Recurring patterns are evident in the history of medicines that may cause dependence or withdrawal. New medicines are seen as an important part of the solution to a condition, resulting in widespread use. Their dependence or withdrawal potential are either unknown at this point, due to a lack of research, or perhaps downplayed. As evidence of harm from dependence or withdrawal emerges, efforts are made to curtail prescribing. The repetition of this pattern is striking.

-Public Health England regarding Gabapentinoids, 2019

Hold 'Em, Fold 'Em, Walk Away or Run?

Rethinking Our Use of GABA-ergic & Antipsychotic Drugs in the Elderly

Katherine Coffey-Vega, MD
Associate Professor, VTCSOM
Certified Internal Medicine, Geriatrics and AAHPM Hospice Medical Director


I have no conflicts of interest to disclose.

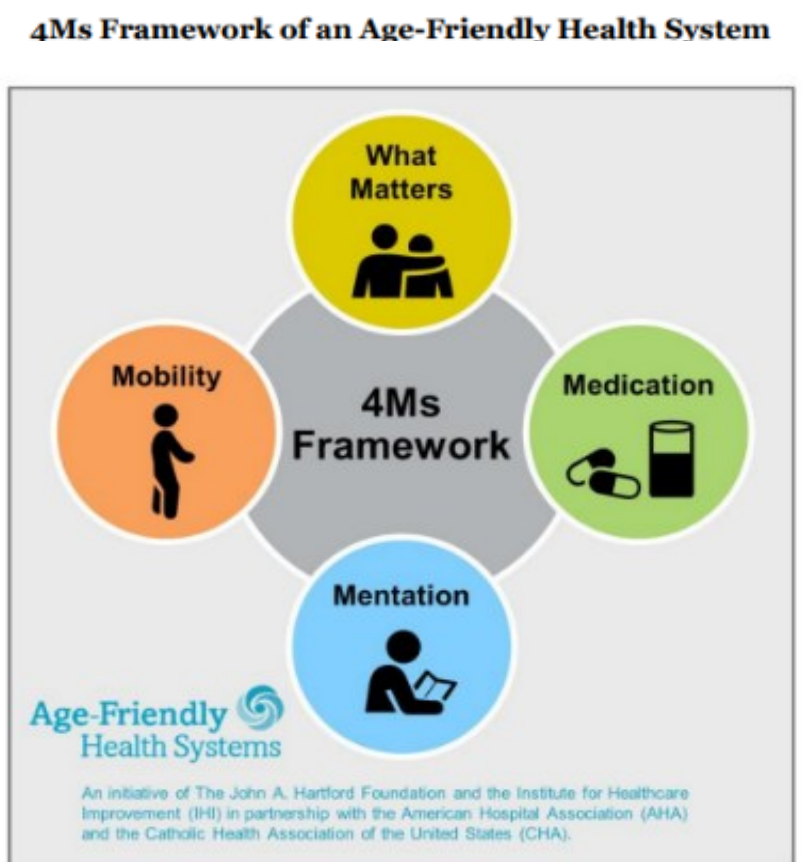
Objective:

Reconsider and better understand the use of gaba-ergic and anti-psychotic drugs in the elderly

Posted August 1, 2024

CMS Approves New 2025 Age-Friendly Hospital Measure

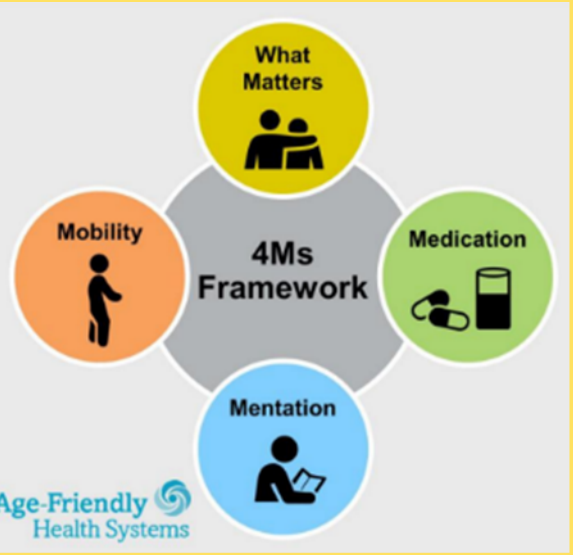
Inpatient Quality Reporting



Medication: If medication is necessary, use **age-friendly medication** that does not interfere with **What Matters** to the older adult, **Mobility, or Mentation** **across settings of care.**

Gabapentinoids and antipsychotics require judicious use in the elderly

Medication frameworks for older adults



High Risk Polypharmacy

Polypharmacy and Hyper-polypharmacy

More specific frameworks:

FRIDS (Fall Risk Increasing Drugs):
Weighted sum of CNS drugs + Cardiovascular drugs + Diuretics

Composite Score (Sedatives + Anticholinergic drugs)
-GABA burden
-Anticholinergic burden

Common mixes:
Benzodiazepine
Gabapentin
Zolpidem
Valproic Acid
Baclofen

Gabapentinoids key take aways

- Evidence for use/off-label use
- Dosing guidelines in elderly
- Deprescribing guidance
- Drug:Drug interactions
- Drug:Disease interactions
- In the inpatient setting
- Withdrawal states
- Abuse potential of Gabapentinoids


Gabapentinoids:
History, trends and restrictions in use

The NEW ENGLAND JOURNAL of MEDICINE

The Neurontin Legacy — Marketing through Misinformation and Manipulation

Authors: C. Seth Landefeld, M.D., and Michael A. Steinman, M.D. Author Info & Affiliations

Published January 8, 2009 | N Engl J Med 2009;360:103-106 | DOI: 10.1056/NEJMp0808659
VOL. 360 NO. 2

Department of Justice

Civil False Claims Act Violations/Fines

2004: Warner-Lambert: **$430 million fines, for promoting "off label use" of Gabapentin**
2009: Pfizer: **$1 billion** for promoting **Lyrica** **for uses that were "not medically accepted indications"**
2012: Pfizer: **$43 million** for illegally marketing **Lyrica** **for "off-label" uses not approved by the FDA**

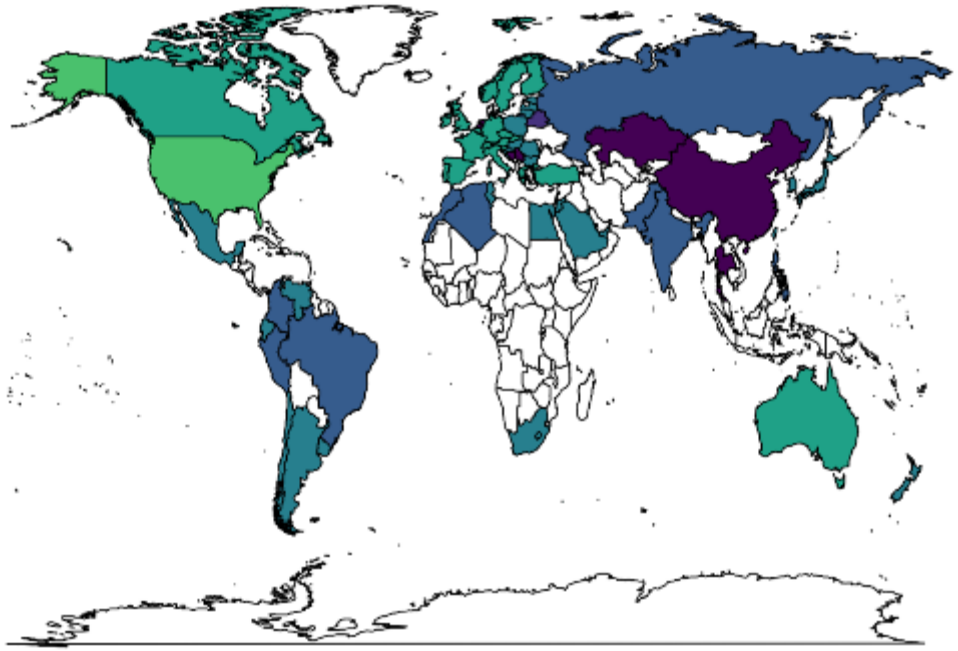
nature communications

Article

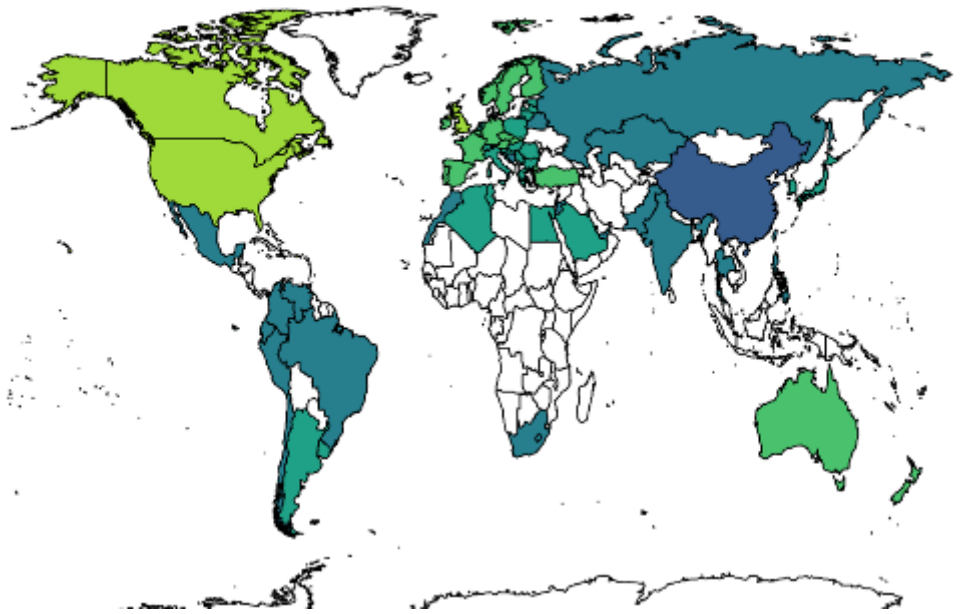
https://doi.org/10.1038/s41467-023-40637-8

Gabapentinoid consumption in 65 countries and regions from 2008 to 2018: a longitudinal trend study

2008

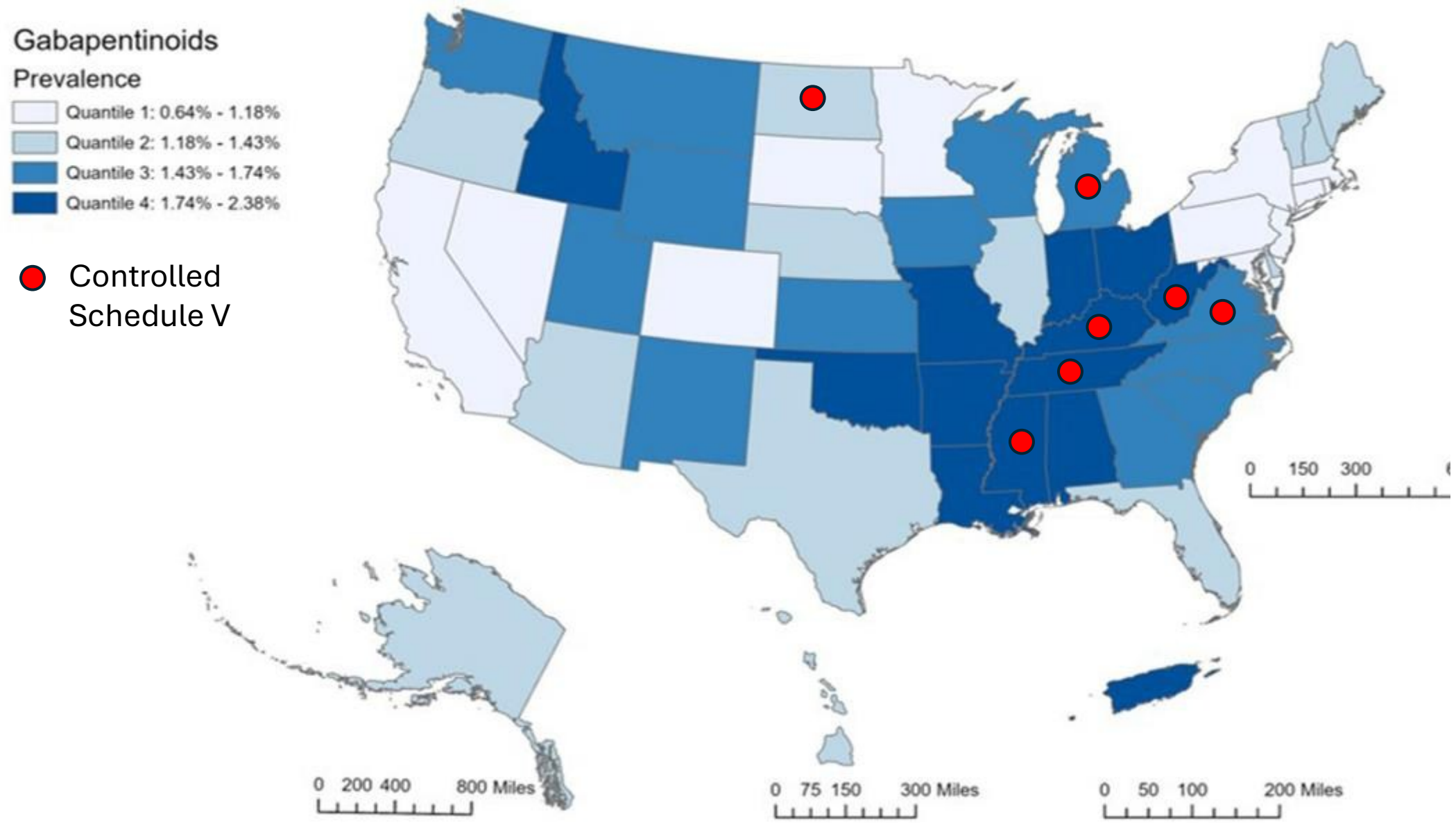


2018



More than four-fold increase use from 2008-2018 and an average increase of 17.2% per year.

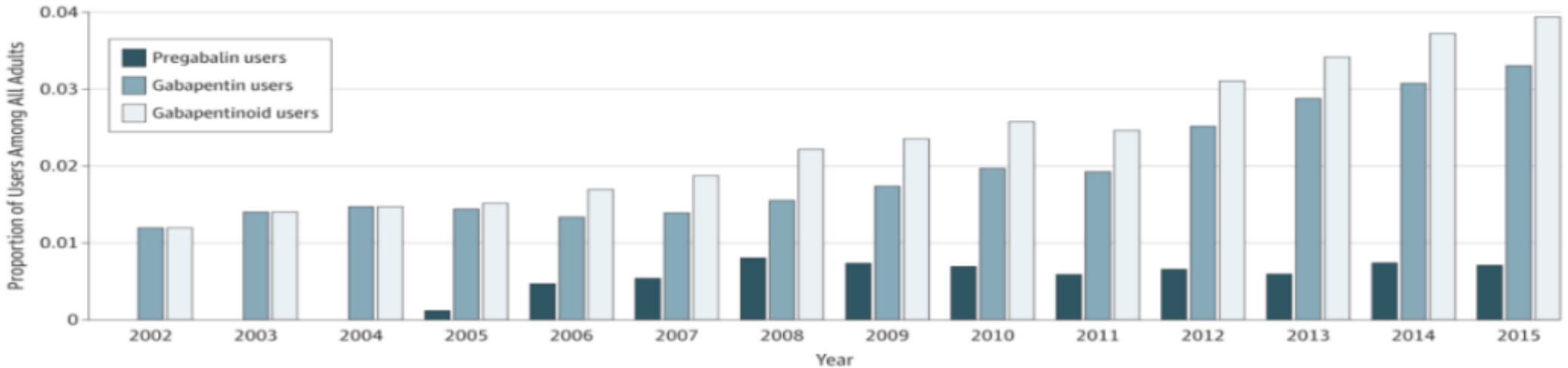
Zhao D, Baek J, Hume AL, McPhillips EA, Lapane KL. Geographic Variation in the Use of Gabapentinoids and Opioids for Pain in a Commercially Insured Adult Population in the United States. J Pain Res. 2022 Feb 11;15:443-454.



The JAMA Network

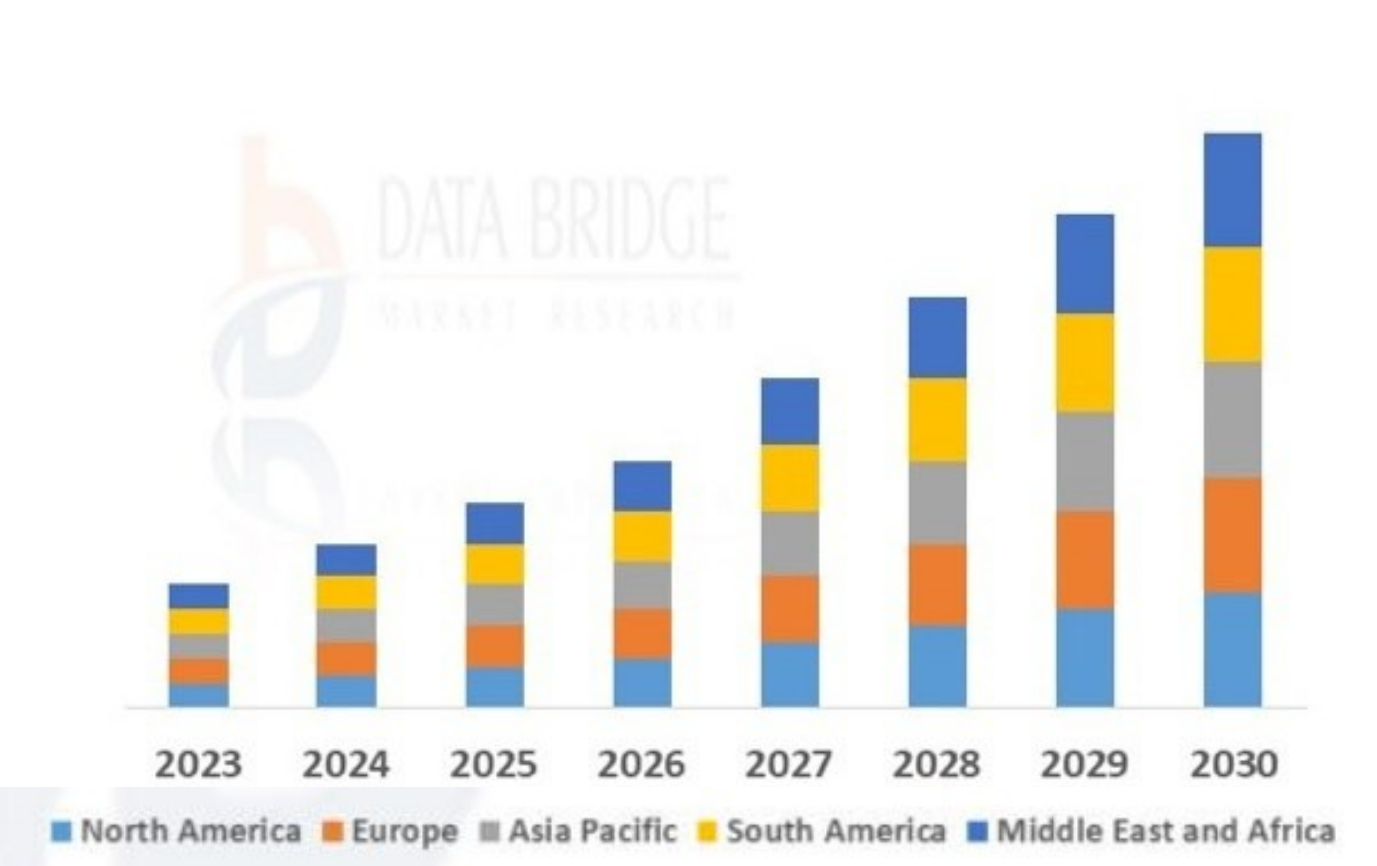
From: **Gabapentinoid Use in the United States 2002 Through 2015**

JAMA Intern Med. Published online January 02, 2018. doi:10.1001/jamainternmed.2017.7856

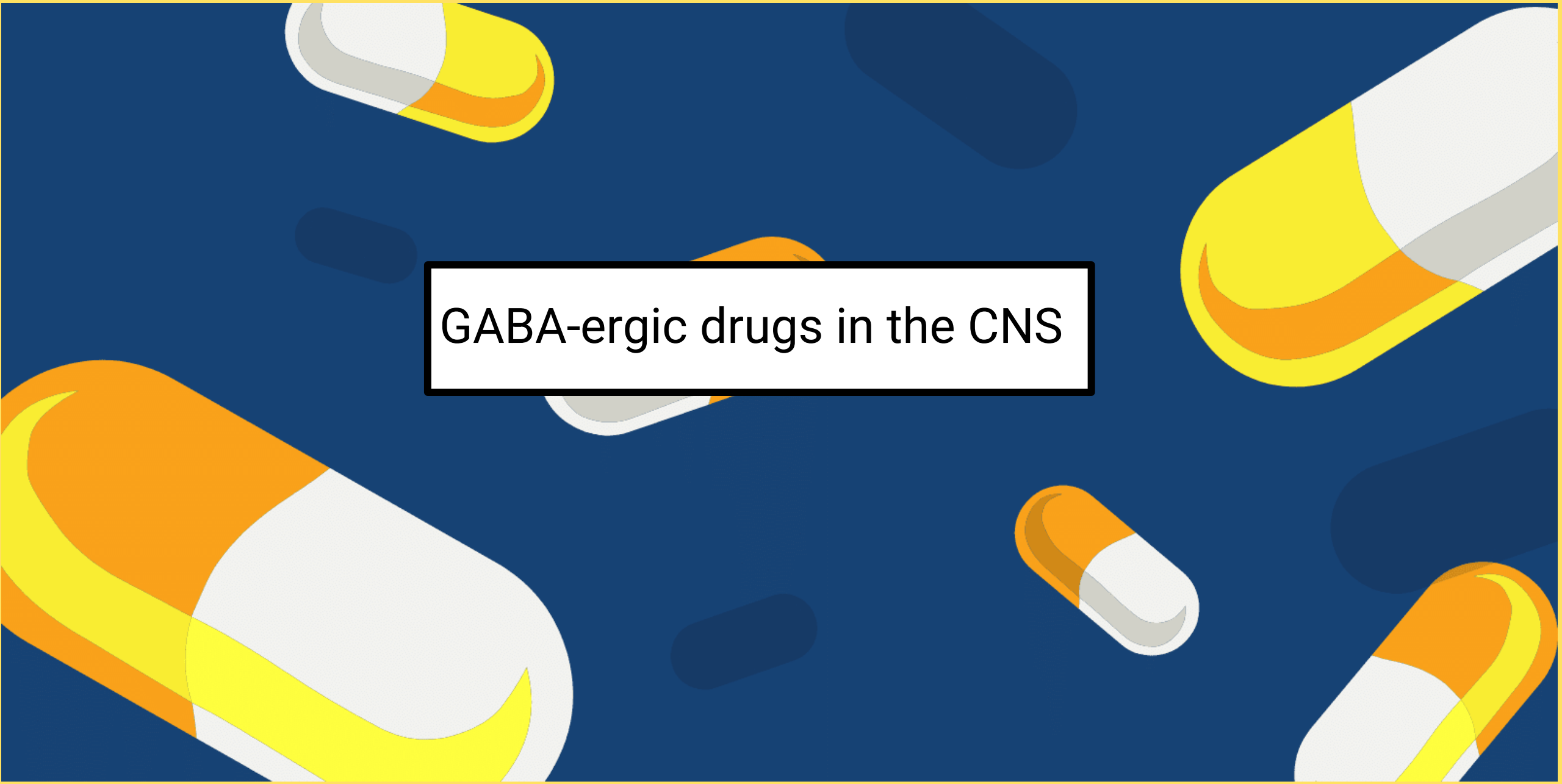


Gabapentinoid Use in the United States, 2002 Through 2015The figure identifies the proportion of adults (>17 years) who reported a filled prescription for gabapentin, pregabalin, or a gabapentinoid during a calendar year between 2002 and 2015.

