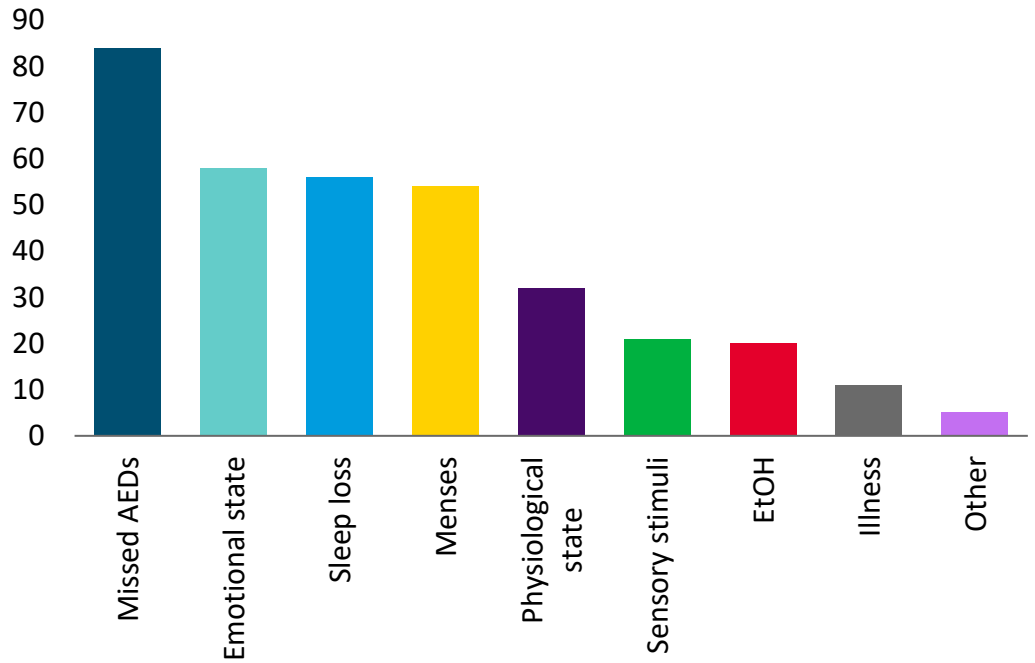
Dose omissions were reported by 71%

45% of patients reported a seizure after a missed dose at some time during treatment

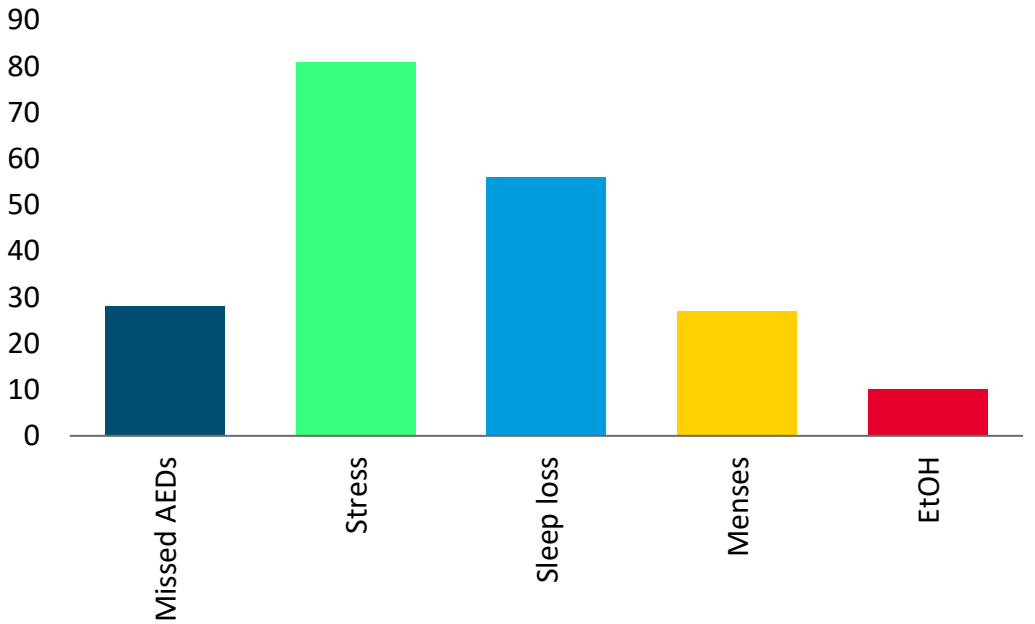
Cramer JA, Glassman M, Rienzi V. The relationship between poor medication compliance and seizures. Epilepsy Behav EB. 2002;3(4):338-342.