Global Gabapentin Market Forecast



Gabapentin is anticipated to garner an annual revenue of 6 billion by the end of 2035, up from 2 billion in the year 2022.


GABA-ergic drugs in the CNS

Yin and Yang of inhibitory and excitatory brain neurotransmitters

GABA (Gamma-Aminobutyric Acid)

- The major **inhibitory** neurotransmitter in the CNS
- Stabilizes cell membrane
- Reduces neuronal excitability
- Potentiating its effects may improve pain and induce relaxation

Glutamate

- The major **excitatory** neurotransmitter in the CNS
- Plays a key role in cognition, learning and memory
- Elevated levels can increase pain

Gabapentinoids

Manufacturer's Claims

Pain of all types
Bipolar Illness
Anxiety Disorders

Nirvana

Gabapentinoids

Geriatrician's concern

GABA (Gamma-Aminobutyric Acid)

- Potentiating its effects may induce ~~relaxation~~ **somnolence**, dizziness, ataxia…

Gabapentinoids

Glutamate

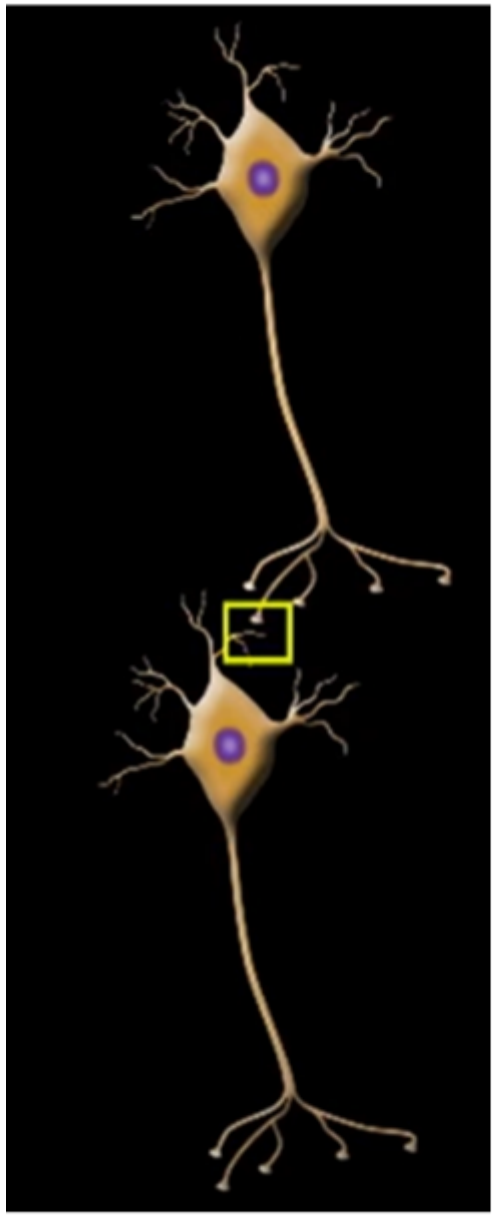
- Inhibiting its effects ~~cognition, learning and memory~~ leads to **confusion and cognitive decline**

Gabapentinoids

Most Common Side Effects

Somnolence (15-20%)
Dizziness (10-18%)
Ataxia (13%)
Fatigue (6-11%)

Psychiatric	**Cognitive**	**Neurological**
Euphoric mood Irritability Insomnia Panic attacks Restlessness Agitation Depressed mood Aggression Mood swings Depersonalisation Abnormal dreams Apathy	Disorientation Memory impairment Impaired attention Confusion	*Dizziness* *Somnolence* *Headache* Ataxia Abnormal co-ordination Tremor Dysarthria Paraesthesia Sedation Balance problems
Miscellaneous	**Musculoskeletal**	**Gastrointestinal**
Blurred vision Diplopia Vertigo Erectile dysfunction Nasopharyngitis Weight gain Increased appetite Decreased libido/ anorgasmia	Muscle cramp Arthralgia Back pain Pain in limb Cervical spasm	Vomiting Nausea Dry mouth Constipation Diarrhoea Flatulence Abdominal distension



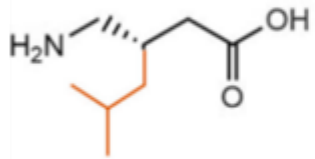
How GABA is affected by GABA-ergic drugs

Gabapentinoids act pre-synaptically to decrease glutamate (excitatory) activity and increase GABA (inhibitory) production.

Neurotransmitter **GABA** is released into synapse

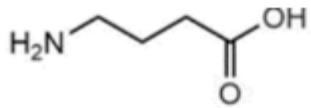
Post-synaptic GABA receptors are modulated by **benzodiazepines, alcohol, zolpidem and other agents** known as **GABA receptor allosteric modulators**. Effects of GABA are upregulated by these agents.

Structurally similar but do not bind at GABA receptor. (Indirect analog)



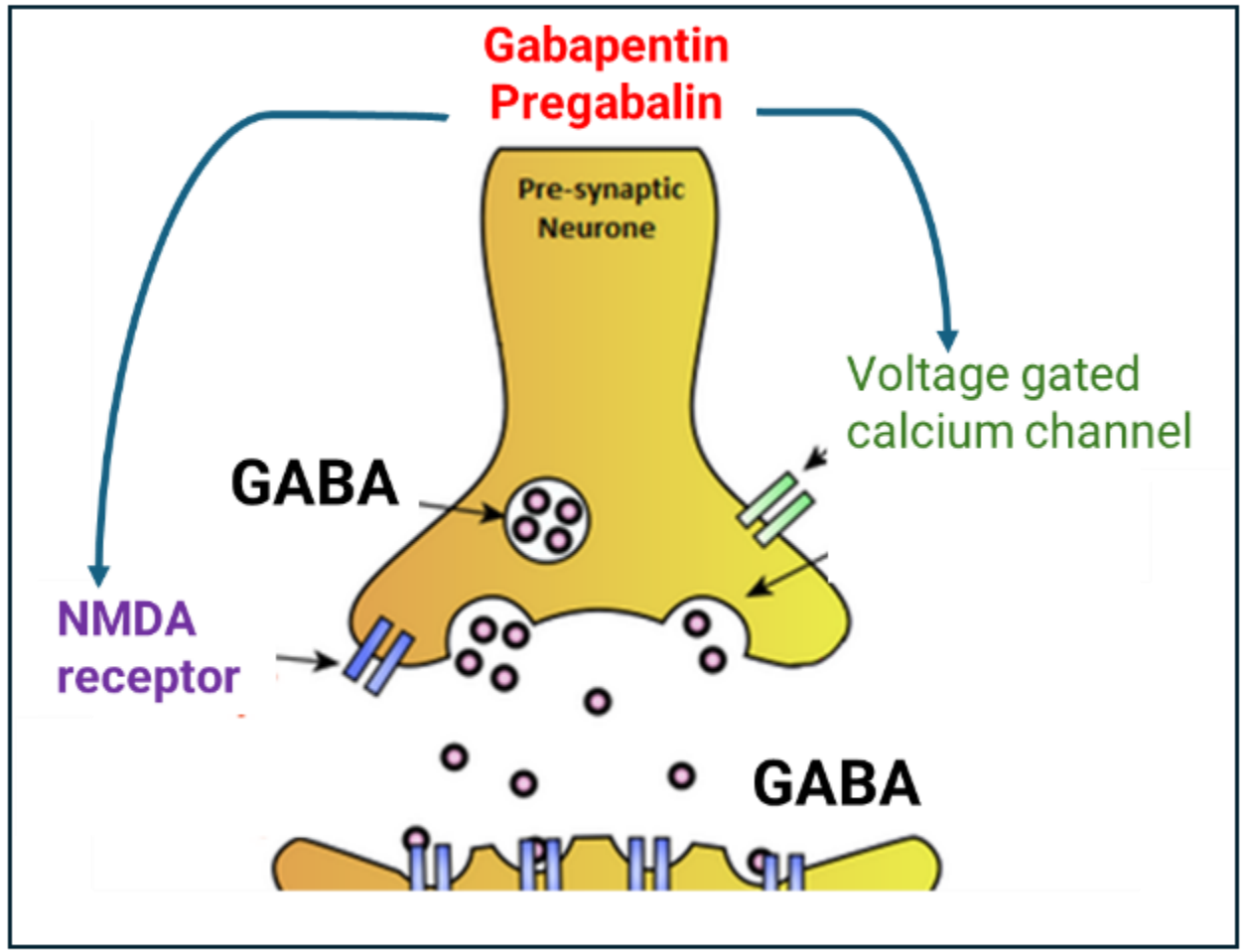
Pregabalin

Gabapentin



GABA

Gabapentinoids



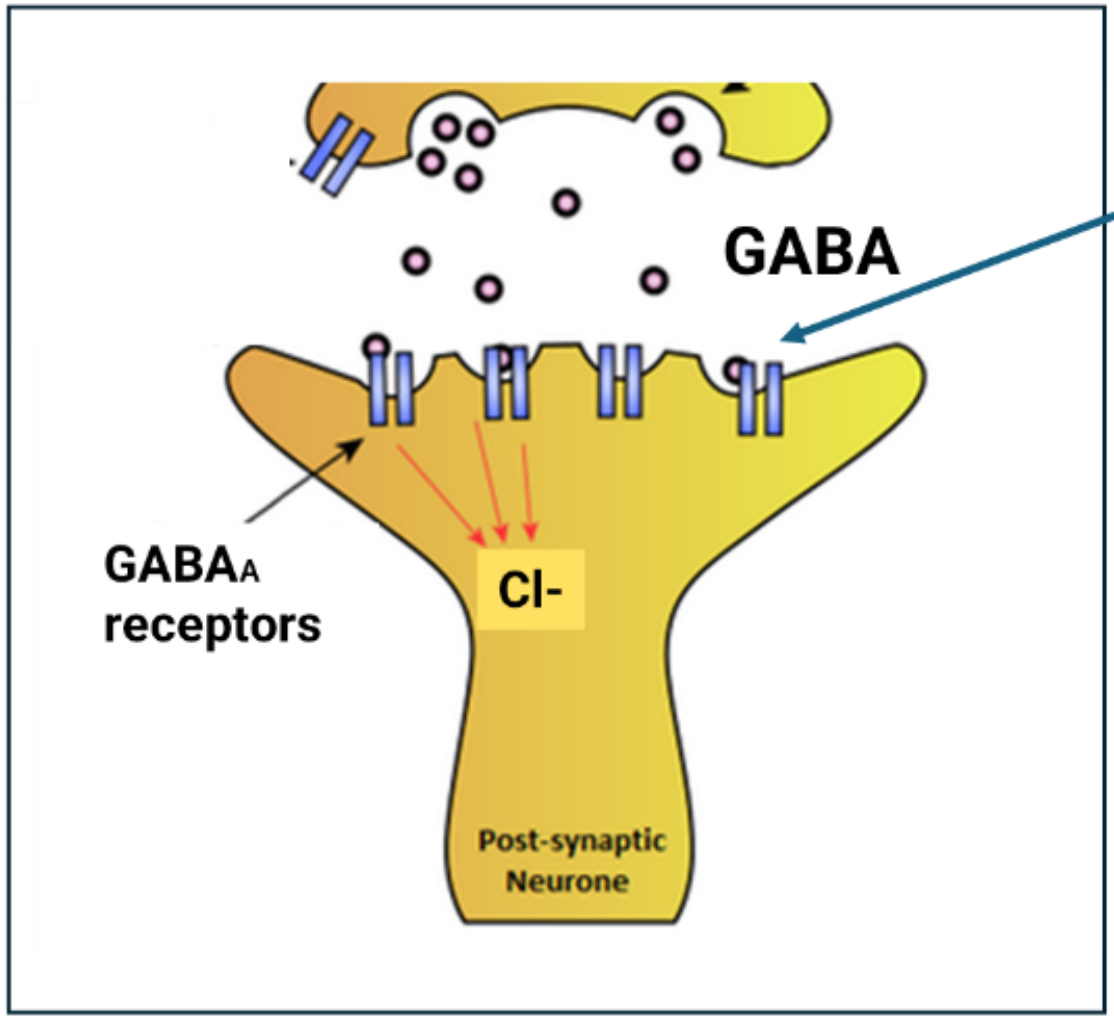
Bind VGCC (a1d2 subunit):
reduce influx of excitatory calcium

Bind NMDA receptor:
reduce glutamate synthesis

Enhance GABA synthesis

Glutamate (excitatory) ▼ GABA (inhibitory) ▲

$GABA_A$ receptor allosteric modulators



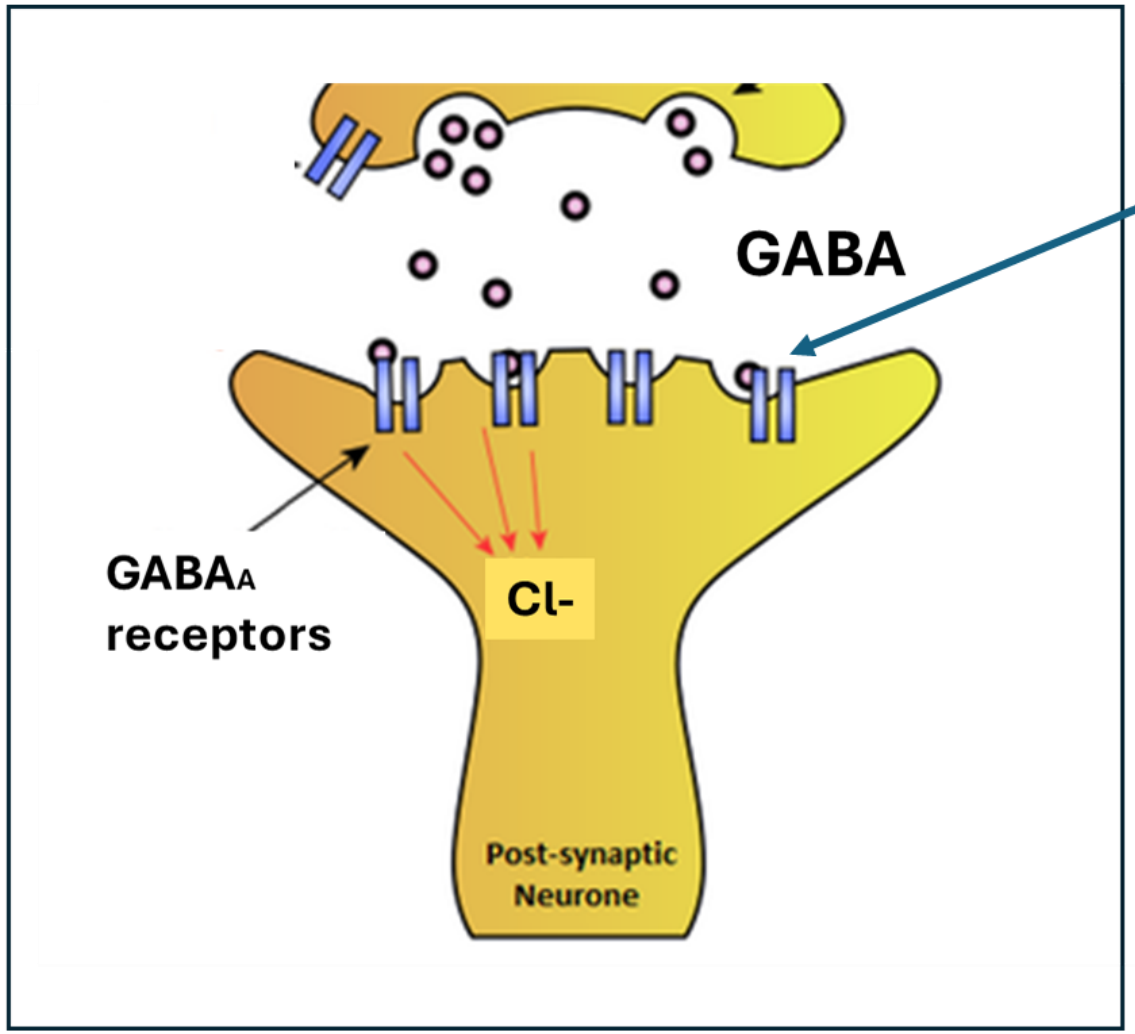
GABA activity ▲

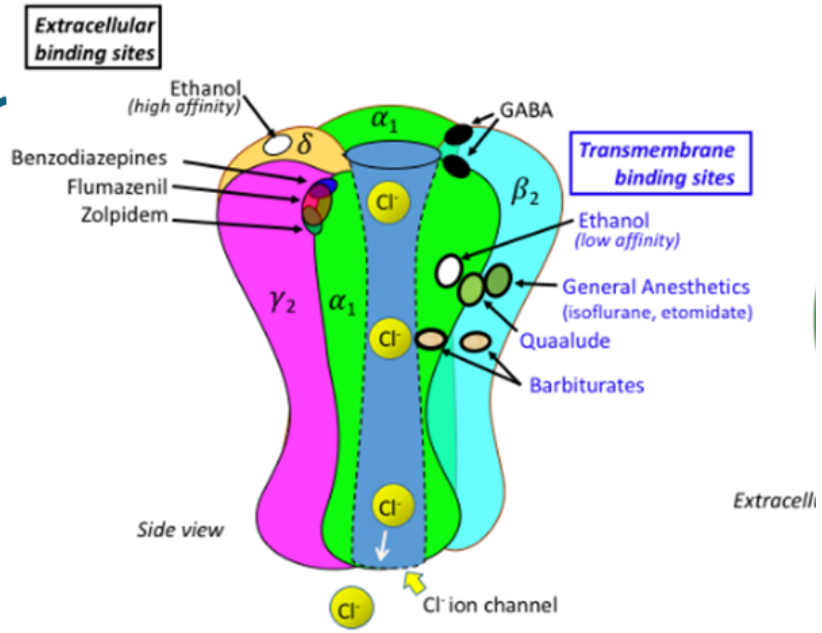
Drugs that Potentiate effects of $GABA_A$

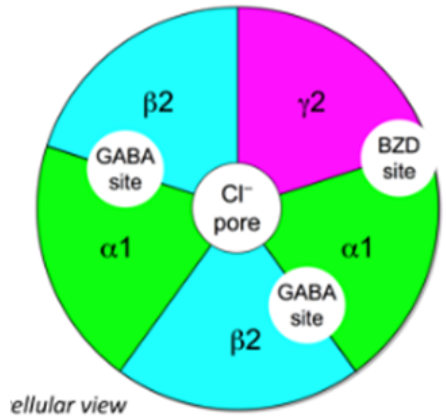
Benzodiazepines
Barbiturates
Ethanol
Zolpidem
Induction anesthetics (Propofol, etomidate)
Topiramate
Carisoprodol

Potentiate effects of $GABA_B$
Baclofen

$GABA_A$ receptor allosteric modulators



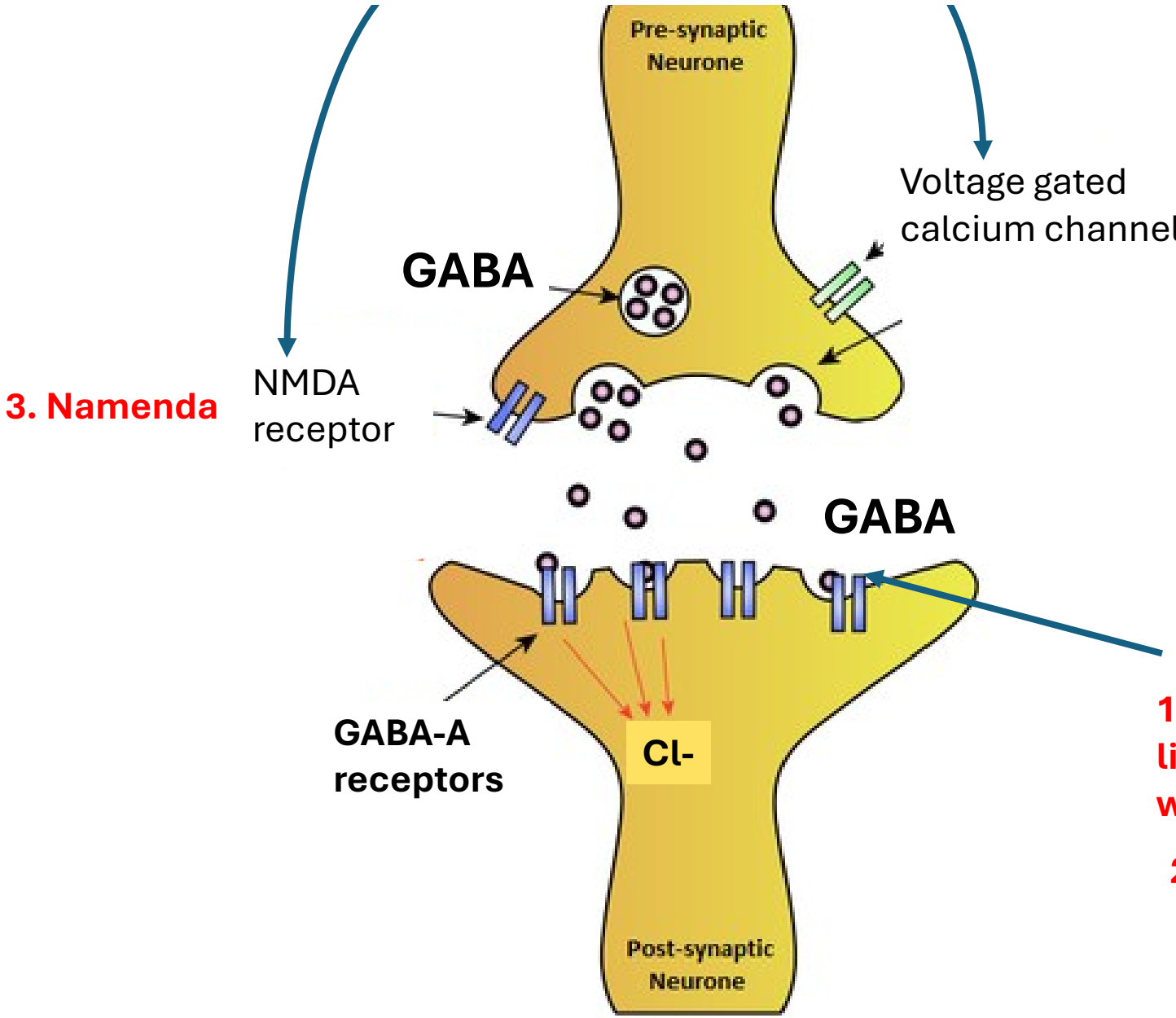




GABA activity ▲

Catatonia=a GABA deficient state

4. (resume Gabapentin or Pregabalin if withdrawal catatonia)



3. Namenda

1. Benzodiazepines first line (vs resume if withdrawal catatonia)

2. Zolpidem

*Do GABA-ergic drugs **cause** dementia?*

*Is there a use for GABA-ergic drugs **in** dementia?*

Do GABA-ergic drugs ***cause*** *dementia?*

An impaired glutamatergic system, and alterations of GABAergic circuits in the brain may increase the development of cognitive impairment and Alzheimer's disease.

Benzodiazepines and Cognitive Impairment

Meta analysis, 2018

Cognitive effects of active use:
Negative effects for cognitive domains of working memory, recent memory, processing speed, divided attention, visuoconstruction, expressive language.

Cognitive effects of persistent use and discontinuation (6 months later):
Persistent deficits after cessation of chronic use: domains of working memory, recent memory, processing speed, visuoconstruction, divided attention and sustained attention.

Simon F Crowe, Elizabeth K Stranks, The Residual Medium and Long-term Cognitive Effects of Benzodiazepine Use: An Updated Meta-analysis, *Archives of Clinical Neuropsychology*, Volume 33, Issue 7, November 2018, Pages 901–911, https://doi.org/10.1093/arclin/acx120

RESEARCH ARTICLE

Gabapentin dose and the 30-day risk of altered mental status in older adults: A retrospective population-based study

Retrospective population based study assessing 30-day risk of hospitalization with altered mental status after initiating Gabapenin in older adults (mean age 76 years) (urgent head CT was ordered)

High dose (>600 mg/day; n = 34,159) compared **to low dose (600 mg/day**; n = 76,025), gabapentin initiated in routine outpatient care

Conclusion: initiation of a high daily dose (>600 mg) of Gabapentin was associated with an increased risk of hospitalization with altered mental status.

Adjusted relative risk 1.29 [95% CI 1.14 to 1.46].

Fleet JL, Dixon SN, Kuwornu PJ, Dev VK, Montero-Odasso M, Burneo J, Garg AX. Gabapentin dose and the 30-day risk of altered mental status in older adults: A retrospective population-based study. PLoS One. 2018 Mar 14

frontiers in Pharmacology

The association of gabapentin initiation and neurocognitive changes in older adults with normal cognition

Retrospective cohort study assessing cognition and falls at 1 and 2 year follow ups after initiation of Gabapentin

Data source: National Alzheimer's Coordinating Center Uniform Data Set

Dates: September 2005-March 2021)

Conclusion: Gabapentin initiation was significantly associated with worsening cognition in older adults with initially normal cognition.

OR/95% CI: 1.55/[1.07, 2.25] /1.94/[1.22, 3.09]

Gabapentin initiation was associated **with increased falls at the year 2 visit (2.51 [1.19, 5.31])**

Oh G, Moga DC, Fardo DW, Abner EL. The association of gabapentin initiation and neurocognitive changes in older adults with normal cognition. Front Pharmacol. 2022 Nov 25

frontiers in Pharmacology

The association between Gabapentin or Pregabalin use and the risk of dementia: an analysis of the National Health Insurance Research Database in Taiwan

Retrospective cohort study; A total of 206,802 patients were enrolled in the study. Of them, 34,467 gabapentin- or pregabalin-exposure and 172,335 non-exposure patients were used for analysis.

18 years of data was considered.

Results: The multivariate-adjusted hazard ratio of risk of dementia for gabapentin or pregabalin exposure versus the matched non-exposed group was 1.45 (95% confidence interval [CI], 1.36–1.55).

The risk of dementia increased with higher cumulative defined daily doses during the follow-up period.

Huang YH, Pan MH, Yang HI. The association between Gabapentin or Pregabalin use and the risk of dementia: an analysis of the National Health Insurance Research Database in Taiwan. Front Pharmacol. 2023 May 30;14

The association between Gabapentin or Pregabalin use and the risk of dementia: an analysis of the National Health Insurance Research Database in Taiwan

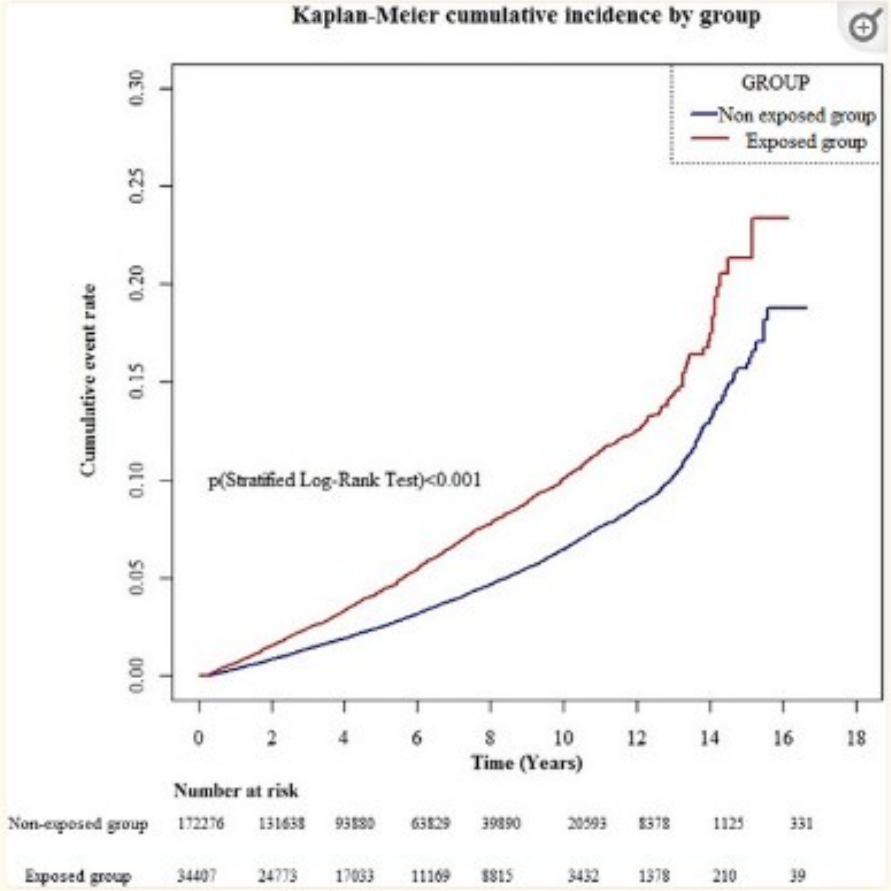


FIGURE 2

Cumulative event rate of dementia.

Risk of dementia increased with increasing cumulative defined daily dose per year

Gabapentin or pregabalin cDDDs per year during follow up	HR (95% CI)	p value
<0.5	1	
0.5-1.95	1.24 (1.09-1.41)	0.001
1.96-9.66	1.69 (1.5-1.92)	<0.001
>9.66	2.44 (2.14-2.78)	<0.001

cDDDs=cumulative Defined Daily Dose

GABA-ergic drugs and cognitive effects, proposed mechanism

-Reduces brain plasticity.
-Blocks the formation of new synapses.
-Down regulates glutamate needed for learning/memory.
-Alters the histomorphology of hippocampus and striatum in animal studies (**neuronal cell death**).

Olaibi OK, Osuntokun OS, Ijomone OM. Effects of chronic administration of gabapentin and carbamazepine on the histomorphology of the hippocampus and striatum. Ann Neurosci. 2014 Apr;21(2):57-61.

*Should GABA-ergic drugs **be used** in dementia?*

The Washington Post

October 12, 2006

Little Benefit Seen in Antipsychotics Used in Alzheimer's

August 10, 2018

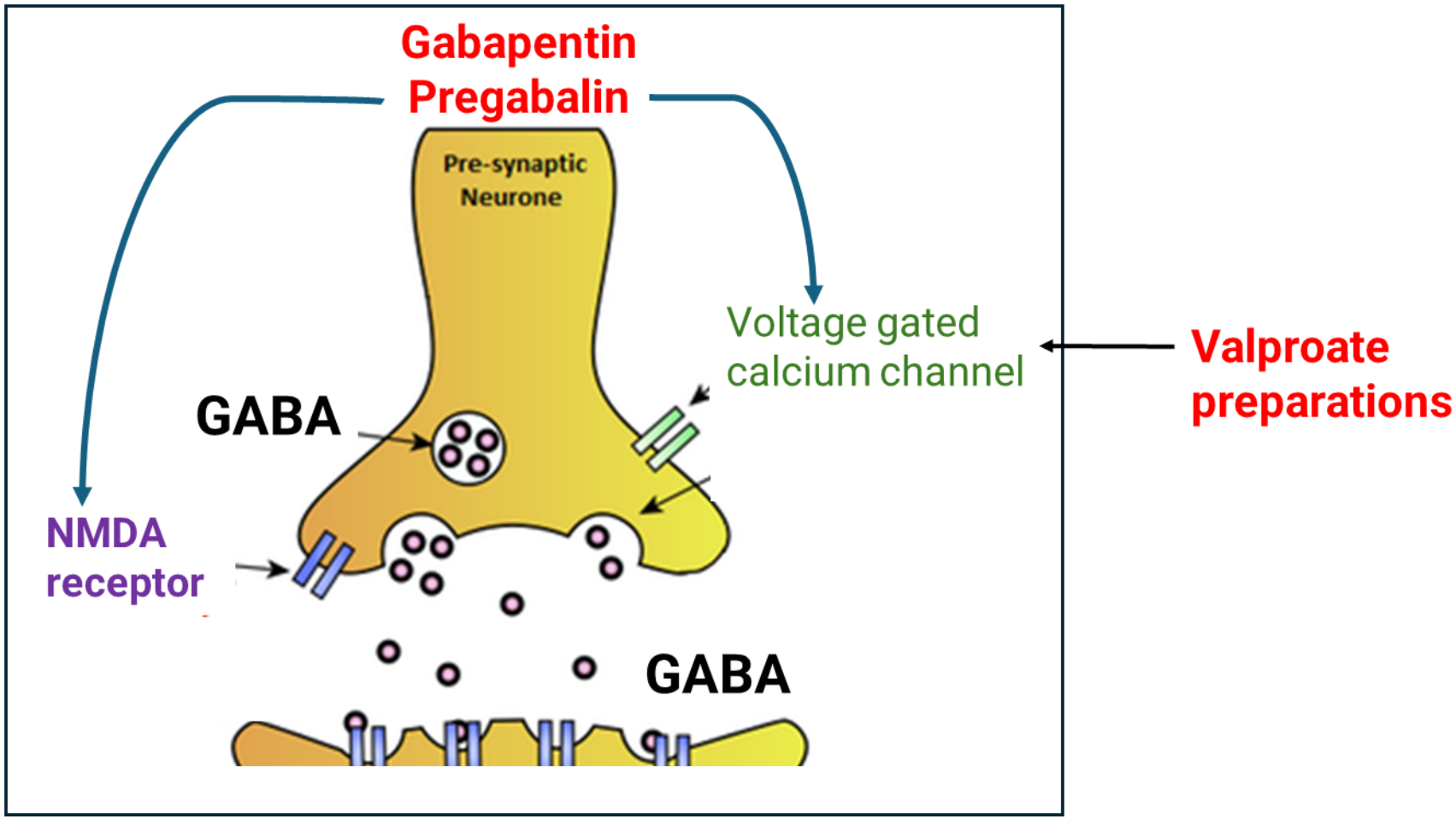
Why are nursing homes drugging dementia patients without their consent?

Nov 17, 2022

Epilepsy drugs as 'chemical restraint' on rise in nursing homes

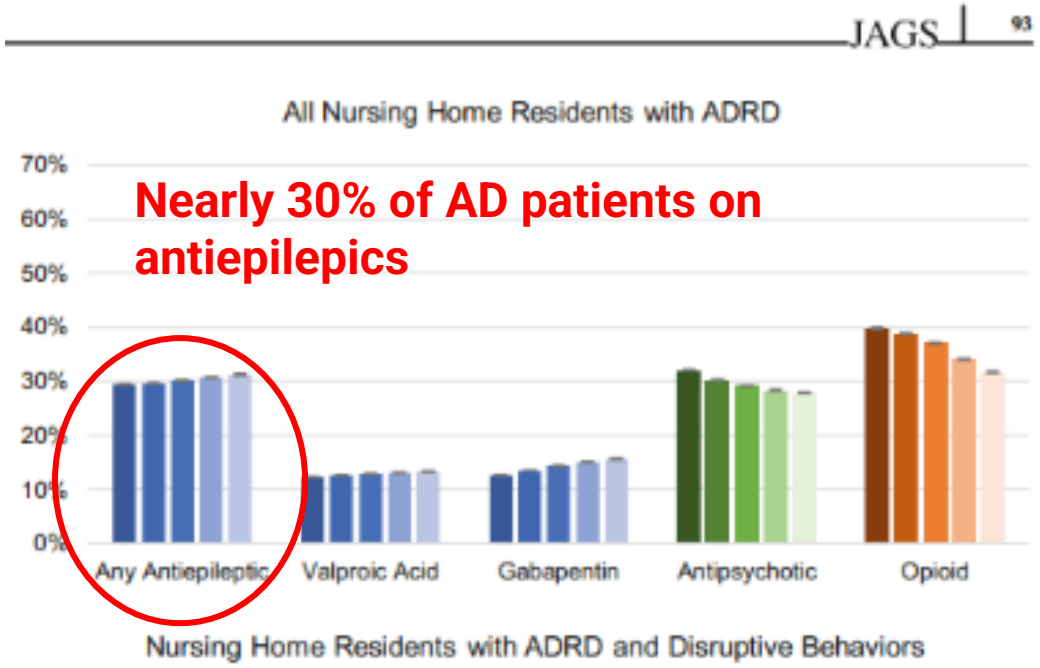
Inspector general's report says increased use of anticonvulsant medications coincided with a reduction in antipsychotic drugs

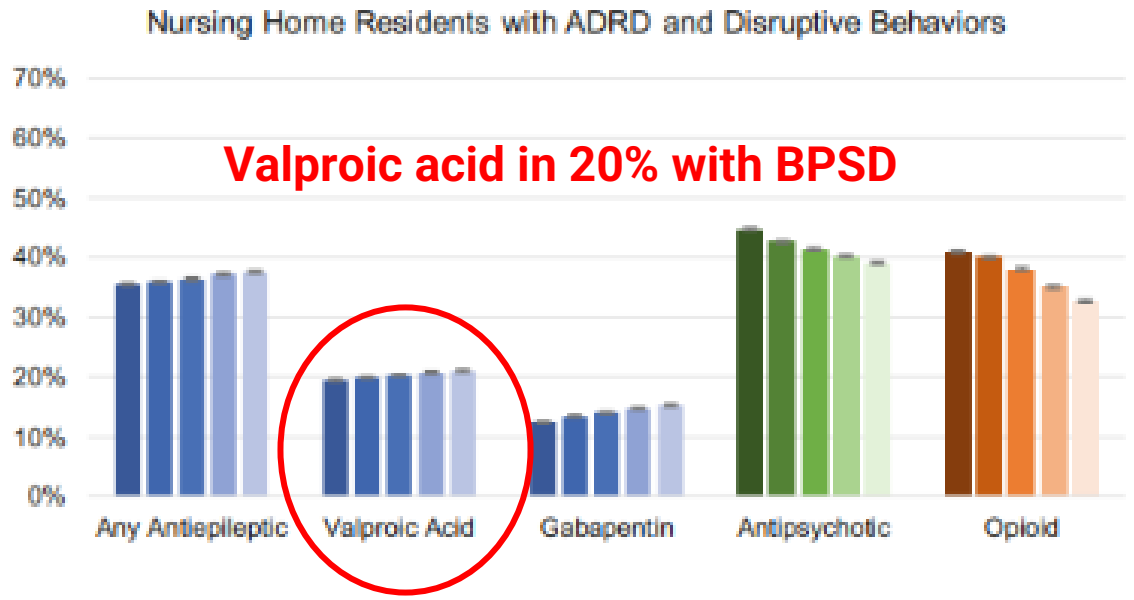
Gabapentinoids and Valproate have similar targets in CNS

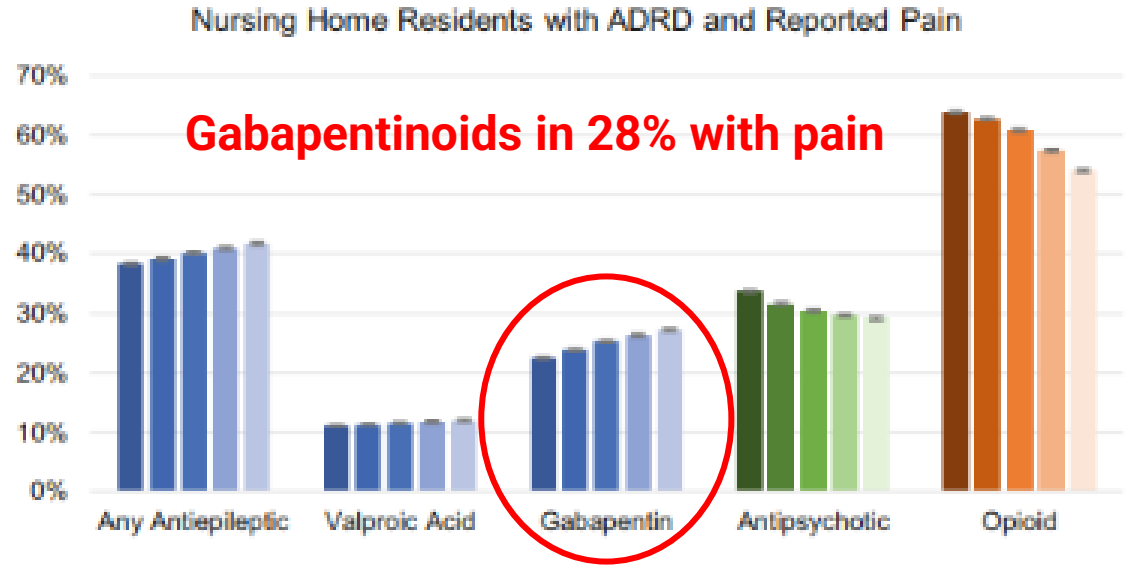


Journal of the
American Geriatrics Society

Antiepileptic prescribing to persons living with dementia residing in nursing homes: A tale of two indications