Non-compliance is a common trigger of seizures in epilepsy

82% OF ALL SEIZURES



28% OF ALL SEIZURES



Mattson RH, Adv Neurol 1991;55:453-60
Klein P et al. Epilepsia 2000, 41; (Suppl. 7):S112

Consequences of seizures

MEDICAL

- Seizure breakthrough
- Injury, including head injury
- Status Epilepticus
- Mortality

MEDICO-ECONOMIC

- Hospital admissions
- ER visits
- $ Cost

PSYCHOSOCIAL

- Driving
- Job loss
- Marriage/relationship
- Self-esteem

Non-adherence is the leading cause of status epilepticus in people with epilepsy

There is clear association with sudden death (SUDEP)

Consequences of ASM non-adherence: Medical

- N=33,658 Medicaid adult epilepsy patients, 1997-2006
- Medication possession ratio was used to evaluate adherence, with MPR < 0.8 defined as non-adherence
- Non-adherence was associated with an >3x increased risk of mortality compared to adherence
- Periods of non-adherence were associated with a higher incidence of ED visits (RR = 1.5), hospital admissions (RR = 1.9), MVA injuries (RR = 2.1), and fractures (RR = 1.2) than periods of adherence

MORTALITY IN NON-ADHERENCE WITH ASMS

	Hazards Ratio	P Value
Adherence status		
Adherent	Reference	
Nonadherent	3.32	<0.001
Untreated	0.92	0.067

SERIOUS CLINICAL EVENT IN NON-ADHERENCE WITH ASMS

ED=emergency department; IRR=incidence rate ratio; MVA=Motor vehicle accident

	Non-adherent quarters (32,365 patient-years)		Adherent quarters (91,678 patient-years)	
Event	**No. of events**	**Incidence rate**	**No. of events**	**Incidence rate**
ED visits	47,859	1.48	90,562	0.99
Hospitalizations	43,167	1.34	65,913	0.72
MVA injuries	349	0.011	477	0.005
Fractures	17,419	0.54	41,039	0.45
Head injuries	11,942	0.37	46,213	0.50

Faught E, Duh MS, Weiner JR, Guérin A, Cunnington MC. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM Study. Neurology. 2008;71(20):1572-1578

Consequences of ASM non-adherence: Economical

AED NON-ADHERENCE WAS ASSOCIATED

- With higher incidence of hospitalizations, inpatient days, and ED visits
- Cost increases related to serious outcomes, including inpatient cost ($4,320 additional cost per quarter) and ED services ($303 additional cost per quarter)

The rate during periods of nonadherence was 39% higher for hospitalizations, 76% higher for inpatient days, and 16% higher for ED visits relative to periods of adherence

	Cost associated with non-adherence with ASMs			
	Mean cost for non-adherent quarters (+SD)	Mean cost for adherent quarters (+SD)	Unadjusted incremental cost	Adjusted incremental cost
Inpatient	$1,670.57 ± $8,293	$746.14 ± $5,837	$924.43	$4,320.44
ED	$101.49 ± $1,819	$68.73 ± $3,366	$32.76	$303.44
Outpatient	$543.10 ± $1,516	$677.49 ± $1,845	-$134.39	-$75.96
Pharmacy				
• AED	$205.60 ± $313	$624.92 ± $809	-$419.32	-$187.14
• Other	$1,083.65 ± $2,158	$1,217.11 ± $2,495	-$133.47	-$280.13

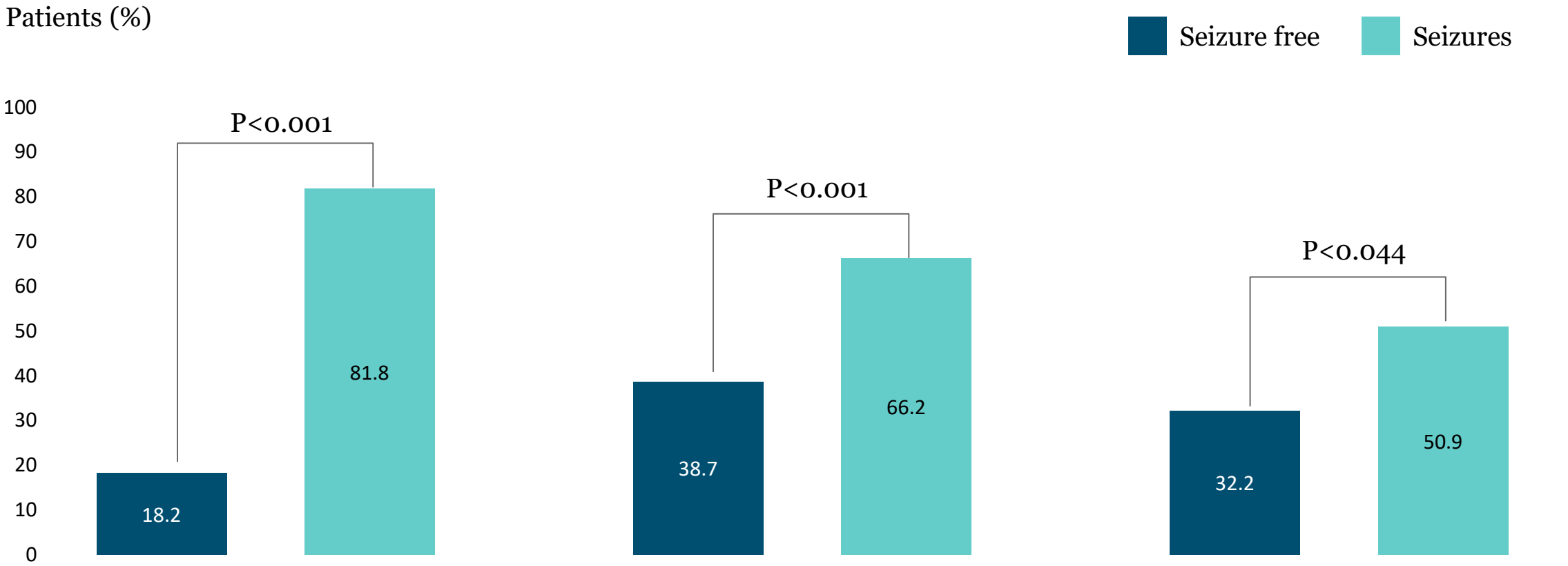
Faught RE, Weiner JR, Guérin A, Cunnington MC, Duh MS. Impact of nonadherence to antiepileptic drugs on health care utilization and costs: findings from the RANSOM study. Epilepsia. 2009;50(3):501-509.