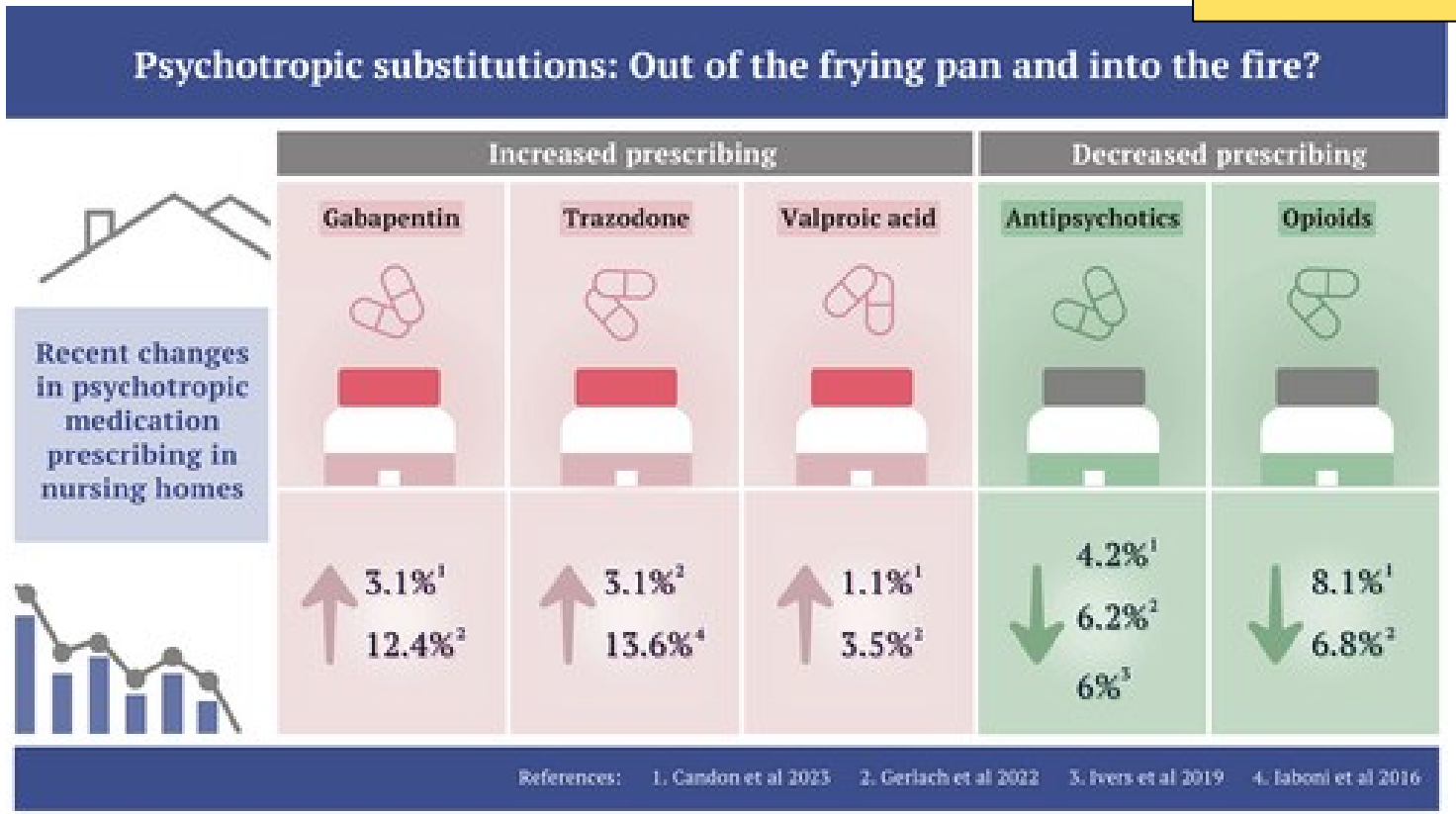
973,074 persons living with ADRD with fee-for-service Medicare and Part D coverage with long-term stays in NHs, between 2015 and 2019.

A consequence of pressures to reduce/eliminate antipsychotics in dementia patients with behaviors.

COMMENTARIES

Journal of the American Geriatrics Socie

Psychotropic substitutions: Out of the frying pan and into the fire



Reppas-Rindlisbacher C, Stall NM, Rochon PA. Psychotropic substitutions: Out of the frying pan and into the fire. J Am Geriatr Soc. 2023 Jun;71(6):2013-2016.

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2019) **85** 690–703 690

REVIEW

Gabapentin and pregabalin to treat aggressivity in dementia: a systematic review and illustrative case report

Preliminary low-grade evidence based on case series and case reviews suggests *possible benefit of gabapentin and pregabalin in patients with BPSD in Alzheimer's disease.* These *benefits cannot be confirmed until well-powered randomized controlled trials are undertaken.*

Conclusion: Gabapentin and pregabalin could be considered for BPSD **when medications having stronger evidence bases** (risperidone, other antipsychotics, carbamazepine and citalopram) **have been ineffective or present unacceptable risks of adverse outcomes.**

Cochrane Library

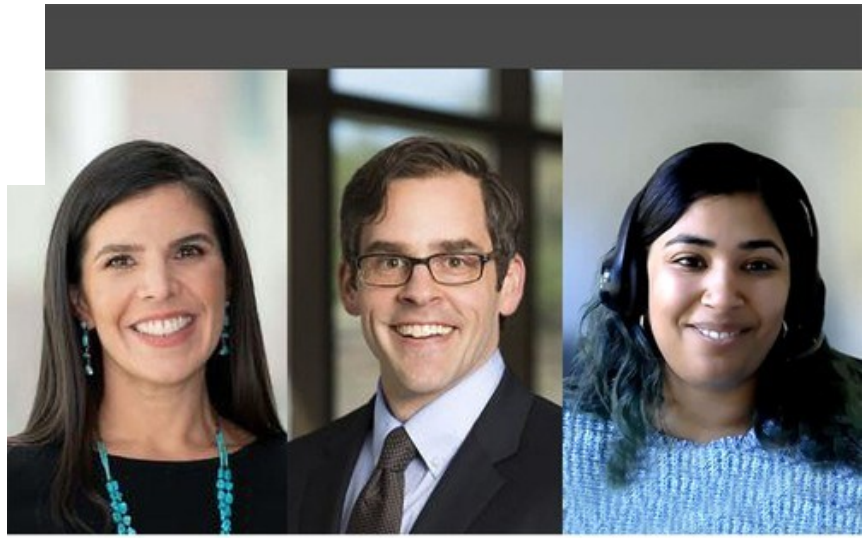
Cochrane Database of Systematic Reviews

Valproate preparations for agitation in dementia (Review)

Baillon SF, Narayana U, Luxenberg JS, Clifton AV

There was probably no difference between valproate and placebo group in agitated behaviors in dementia patients after six weeks of treatment.

PODCAST



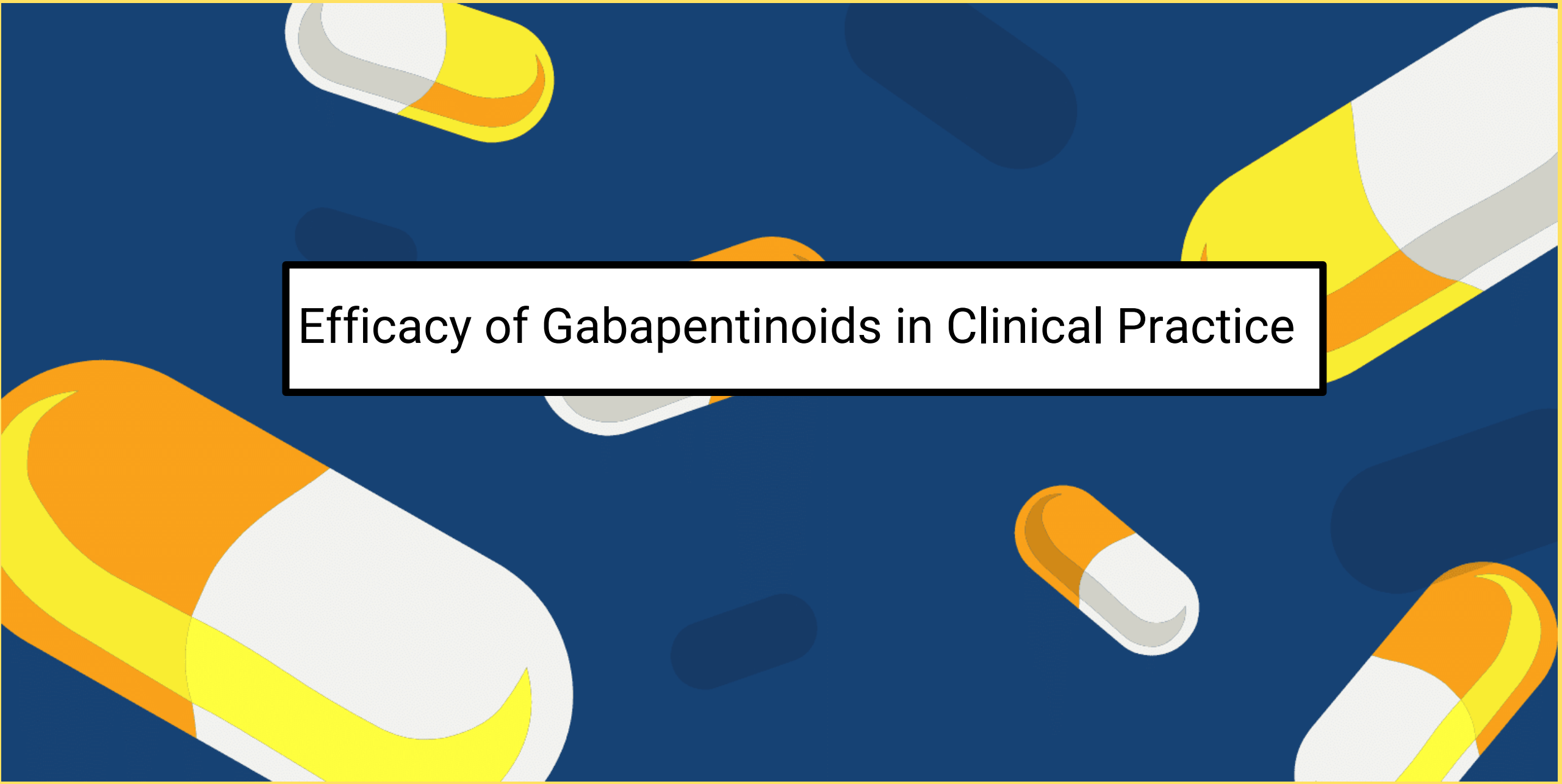
GeriPal PODCAST

Guests:
Tasce Bongiovanni
Donovan Maust
Nisha Iyer

EP255

Gabapentinoids - Gabapentin and Pregabalin

https://geripal.org/gabapentinoids-gabapentin-and-pregabalin-tasce-bongiovanni-donovan-maust-and-nisha-iyer/


Efficacy of Gabapentinoids in Clinical Practice

The New York Times

May 20, 2019

PERSONAL HEALTH

Millions Take Gabapentin for Pain. But There's Scant Evidence It Works.

"There is very little data to justify how these drugs are being used and why they should be in the top 10 in sales," a researcher said.

Gracia Lam

Aug. 17, 2024

THE NEW OLD AGE

The Painkiller Used for Just About Anything

In huge numbers, older people are taking gabapentin for a variety of conditions, including itching, alcohol dependence and sciatica. "It's crazy," one expert said.

Luisa Jung

Clinical Review & Education

JAMA Internal Medicine | Special Communication | LESS IS MORE

A Clinical Overview of Off-label Use of Gabapentinoid Drugs

Christopher W. Goodman, MD; Allan S. Brett, MD

CONCLUSIONS Clinicians who prescribe gabapentinoids off-label for pain should be aware of the limited evidence and should acknowledge to patients that potential benefits are uncertain for most off-label uses.

Goodman CW, Brett AS. A Clinical Overview of Off-label Use of Gabapentinoid Drugs. JAMA Intern Med. 2019 May 1;179(5):695-701

PERSONAL HEALTH

Millions Take Gabapentin for Pain. But There's Scant Evidence It Works.

"There is very little data to justify how these drugs are being used and why they should be in the top 10 in sales," a researcher said.

Drug		Licensed indications	Unlicensed uses
Pregabalin	USA[10]	▪ Neuropathic pain associated with diabetic peripheral neuropathy ▪ Neuropathic pain associated with spinal cord injury ▪ Postherpetic neuralgia ▪ Fibromyalgia ▪ Adjunctive therapy for partial-onset seizures in patients 4 years of age and older	▪ GAD ▪ Social anxiety disorder ▪ Bipolar disorder ▪ Insomnia ▪ Other chronic pain conditions ▪ Chronic pruritus ▪ Chronic cough ▪ RLS ▪ Insomnia ▪ Alcohol use disorder

PERSONAL HEALTH

Millions Take Gabapentin for Pain. But There's Scant Evidence It Works.

"There is very little data to justify how these drugs are being used and why they should be in the top 10 in sales," a researcher said.

		Licensed Indications	Unlicensed uses
Gabapentin	USA[13]	▪ Postherpetic neuralgia ▪ Adjunctive therapy in the treatment of partial seizures with or without secondary generalisation in patients over the age of 12 with epilepsy, and 3 to 12 year olds with a partial seizure ▪ Moderate to severe RLS	▪ Neuropathic pain ▪ Fibromyalgia ▪ Bipolar disorder ▪ Postmenopausal hot flushes ▪ Essential tremors ▪ Anxiety ▪ Resistant depressant and mood disorders ▪ Irritable bowel syndrome (IBS) ▪ Alcohol withdrawal ▪ Postoperative analgesia ▪ Nausea and vomiting ▪ Migraine prophylaxis ▪ Headache ▪ Interstitial cystitis ▪ Painful diabetic neuropathy ▪ Social phobia ▪ Generalized tonic-clonic seizures ▪ Pruritus (itching) ▪ Insomnia ▪ Post-traumatic stress disorder (PTSD) ▪ Refractory chronic cough

Add:
BPSD in dementia

FDA approved pain indications, Efficacy

Drug		Licensed indications
Pregabalin	USA[10]	▪ Neuropathic pain associated with diabetic peripheral neuropathy ▪ Neuropathic pain associated with spinal cord injury ▪ Postherpetic neuralgia ▪ Fibromyalgia

Painful diabetic neuropathy: AAN: Pregabalin is possibly more likely than placebo to improve pain (SMD 0.29; 95% CI, 0.13–0.45; small effect, low confidence; 8 Class I and 7 Class II studies).

SCI: Cochrane review: Low-quality evidence suggests that oral pregabalin is effective after trauma due to stroke or spinal cord injury.

PHN: Cochrane review: Moderate-quality evidence shows that oral pregabalin (300 mg or 600 mg/day) has an important effect on pain in some people with moderate or severe neuropathic pain after shingles, or due to diabetes. **Pain reduced by 50% or more 3/10 receiving pregabalin; 2/10 receiving placebo.**

Fibromyalgia: Cochrane review:
10% of patients with moderate to severe fibromyalgia experienced a **50% reduction in pain** over several months of treatment.

FDA approved pain indications, Efficacy

Gabapentin	USA[15]	▪ Postherpetic neuralgia

PHN:Cochrane review: Gabapentin 1200+ mg/day: more participants **(32%) had substantial benefit (at least 50% pain relief vs placebo (17%)** (RR 1.8 (95% CI 1.5 to 2.1); NNT 6.7 (5.4 to 8.7) participants **(46%) had moderate benefit (at least 30% pain relief) vs placebo (25%)** (RR 1.8 (95% CI 1.6 to 2.0); NNT 4.8 (4.1 to 6.0); 8 studies, 2260 participants, **moderate-quality evidence**).

Wiffen PJ, Derry S, Moore RA, Aldington D, Cole P, Rice AS, Lunn MP, Hamunen K, Haanpaa M, Kalso EA. Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews. Cochrane Database Syst Rev. 2013 Nov 11;2013

Wiffen PJ, Derry S, Bell RF, Rice AS, Tölle TR, Phillips T, Moore RA. Gabapentin for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2017 Jun 9

Derry S, Bell RF, Straube S, Wiffen PJ, Aldington D, Moore RA. Pregabalin for neuropathic pain in adults. Cochrane Database Syst Rev. 2019 Jan 23

SPECIAL ARTICLE Level of Recommendation

Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary

Report of the AAN Guideline Subcommittee

Gabapentin is probably more likely than placebo to improve pain (SMD 0.53; 95% confidence interval [CI], 0.22–0.84; medium effect, moderate confidence; 1 Class I study).

Pregabalin is possibly more likely than placebo to improve pain (SMD 0.29; 95% CI, 0.13–0.45; small effect, low confidence; 8 Class I and 7 Class II studies).

Table 1 Medication Dosage and Duration Information

Medication class	Medication	Dosage, mg/d	Duration, wk
SNRI	Duloxetine	40–60	12
SNRI	Venlafaxine	150–225	6
SNRI	Desvenlafaxine	200	13
Gabapentinoid	Gabapentin	900–3,600	4–8
Gabapentinoid	Pregabalin	300–600	5–12
Gabapentinoid	Mirogabalin	15–30	5
Sodium channel antagonist	Oxcarbazepine	1,400–1,800	16
Sodium channel antagonist	Lamotrigine	200–400	6
Sodium channel Antagonist	Lacosamide	400	12
Sodium channel blocker	Valproic acid	1,000–1,200 or 20 mg/kg/d	4–12
TCA	Amitriptyline	75–150	6
Capsaicin	Capsaicin	8% for 30 min/ application or 0.075% 4 times per day	12

Price R, Smith D, Franklin G, Gronseth G, Pignone M, David WS, Armon C, Perkins BA, Bril V, Rae-Grant A, Halperin J, Licking N, O'Brien MD, Wessels SR, MacGregor LC, Fink K, Harkless LB, Colbert L, Callaghan BC. Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary: Report of the AAN Guideline Subcommittee. Neurology. 2022 Jan 4;98(1):31-43

High quality studies or Cochrane reviews have found:

NO benefit of gabapentinoids for:
Low back pain
Sciatica
Spinal stenosis
Episodic Migraine


Gabapentinoids and Drug:Drug interactions

Gabapentin and Opioids

<u>Potentiate each other (x2)</u>

-Opiates increase the absorption of Gabapentin by slowing bowel motility

-Increases euphoria

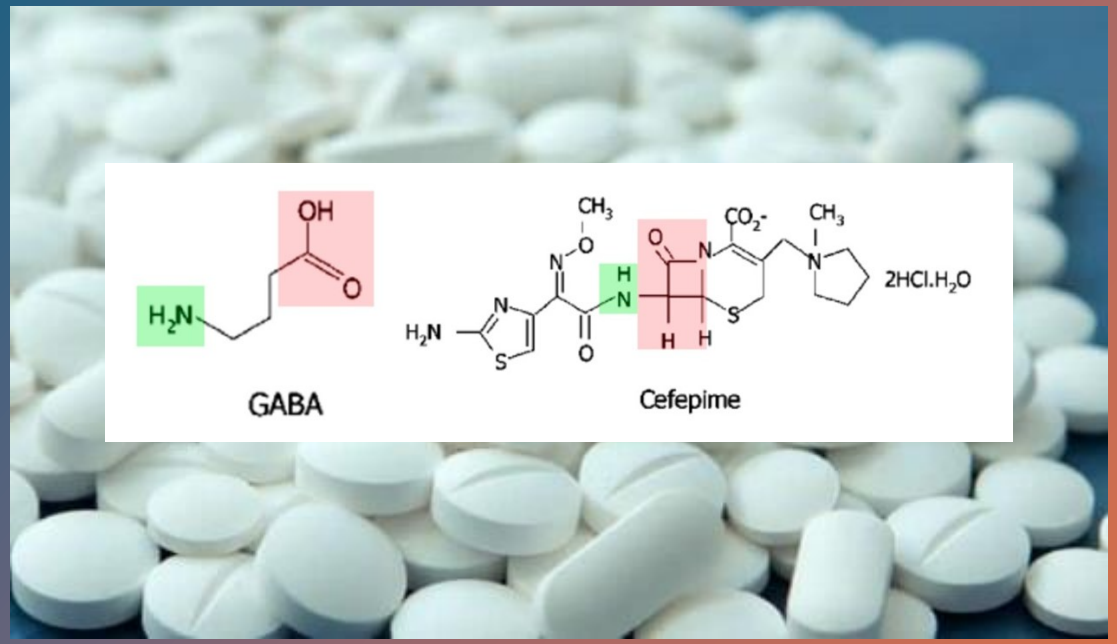
-Act synergistically in CNS to cause somnolence and respiratory depression

<u>Increase fatal overdoses</u>

-Toxicology reports show Gabapentin was present in 52% of patients with opiate overdose deaths*

Study of 58,000 deaths patients, 23 states, 2019-2020

Gabapentin and Cefepime



Language dysfunction/aphasia most common in cefepime-associated encephalopathy (**nearly 30% of reported cefepime-related AAE cases**).

HARVARD MEDICAL SCHOOL

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Trends in Medicine

Cefepime-Induced Neurotoxicity

Martina McGrath, MD | February 20, 2018

Neurology®

The most widely read and highly cited peer-reviewed neurology journal

VIEWS & REVIEWS | February 17, 2016 |

Antibiotic-associated encephalopathy

Cefepime-induced neurotoxicity, J Neurocrit Care 2019;12(2):74-84. 24 December 2019

DOI: https://doi.org/10.18700/jnc.190109

Payne LE, Gagnon DJ, Riker RR, Seder DB, Glisic EK, Morris JG, Fraser GL. **Cefepime-induced neurotoxicity: a systematic review**. Crit Care. 2017 Nov 14;21(1):276. doi: 10.1186/s13054-017-1856-1. PMID: 29137682; PMCID: PMC5686900.

U.S. FOOD & DRUG ADMINISTRATION

12-19-2019 FDA Drug Safety Communication

FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR)

When used with CNS depressants or in patients with lung problems

Gabapentinoids in patients with COPD

ORIGINAL RESEARCH

Annals of Internal Medicine

Gabapentinoids and Risk for Severe Exacerbation in Chronic Obstructive Pulmonary Disease

A Population-Based Cohort Study

Gabapentinoid use was associated with **significantly higher risk for severe COPD exacerbations requiring hospitalization** (15.1% vs. 8.3% annually; adjusted hazard ratio, 1.4).

New users of gabapentinoids also had **significantly higher risks for respiratory failure** (5.7% vs. 3.6% annually, aHR, 1.3) and **moderate-to-severe COPD exacerbations** (53% vs. 29% annually; aHR, 1.1).

Gabapentin did not differ from pregabalin in risk for severe COPD exacerbations.

Rahman AA, Dell'Aniello S, Moodie EEM, Durand M, Coulombe J, Boivin JF, Suissa S, Ernst P, Renoux C. Gabapentinoids and Risk for Severe Exacerbation in Chronic Obstructive Pulmonary Disease : A Population-Based Cohort Study. Ann Intern Med. 2024 Feb;177(2):144-154.

Gabapentinoids, Edema and Prescribing Cascades

JOURNAL OF THE AMERICAN GERIATRICS SOCIETY

Clinical Investigation

Evidence of a gabapentinoid and diuretic prescribing cascade among older adults with lower back pain

Ontario, Canada: 260,000 adults >65 yo, new dx back pain or sciatica

Older adults with new initiations on gabapentinoid:

- **new gabapentinoid users had a higher rate of being dispensed a diuretic within 90 days** of initiation compared with those not prescribed a gabapentinoid **HR: 1.44, [95%CI: 1.23, 1.70]**.
- rate of diuretic prescription among new gabapentinoid users **increased with increasing gabapentinoid dosages**. (High dose>900 mg/day).

Read SH, Giannakeas V, Pop P, Bronskill SE, Herrmann N, Chen S, Luke MJ, Wu W, McCarthy LM, Austin PC, Normand SL, Gurwitz JH, Stall NM, Savage RD, Rochon P. Evidence of a gabapentinoid and diuretic prescribing cascade among older adults with lower back pain. J Am Geriatr Soc. 2021 Oct

Gabapentinoids, Edema and Prescribing Cascades

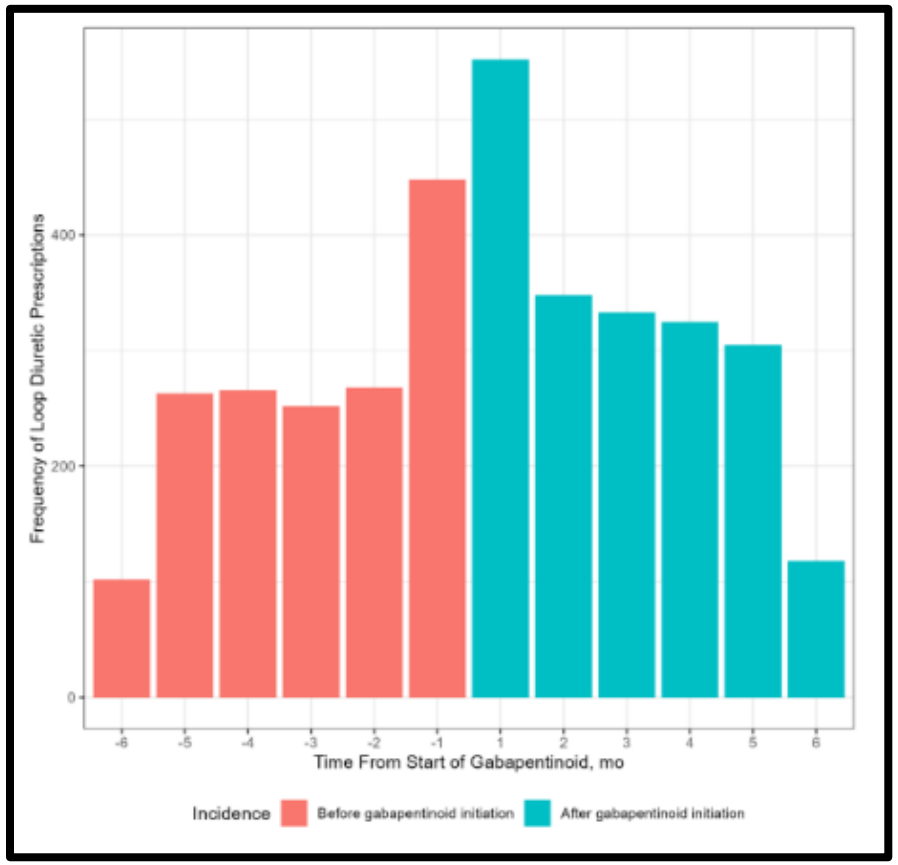
JOURNAL OF THE AMERICAN GERIATRICS SOCIETY

CLINICAL INVESTIGATION | Full Access

Which older adults are at highest risk of prescribing cascades? A national study of the gabapentinoid–loop diuretic cascade

2024: VAMC study confirmed findings of prescribing cascade with new gabapentin.

Only subgroup found to have increased risk of this were those with **hyperpolypharmacy (≥10 medications)** .



Growdon ME, Jing B, Morris EJ, Deardorff WJ, Boscardin WJ, Byers AL, Boockvar KS, Steinman MA. Which older adults are at highest risk of prescribing cascades? A national study of the gabapentinoid-loop diuretic cascade. J Am Geriatr Soc. 2024 Jun;72(6):1728-1740.

Gabapentinoids and “multi-modal pain control”

JAMA Internal Medicine | Original Investigation | LESS IS MORE

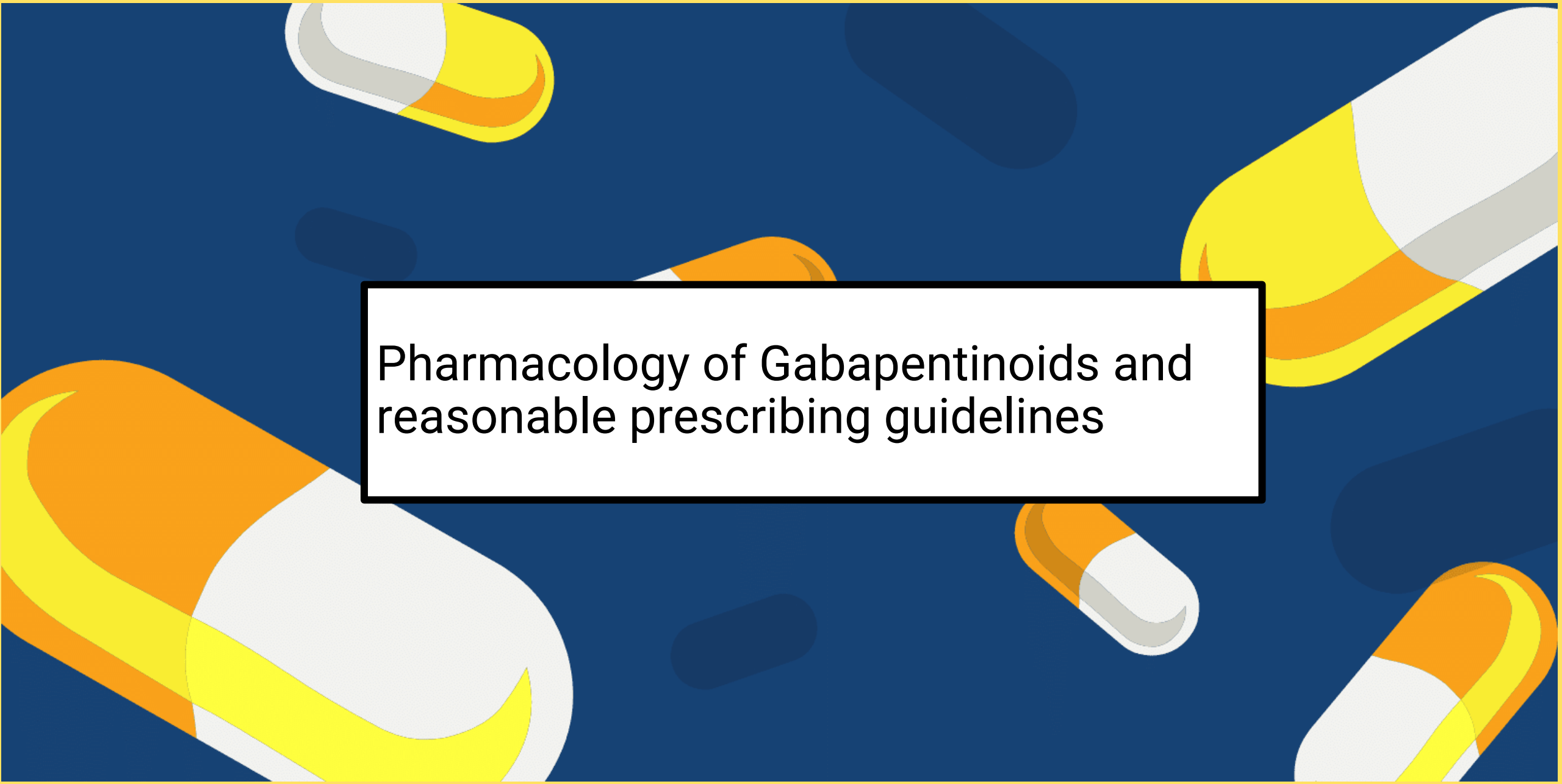
Perioperative Gabapentin Use and In-Hospital Adverse Clinical Events Among Older Adults After Major Surgery

Chan Mi Park, MD, MPH; Sharon K. Inouye, MD, MPH; Edward R. Marcantonio, MD, ScM; Eran Metzger, MD; Brian T. Bateman, MD, ScM; Jessica J. Lie, MD, MPH; Su Been Lee, BA; Raisa Levin, MS; Dae Hyun Kim, MD, ScD

In this cohort study, years 2009-2018, nearly 1 million Medicare recipients were studied. **Peri-operative gabapentin use was associated with increased risk of delirium, new antipsychotic use, and pneumonia among older patients after major surgery.** These results suggest careful risk-benefit assessment before prescribing gabapentin for peri-operative pain management

Risk of delirium among gabapentin users was greater in subgroups with high combined comorbidity index and those with CKD.

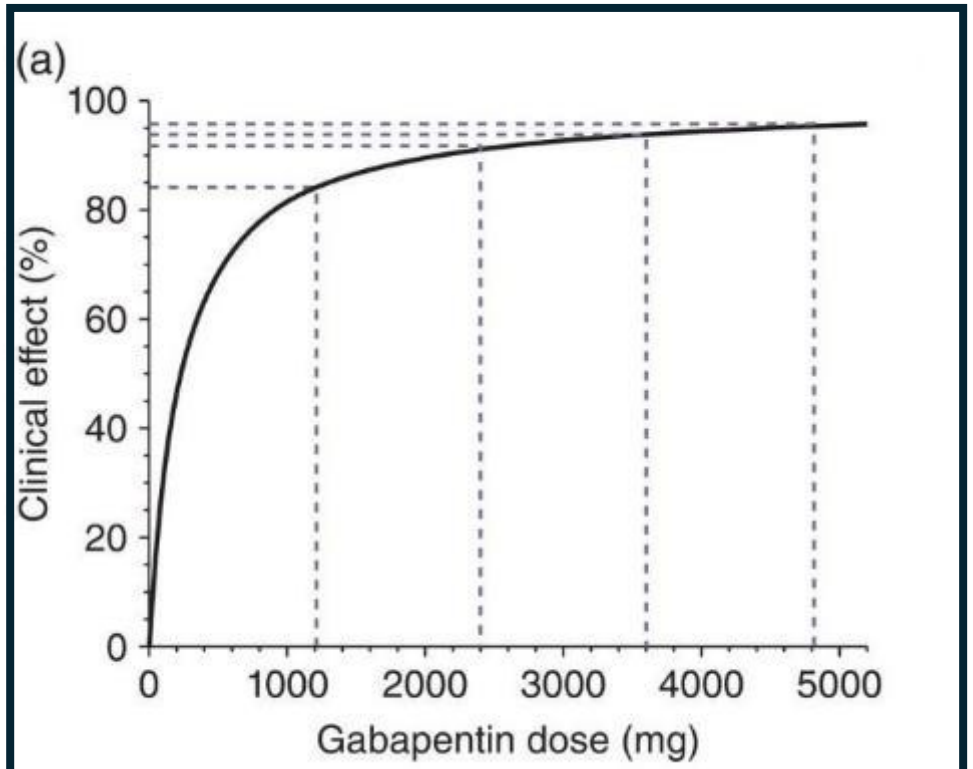
Prescribing momentum: Another study in JAGS in 2022 showed that 20% of elders started on gabapentin peri-operatively were still on it at 90 days post op.


Pharmacology of Gabapentinoids and reasonable prescribing guidelines

Gabapentinoids:
Pharmacokinetics, Pharmacodynamics, Properties

Drug	Gabapentin	Pregabalin
Absorption	**Highly variable pharmacokinetic profile** Small intestine Zero-order saturable absorption **Bioavailability depends on dose 27%-60%** Peak Plasma Concentration dose dependent 100 mg: 1.7 hrs, 3-4 hrs higher doses **Increased absorption when used with opiates**	**Predictable pharmacokinetic profile** Small intestine +Ascending Colon Linear absorption **Bioavailability >90% regardless of dose** Peak Plasma Concentration dose independent, 1 hour **No change in absorption when used with opiates**
Elimination	Renal excretion, unchanged Affected by CrCl Half-life around 6-7 hours	Renal excretion, unchanged Affected by CrCl Half-life around 6-7 hours
Drug:Drug	Reduced absorption with oral antacids	
Potency		**6 times higher binding affinity** to d2a1 receptor
Abuse potential	Higher with opiates	Higher than gabapentin when used alone
Control	Schedule V in 7 states (since 2017)	Schedule V all states (since 2004)

Gabapentin-the questionable utility of dose escalation



Hyperbolic relationship of Gabapentin and its effect on target receptors.

TABLE 2. Decreasing Bioavailability of Gabapentin With Increased Dosing

Gabapentin dose in mg (total/day)	900	1200	2400	3600	4800
Gabapentin % bioavailability	60	47	34	33	27

Maximum Gabapentin Dosing (all ages)

-Manufacturer: Up to 3600 mg/day

-ANA: up to 3,600 mg/day

-**Analgesic ceiling at 1800 mg in adults** with **no additional proven clinical benefit** at higher doses for FDA approved indications.

-European Medicines Agency generally recommends dosing up to 1800 mg in adults.

General consensus in research on dosing “brackets”

Low dose Gabapentin: **600-900 mg/day**
High dose Gabapentin **900-1800+ mg/day**

High dose Gabapentin:

-Associated with **twofold increase in adverse effects** including somnolence, tremors, ataxia and nystagmus.

-Studies have demonstrated **dose dependent likelihood of side effects and unintended consequences**.

-**60% increase in risk of opioid-related death** compared with opioids alone.

Lennox R, Mangin D. Gabapentin misuse. CMAJ. 2019 Jan 14;191(2):E47.

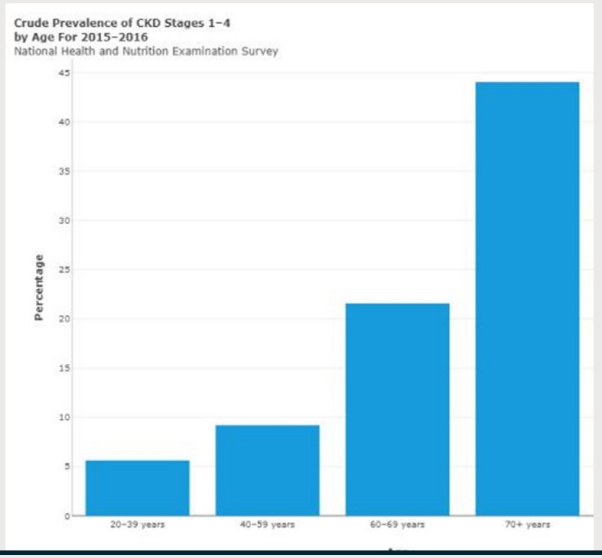
Medications that are renally excreted in the elderly

-Sulfonylureas-avoid in elderly-risk of hypoglycemia too great

-Atenolol-avoid in elderly-risk of bradycardia too great

-Gabapentin…risk of toxicity, falls, somnolence… not too great?

Nearly half of all patients over the age of 70 in the US have some degree of CKD



Geriatric Gabapentin Dosing Recommendations

Recommendations:

Maintain doses <900 mg/day in elderly patients as a general goal= (<150/day Pregabalin)

Start at 100 mg qhs and increase slowly.

Avoid TID dosing in any elder with CKD.