Seizures reduce the quality of life

PREVENTION FROM DRIVING

LIMITATIONS IN EMPLOYMENT[1]

LIMITATIONS IN EDUCATION RECEIVED[1]



Josephson CB, Patten SB, Bulloch A, et al. The impact of seizures on epilepsy outcomes: A national, community-based survey. Epilepsia. 2017;58(5):764-771.

Mitigating against non-adherence

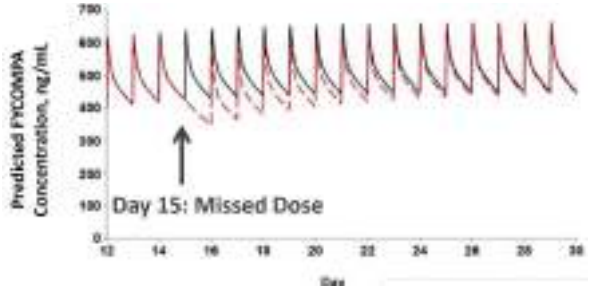
1. ADJUST TREATMENT TO MINIMIZE PATIENT BURDEN

Methods to improve adherence to antiepileptic drug treatment

Problem areas	Interventions
Complex drug regimens	Reduction of unnecessary polytherapy and dosing frequency. Simple dosing tailored to individual habits and daily routines
Cognitive problems/memory impairment	Drug dispensers, alarms (smart phone, wrist watch). Alliance with proxies. Social support with regular visits from community nurses
Insufficient knowledge, motivation and awareness of the need for treatment. Negative attitude to pharmaceuticals	Education, increased frequency of outpatient follow-up. Clear procedures related to missed drug intake. More involvement in treatment decisions. Epilepsy nurse and pharmacist support. Telephone contacts
Adverse drug reactions	Improved communication. Treatment modification
Depressed mood	Antidepressive and cognitive treatment
Oral intake barriers (swallowing/motor and intellectual deficits/behavior/aversion to medication/intercurrent illness)	Modified drug formulations (soluble, liquid, granular, powder), as well as size and taste of tablets. Alternative routes (rectal, i.v.)

2. MEMORY AIDS: ASSOCIATING DOSES WITH DAILY ROUTINES (TOOTHBRUSHING, MORNING COFFEE), FILLING PILL BOXES

3. ASMS WITH LONG HALF LIFE: REDUCE PEAK TO TROUGH LEVEL VARIATION



ASM half life: Very long

Zonisamide: ~50-70 h

Perampanel: 105 h

Cenobamate: 60 h

Brodtkorb E, Samsonsen C, Sund JK, Bråthen G, Helde G, Reimers A. Treatment non-adherence in pseudo-refractory epilepsy. Epilepsy Res. 2016;122:1-6

Real life experience: Follow up

31 YO W with cryptogenic right temporal lobe epilepsy stating aged 28, with focal to bilateral tonic clonic seizures, normal examination and MRI. Works as an accountant. Meds: Lev 2000 mg/day. No side effects. Forgot to take medication for 2 days> seizure x 2 at work> hospitalization, ICU for 2 days, lost job

MANAGEMENT	Change of levetiracetam from 1000 mg bid to Extended Release 2000 mg qhs	Suggested routine: take meds at night when brushing teeth	Smart phone reminder – just before bedtime	Addition of zonisamide to levetiracetam (long half life)

Conclusion

- Non-adherence with antiseizure medications in patients with epilepsy is common
- Has diverse etiology
- Commonly leads to seizures with often severe impact on patients' lives
- Contributes to health care cost of epilepsy
- Mitigations efforts against it include supportive care; memory aids; simplification of treatment schedule; avoidance of medication/doses with side effects; and use of antiseizure medications with long half life