Consider comorbidities (COPD, disease states causing or worsened by edema)

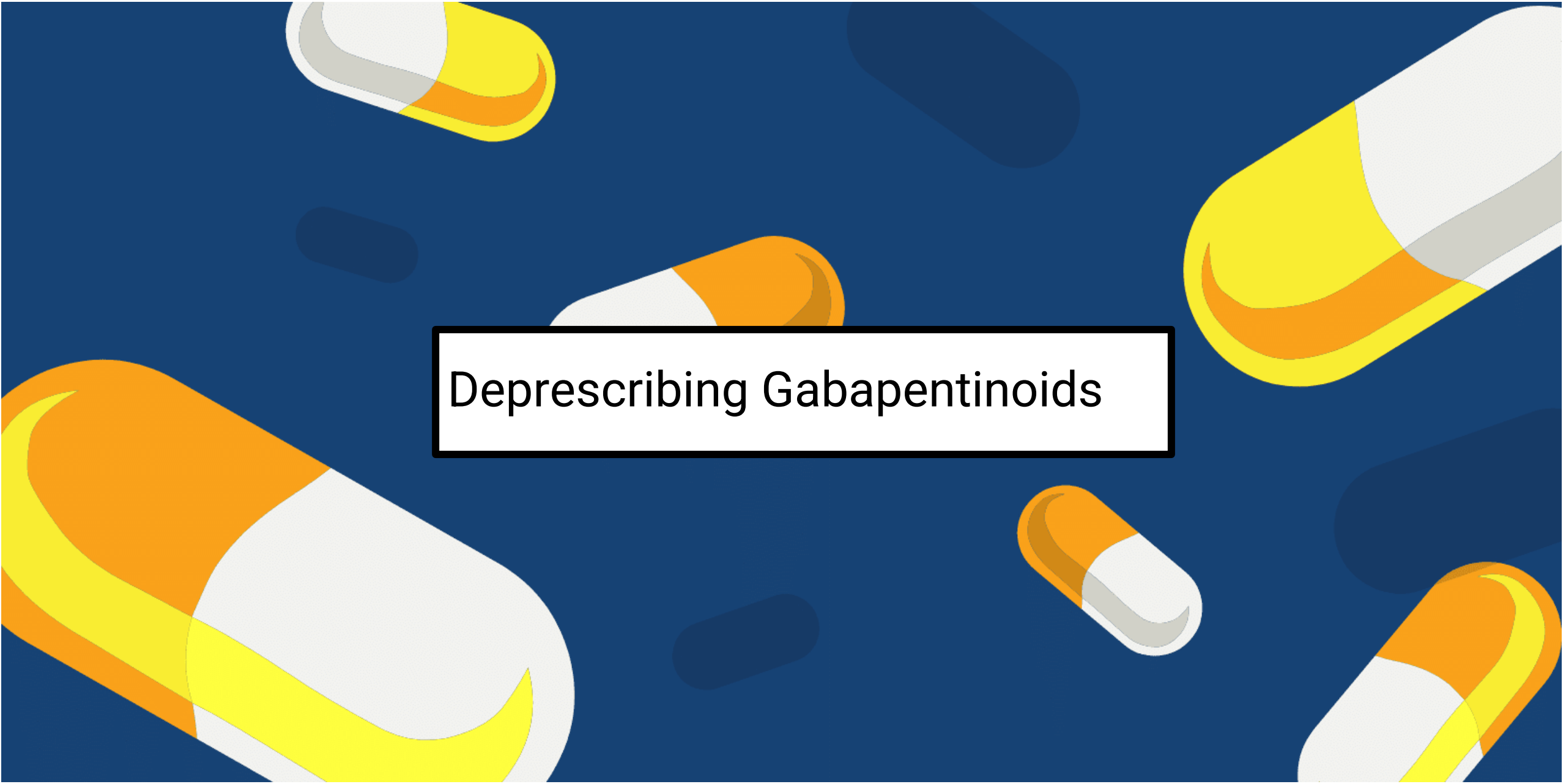
Know their other medications if starting Gabapentin (other GABA-ergic/CNS drugs)

Benefits of these limits:

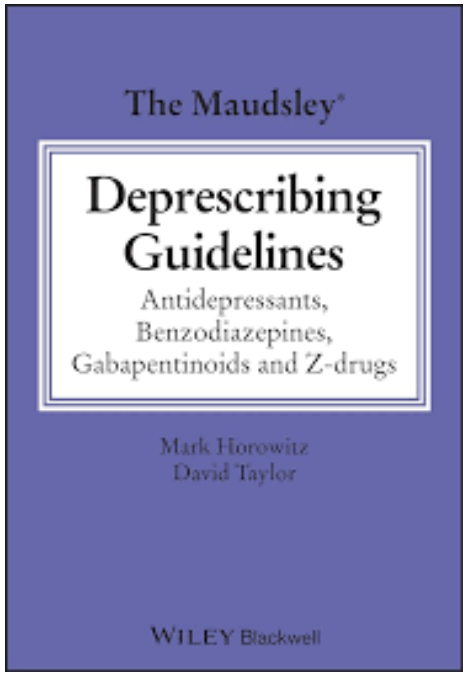
Maintains geriatric patient in “low dose” bracket

Less likely to result in toxicity in times of illness/dehydration

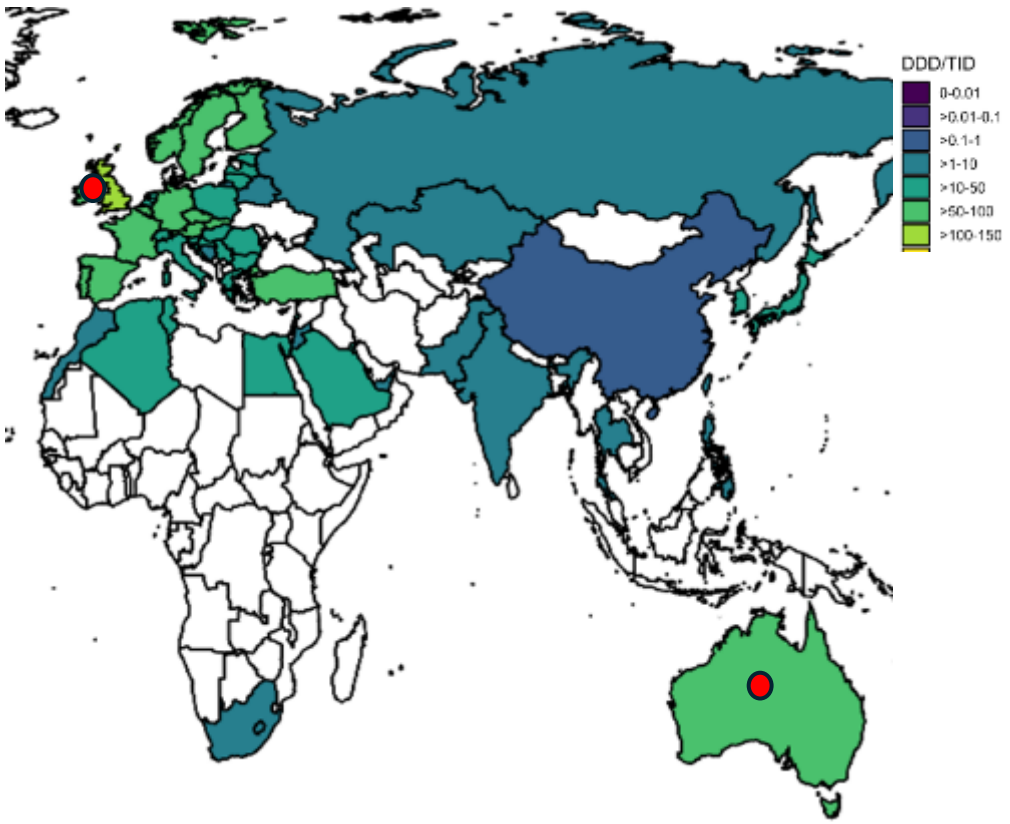
Balances maximizing efficacy/bioavailability while reducing likelihood of side effects

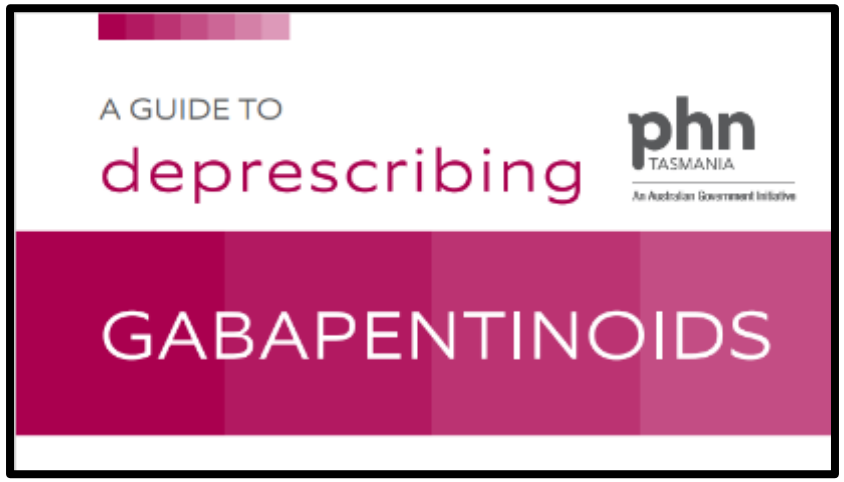

Deprescribing Gabapentinoids

Deprescribing concepts… some international guidance



- England:
  https://www.sussexccgs.nhs.uk/wp-content/uploads/2021/10/Analgesic-tapering-guidance-Sussex-CCG.pdf
- Scotland:
  https://www.nhsfife.org/media/290vs85e/gabapentinoid-reduction-leaflet.pdf
- Australia:
  https://www.primaryhealthtas.com.au/wp-content/uploads/2023/03/A-guide-to-deprescribing-gabapentinoids.pdf



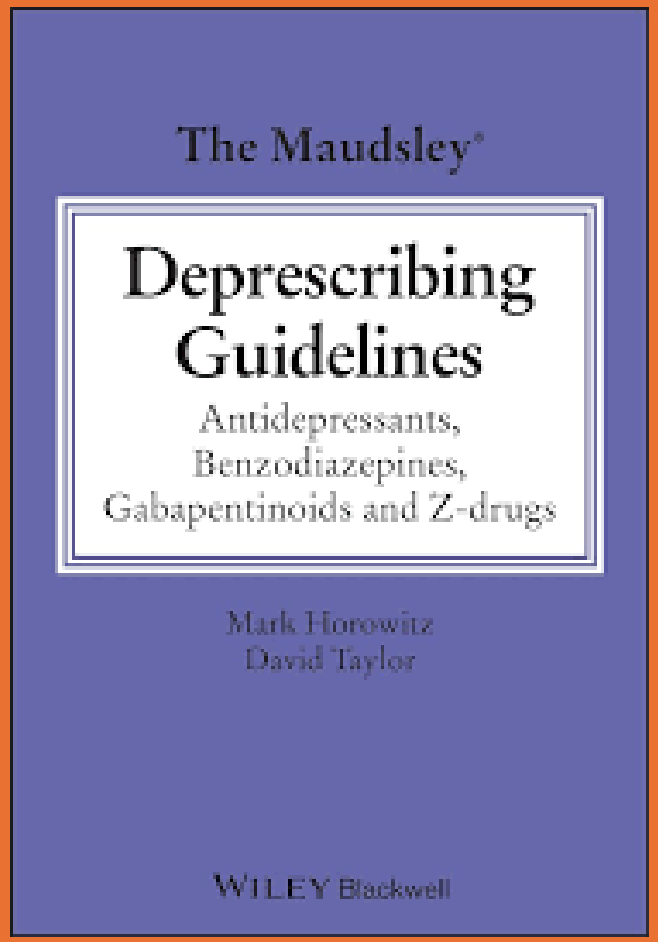


-Don’t abruptly stop gabapentinoids

-Tapering can be done over **1-2 weeks** for patients on **lowest doses/short duration**

- Tapering over **4-8 weeks** for patients who have been **taking gabapentinoids long term** (greater than 6 months) **or at high doses**.

https://www.primaryhealthtas.com.au/wp-content/uploads/2023/03/A-guide-to-deprescribing-gabapentinoids.pdf



If on Gabapentin 3600 mg/day it would take 3-12 months to get them off following these guidelines!

Recommendations (Maudsley):

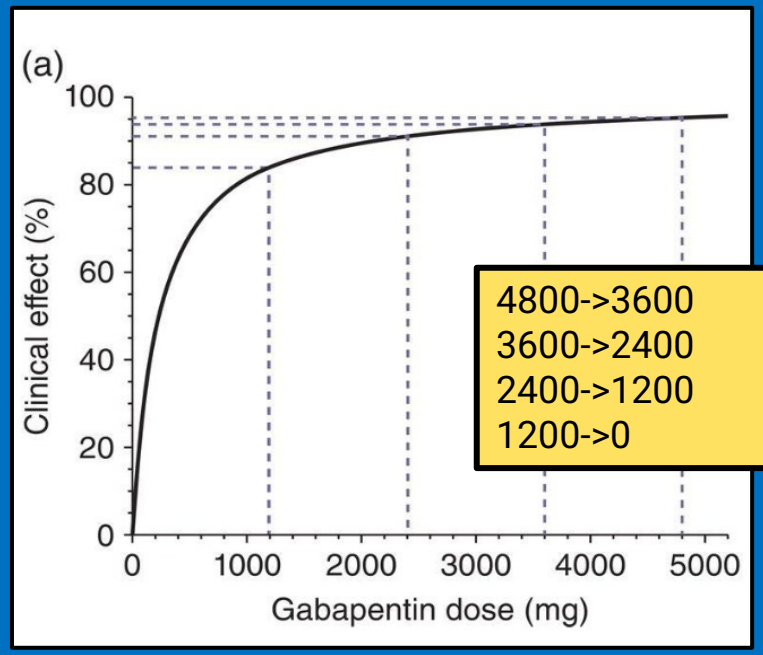
Reduce Gabapentin by 300 mg every 1-4 weeks

Reduce Lyrica by 50 mg every 1-4 weeks

Deprescribing

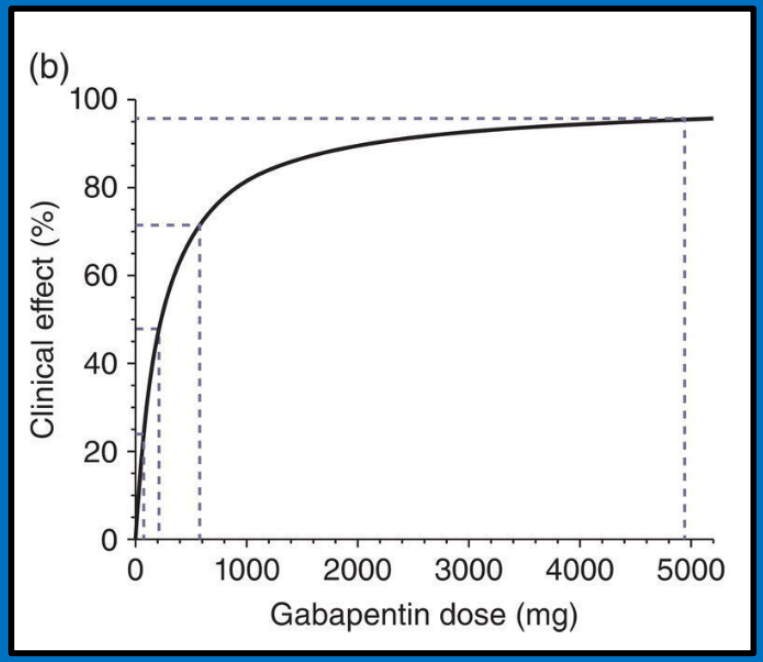
Hyperbolic tapering may be necessary for Gabapentin

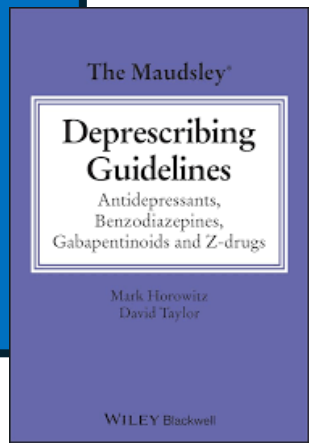
Linear dose reductions cause increasingly large reductions in clinical effect



4800->3600	1.4%
3600->2400	2.7%
2400->1200	7.3%
1200->0	84%

Hyperbolic dose reductions produce even reductions in clinical effects





Equality and Diversity

NHS Fife

Gabapentinoid Reduction

Patient Information Leaflet

The Fife Pain Management Service

GETTING YOU ON TRACK TO RECOVERY

NHS Fife provides accessible communication in a variety of formats including for people who are speakers of community languages, who require Easy Read versions, who speak BSL, read Braille or use Audio formats.

NHS Fife SMS text service number 07805800005 is available for people who have a hearing or speech impairment.

To find out more about accessible formats contact:
fife-UHB.EqualityandHumanRights@nhs.net or phone 01592 729130

Gabapentinoids includes the medications gabapentin and pregabalin

This leaflet applies to gabapentinoid use in chronic pain only

What are gabapentinoids?

Gabapentinoids are medications used to help manage nerve (neuropathic) pain. Neuropathic pain is a type of pain that follows after damage to a nerve. It is thought to result from a "rewiring" of the nerves of the spinal cord .They become very sensitive and send too many pain signals. The pain can be there all the time or can come and go. Normal touch can feel painful. There is often a "burning" or "shooting" feeling, or pins and needles.

Why reduce?

A trial reduction of gabapentinoid should be considered every 6-12 months, when prescribed for chronic pain.

A review and trial reduction can be useful to check:

- Whether nerve pain is still a problem
- Whether you are still getting benefit
- If it is causing any side effects

How to reduce gabapentinoids

The dose should be reduced gradually each week as this will minimise withdrawal effects. It will also allow you to check if there is any change in your pain. The amount and time will depend on your current dose and how long you have been taking the medication.

Often the dose can be reduced in reverse order to how it was increased for example;

- Gabapentin could be reduced by 300mg per week
- Pregabalin could be reduced by 75mg per week

Please follow your reduction plan. Gabapentin and pregabalin come in different strengths. You may require different strengths to allow you to follow the reduction plan.

https://www.nhsfife.org/media/290vs85e/gabapentinoid-reduction-leaflet.pdf


GABA-ergic Withdrawal Syndromes

What to do with Gaba-ergic drugs in the acute setting?

Depends on:

-Withdrawal potential

-Renal function

-If toxicity is suspected (overdose, renal failure, both)

Likelihood of withdrawal is affected by:

-Chronicity of use

-Last dose taken

-Half-life of drug

-Interacting drugs (newly added)

-Changes in metabolism (renal or hepatic dysfunction)

Common pitfalls: GABA-ergics in the acute setting

-Changing scheduled benzos to prn in elders with history of /prone to catatonia

-Not realizing that prn medications in NH can be essentially scheduled medications

-Abrupt discontinuation of medications because they “on Beer’s list” or because of altered mental status

-Being unaware patient is on habituating medications (MAR, PDMP)

-Holding Gabapentinoids in setting of acute renal failure and not resuming any once patient’s renal function normalizes

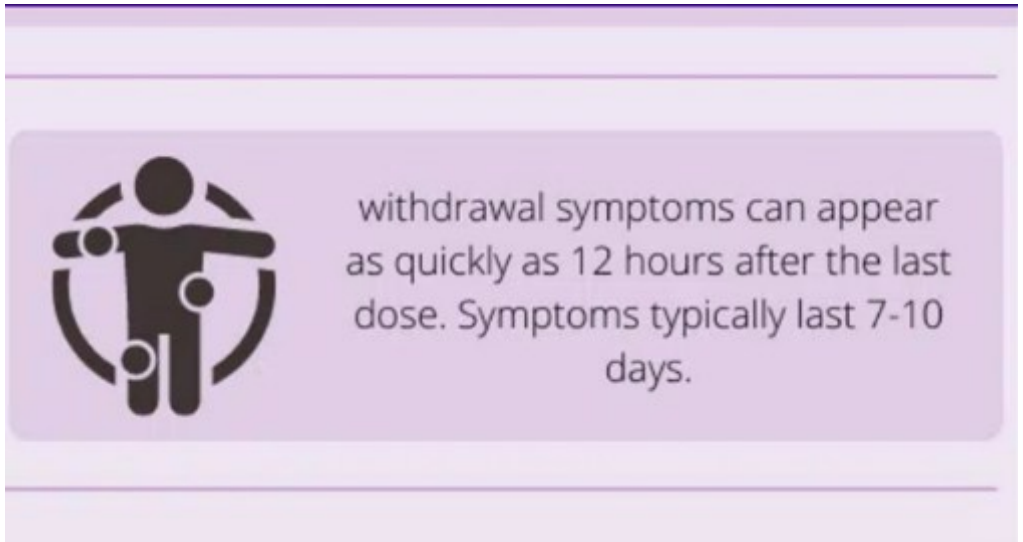
-Not appreciating the long window in which withdrawal can still occur

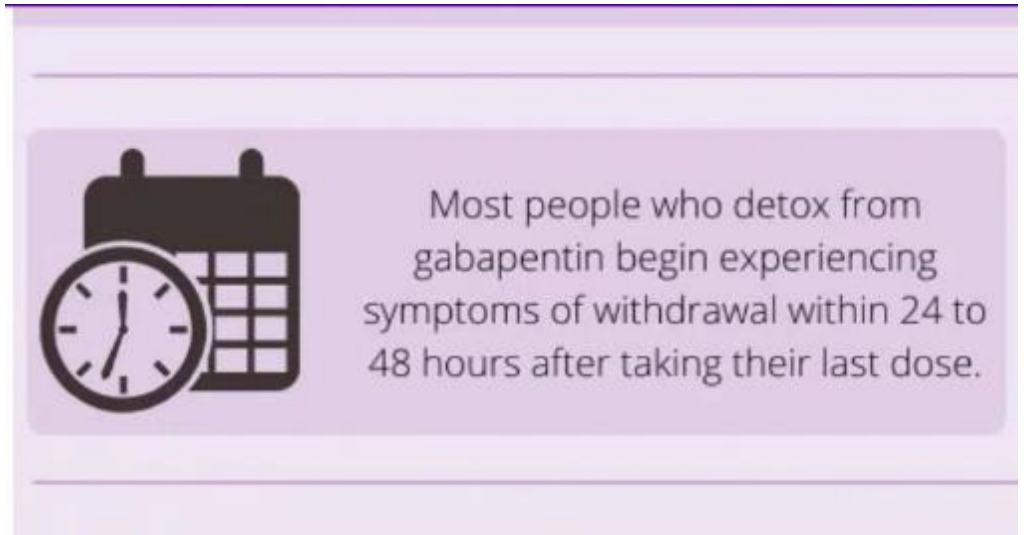
-Initiating antipsychotic/anticholinergic medications for agitated patient driven by a state of GABA-ergic drug withdrawal

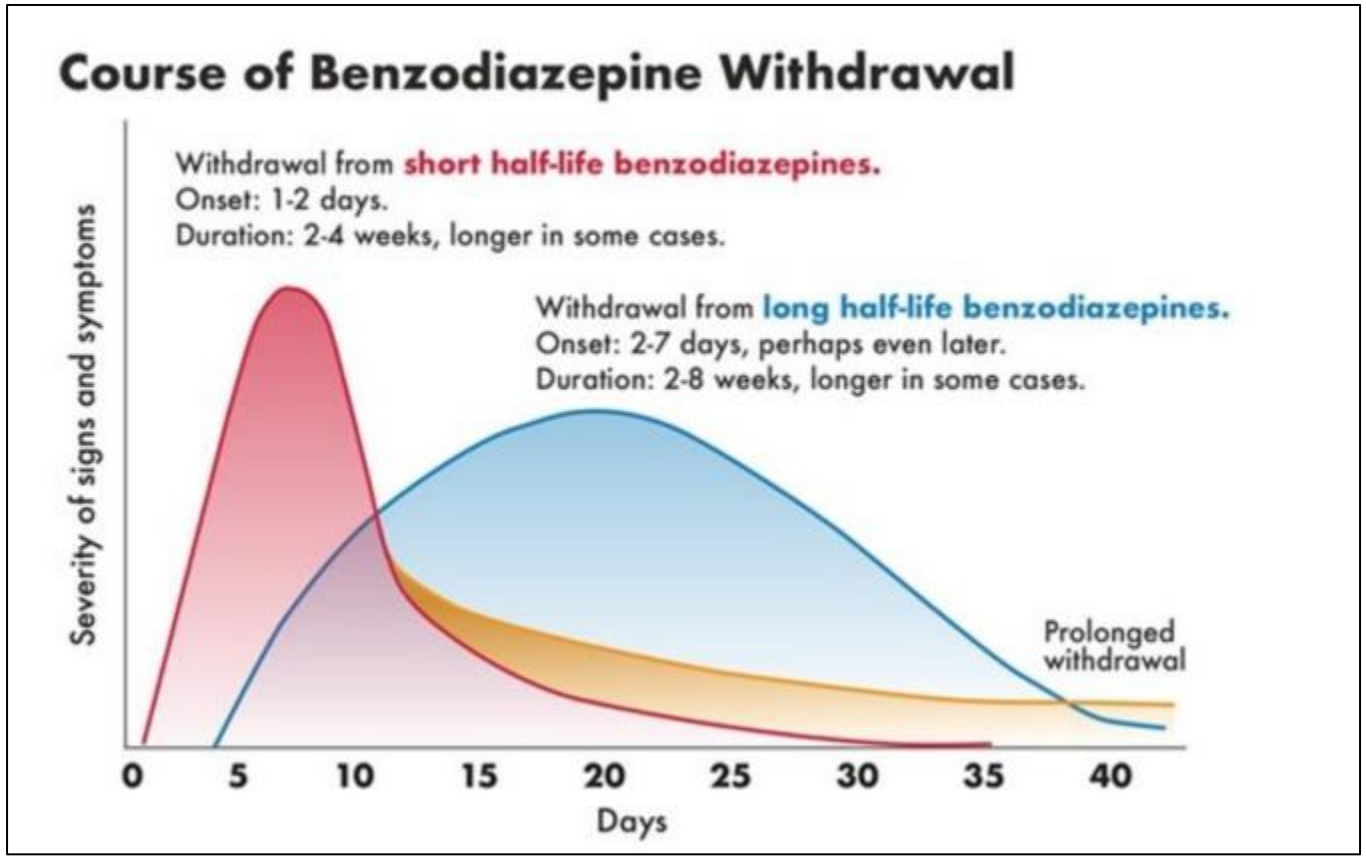
Gabapentinoid withdrawal syndromes

-can occur after only one month of use

-severity depends on age, total daily dose, duration of use







Short acting benzos<5 hr half life

Alprazolam (Xanax)
Triazolam (Halcion)
Midazolam (Versed)

Long acting benzos: >24 hr half life

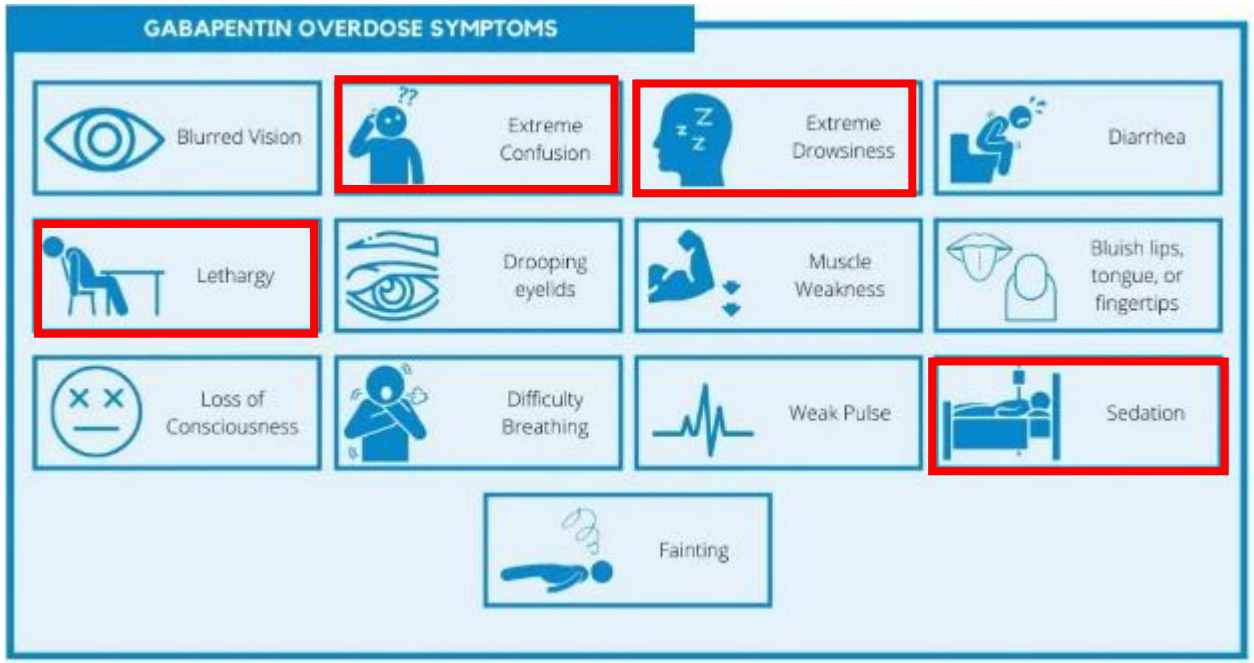
Clordiazepoxide (Librium)
Clonazepam (Klonapin)*
Diazepam (Valium)*

*Cytochrome P450 metabolism-**half life increases with age and hepatic dysfunction, can be up to 60-90 hours.**

Gabapentinoid withdrawal

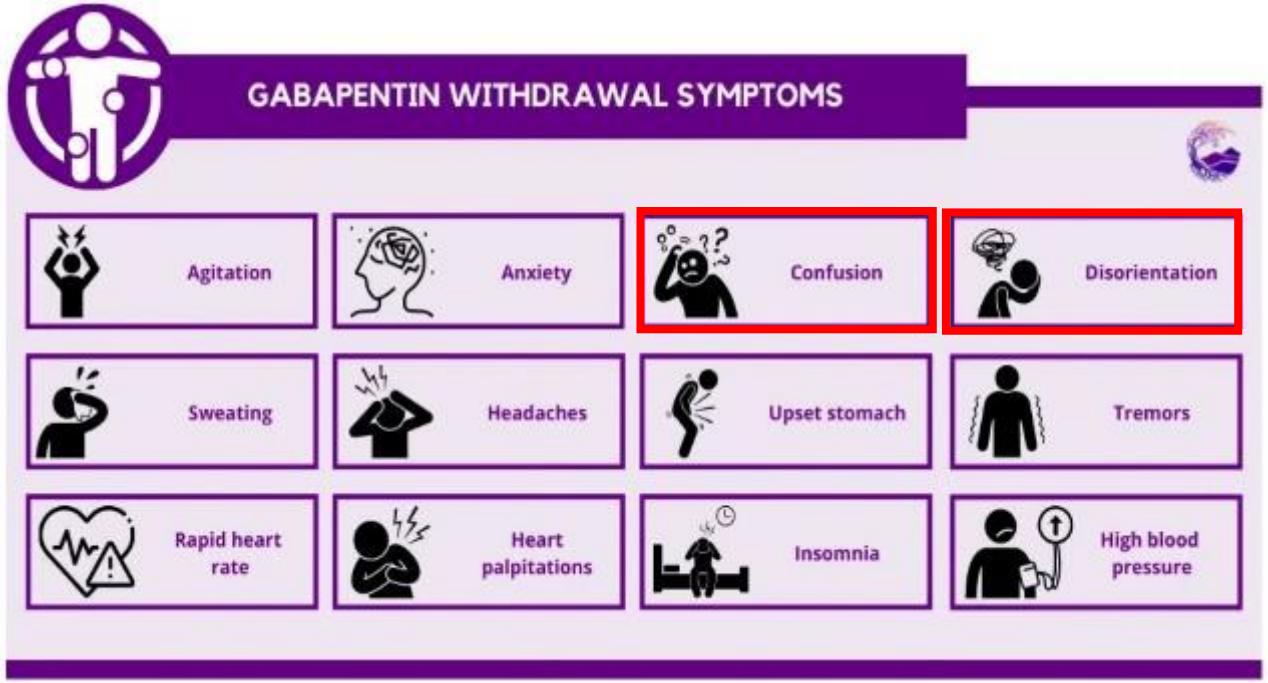
General	Emotional
Insomnia	*Agitation*
Diaphoresis	Dysphoria
Pain	Irritability
Light-headedness	Depersonalisation
Dizziness	Anxiety
Fatigue	**Gut**
Flu-like symptoms	*Gastrointestinal discomfort/symptoms*
Chills	Nausea
Neurological	**Cardiovascular**
Confusion	*Tachycardia*
Disorientation	*Hypertension*
Tremor	Palpitations
Gait instability	**Psychiatric**
Vertigo	Delusions*
Myoclonus	Hallucinations*
Muscle spasms	
Numbness	
Asterixis	
Increased tactile sensations	
Akathisia*	
Catatonia*	
Seizures*	

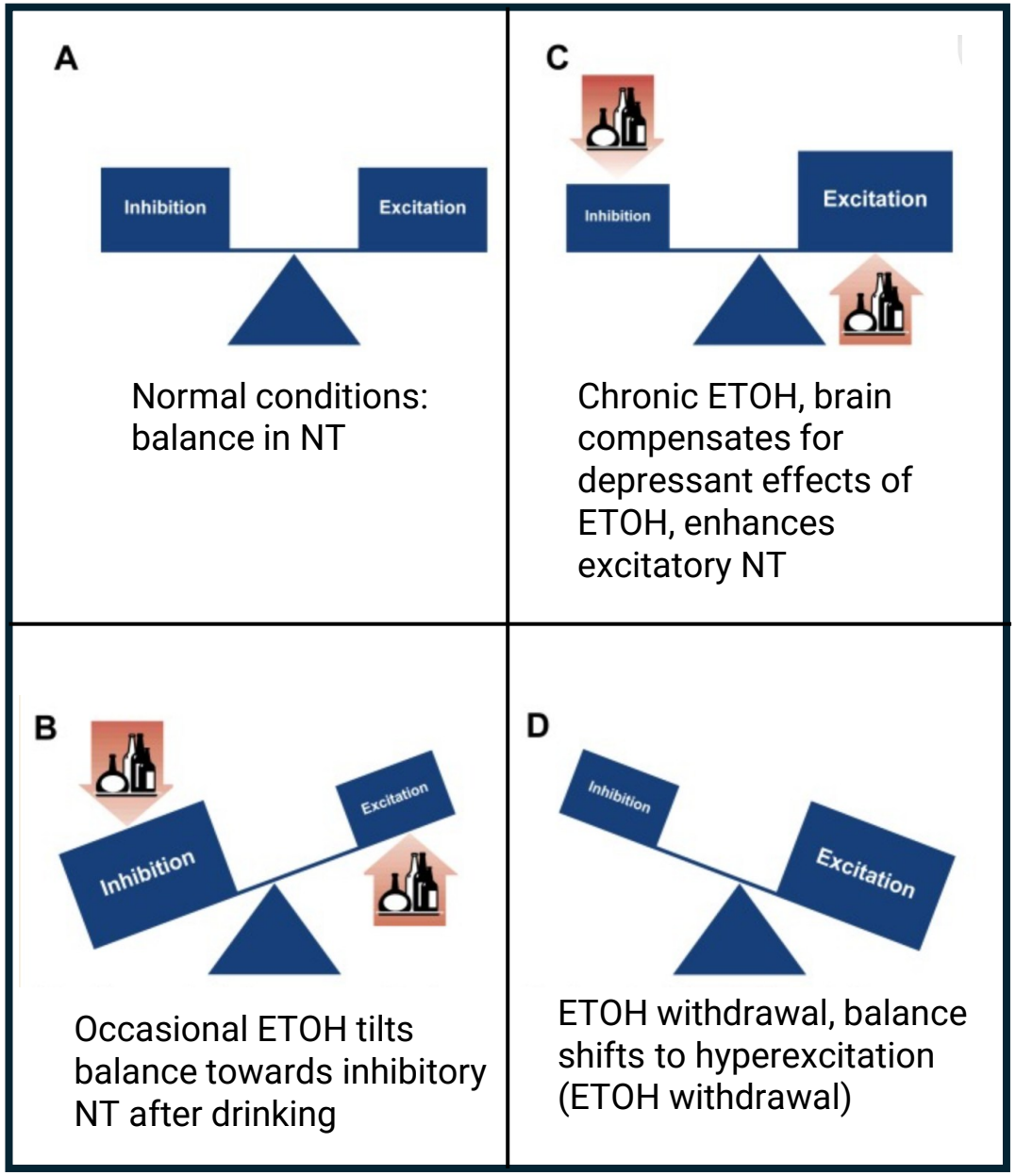
GABA-ergic drug overdose vs withdrawal



When the patient has confusion/altered mentation, which is it?

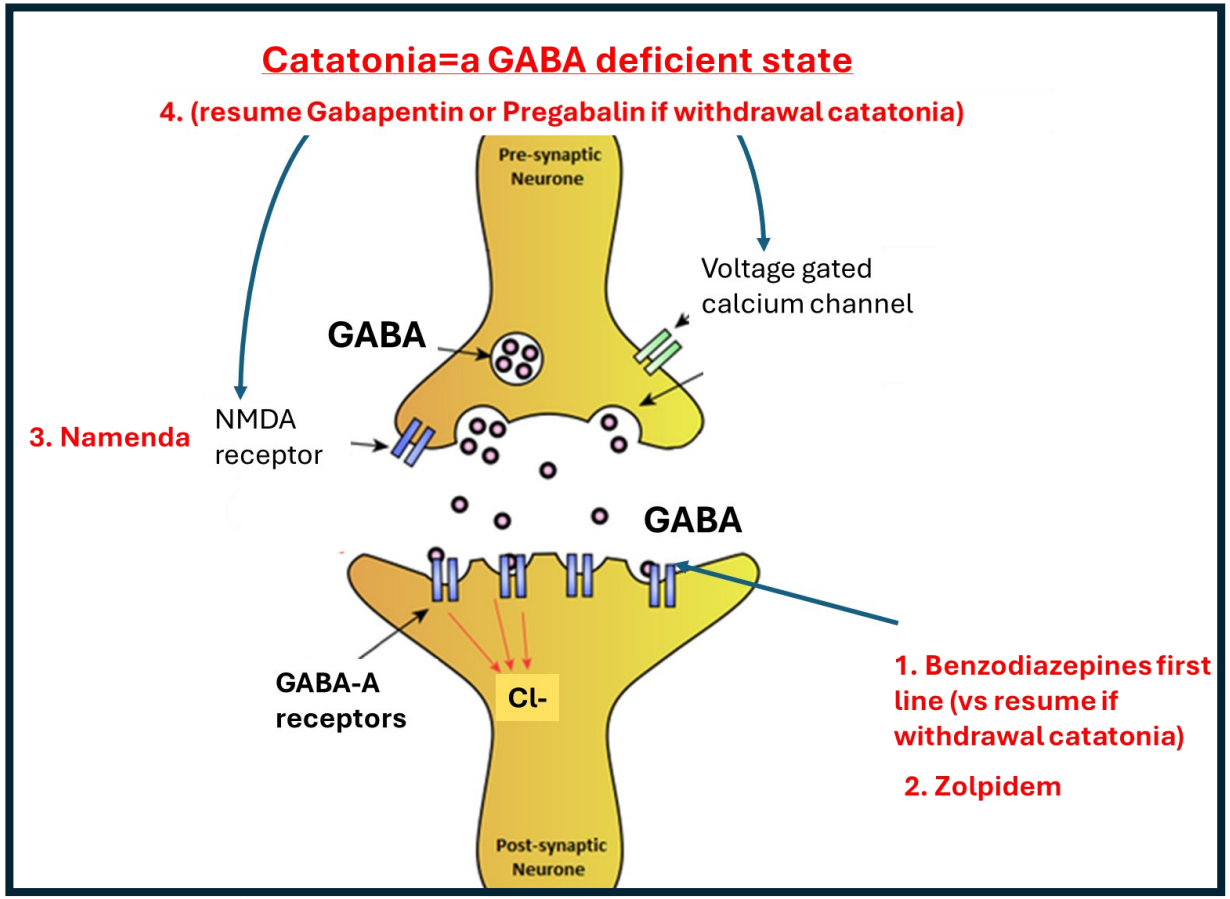
When the elderly patient is being admitted with AMS, what to do with their GABA-ergic drugs?



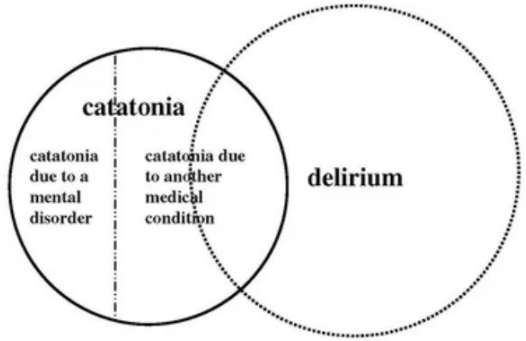


Same can apply to any GABA-ergic use/withdrawal

VS



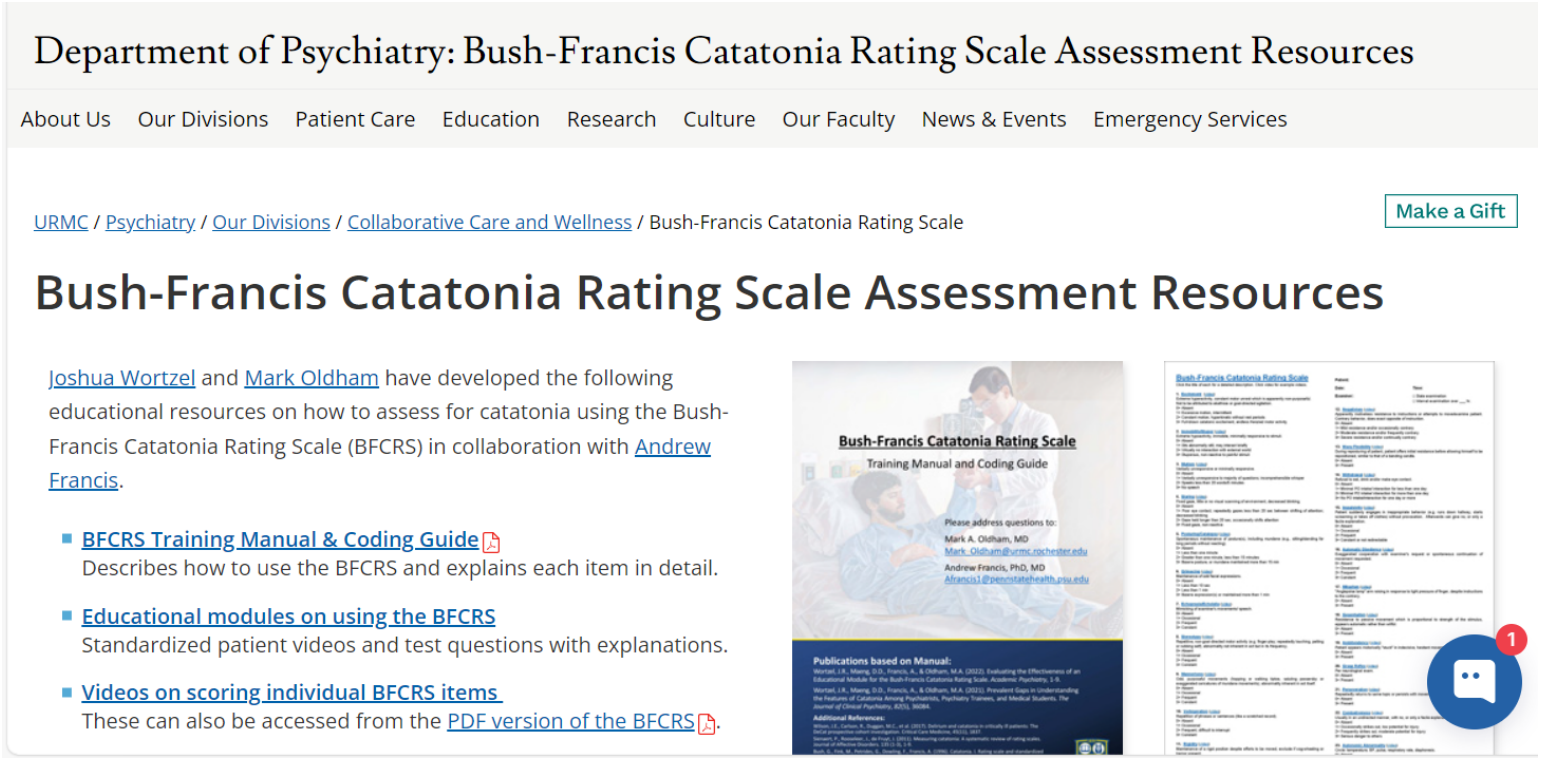
Catatonia-a GABA-ergic delirium



Catatonia is a GABA-ergic Delirium!

Catatonia

Excellent (and enjoyable) resource to sharpen your skills



https://www.urmc.rochester.edu/psychiatry/divisions/collaborative-care-and-wellness/bush-francis-catatonia-rating-scale.aspx

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Letters to the Editor | Free Access

Gabapentin Withdrawal: Case Report in an Older Adult and Review of the Literature

Linda Mah MD, FRCPC, MHS, Michelle Hart MD, CCFP, MScCH

First published: 12 September 2013 | https://doi.org/10.1111/jgs.12427 | Citations: 22

Case report summaries:
-Included 11 withdrawal cases
-9/11 involved abrupt discontinuation of gabapentin
-Array of withdrawal symptoms which resolved with reinitiation of gabapentin

Advanced age may increase risk of withdrawal from gabapentin because of age-related reduction of GABA-mediated cortical inhibition or alterations in expression of glutamate receptors.

Withdrawal Akathisia

- Can be INDUCED by gabapentinoid withdrawal
- Patient can become agitated, pacing, restless (visibly)
- Patient can feel internally irritable, restless and tense
- Can be misdiagnosed as mania, psychosis

Treatment

- Reinstate gabapentin at the same dose at which patient was previously stable

Akathisia Induced by Gabapentin Withdrawal

June 2011 · Annals of Pharmacotherapy 45(6):e31

45(6):e31

DOI:10.1345/aph.1Q057

Source · PubMed

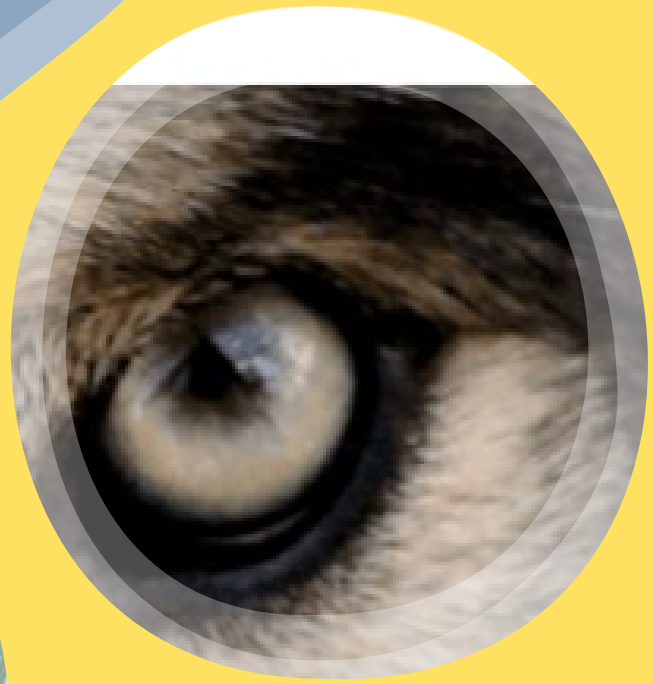
Gabapentinoids:
Limit/use with caution (Walk away)

In Parkinson's patients=complicate matters with
fluctuating GABA + Dopamine dysregulation in Basal Ganglia

In patients:

- on high dose opiates
- with ESRD
- with high GABA-ergic burden already
- with disease states causing edema
- with COPD
- with numerous other CNS acting drugs
- with gait and balance issues

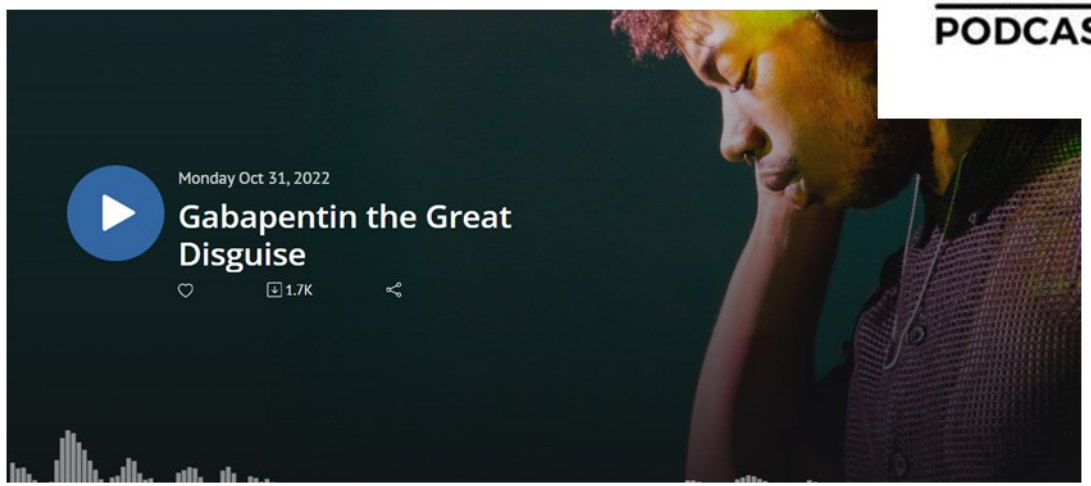

Addiction



Those who abuse gabapentin may try to achieve a high that elevates their mood and makes them feel calm and relaxed.

The addiction files

PODCAST



https://theaddictionfiles.podbean.com/

Addictionologists Paula Cook, MD and Darlene Peterson, MD

Describe difficulty of **managing Gabapentin withdrawal inpatient rehab centers** and even the use of benzodiazepines, phenobarbital, depakote, carbamazepine to manage Gabapentin withdrawal!

Recommendations:

Gabapentinoids:

-Should be Schedule 2 federally
-Should be part of standard drug tox screens
-Prescribers should educate patients re: risk
-Treat as a high-risk drug for high- risk patients

Geriatric **A**ged **B**rain (and other) mis**A**dventures

- **G**eriatric **A**ged **B**rain (and other) mis**A**dventures abound in the use of **GABA**ergic drugs, especially when multiple agents are used in combination or at high doses
- We are only beginning to understand the clinical implications (drug:disease causation and interactions) with Gabapentinoid use
- Use of Gabapentinoids carries real risk of side effects and prescribing cascades
- Increased awareness of clinical efficacy of Gabapentinoids is needed
- Risk:Benefit discussions are critical with Gabapentinoids
- Deprescribing efforts are critical for our patients

Behavioral and Psychological Symptoms of Dementia (BPSD)

Antipsychotic use in the elderly

Acute management

DSD (Delirium in setting of Dementia)

Secondary BPSD in dementia

Episodic BPSD in dementia

Chronic management

BPSD with psychosis, agitation, wandering

Behavioral and Psychological

Symptoms of Dementia

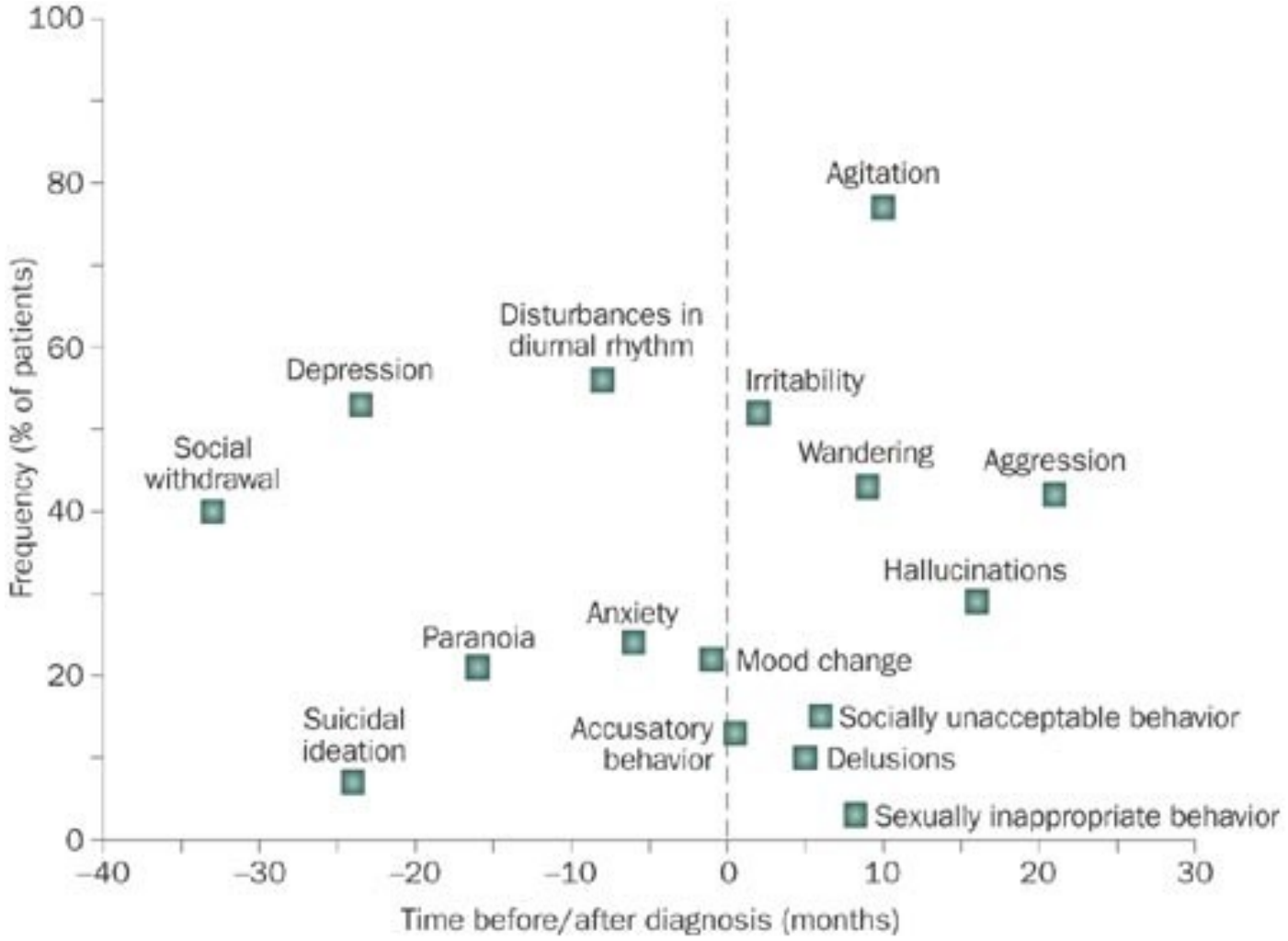
ART WALASZEK, M.D.

Recognizing and treating BPSD
(Behavioral and Psychological Symptoms of Dementia)

A heterogeneous range of psychological reactions, psychiatric symptoms and behaviors that may be unsafe, disruptive and impair the care of the patient in a given environment.

Barucha et al, CNS Spectrum, 2002

Peak frequency of behavioral symptoms as Alzheimer's disease progresses.



BPSD will affect up to 90% of patients with Alzheimer's Dementia

Lewy body dementia = visual hallucinations
Frontotemporal dementia = behavioral disinhibition and apathy

Frequency of occurrence
Agitation 75%
Wandering 60%
Depression 50%
Psychosis 30%
Screaming 20%

Jost, B. C. & Grossberg, G. T. J. Am. Geriatr. Soc. 44, 1078–1081 (1996).

BPSD (Behavioral and Psychological Symptoms of Dementia)

Primary BPSD: A common reason for ED visits

-90% of dementia patients

-“Clusters” (affective, psychotic, sleep-wake disturbance, behavioral)

-A caregiver problem

-Increases risk of institutionalization

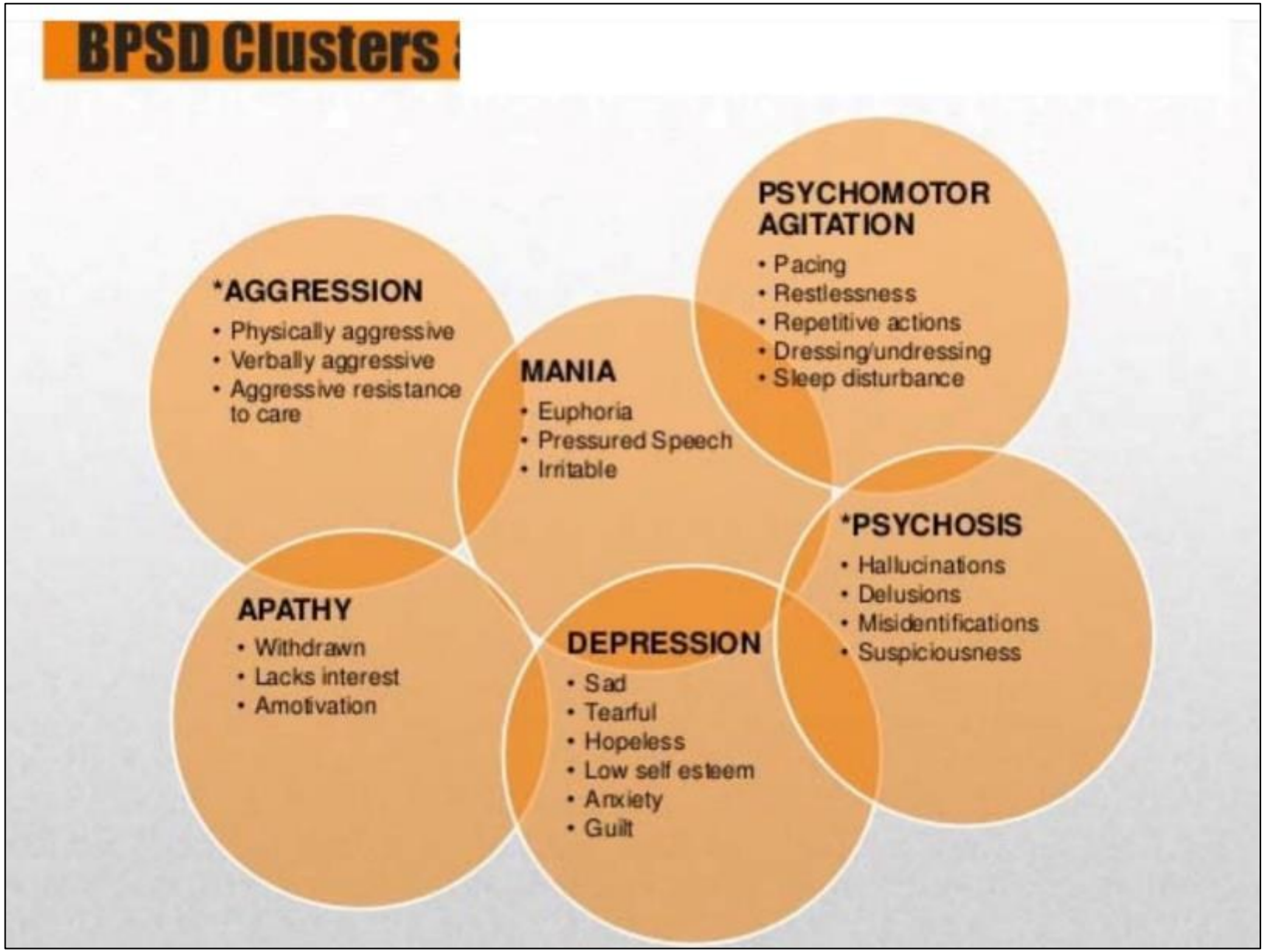
-Can be fluctuating and progressive

Treatment:

-Behavioral interventions first

-Cautious medicating (there is only one FDA approved drug for AD agitation)

-Medications used to target the analogous psychiatric“cluster”



Bugden. Antipsychotics and Dementia: Part of the solution or part of the problem, Dementia Care Conference 2012.

BPSD (Behavioral and Psychological Symptoms of Dementia)

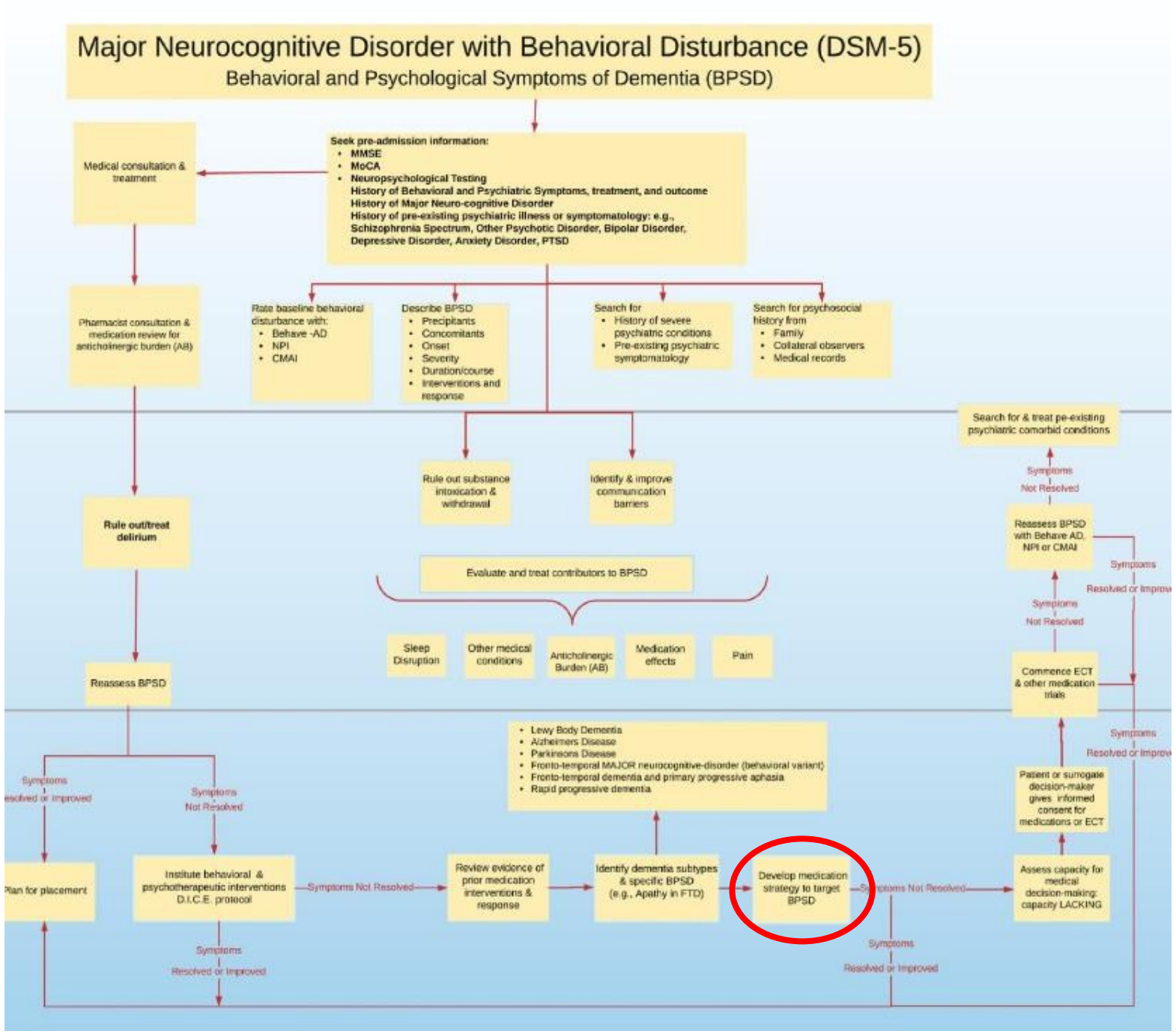
Secondary BPSD vs DSD (Delirium in setting of Dementia)

-Due to an underlying medical issue or drug effect
-Interferes with care
-Health care provider challenge
-Address underlying etiology/remove offending agent
-Environmental adaptations are needed
-Behavioral interventions first
-Cautious medicating

Choosing Wisely®

An initiative of the ABIM Foundation

Don't prescribe antipsychotic medications for behavioral and psychological symptoms of dementia (BPSD) in individuals with dementia unless management of underlying causes fails to respond to best treatment practices. Only use for symptoms that severely impact quality of life or safety from self and/or others, in lowest dose possible and with frequent re-assessment for necessity and efficacy.


Major Neurocognitive Disorder with Behavioral Disturbance (DSM-5)
Behavioral and Psychological Symptoms of Dementia (BPSD)
Medical consultation & treatment
Seek pre-admission information:
MMSE
MoCA
Neuropsychological Testing
History of Behavioral and Psychiatric Symptoms, treatment, and outcome
History of Major Neuro-cognitive Disorder
History of pre-existing psychiatric illness or symptomatology: e.g., Schizophrenia Spectrum, Other Psychotic Disorder, Bipolar Disorder, Depressive Disorder, Anxiety Disorder, PTSD
Pharmacist consultation & medication review for anticholinergic burden (AB)
Rate baseline behavioral disturbance with:
Behave -AD
NPI
CMAI
Describe BPSD
Precipitants
Concomitants
Onset
Severity
Duration/course
Interventions and response
Search for
History of severe psychiatric conditions
Pre-existing psychiatric symptomatology
Search for psychosocial history from
Family
Collateral observers
Medical records
Rule out substance intoxication & withdrawal
Identify & improve communication barriers
Search for & treat pe-existing psychiatric comorbid conditions
Symptoms Not Resolved
Reassess BPSD with Behave AD, NPI or CMAI
Symptoms Resolved or Improved
Rule out/treat delirium
Evaluate and treat contributors to BPSD
Sleep Disruption
Other medical conditions
Anticholinergic Burden (AB)
Medication effects
Pain
Symptoms Not Resolved
Commence ECT & other medication trials
Reassess BPSD
Lewy Body Dementia
Alzheimers Disease
Parkinsons Disease
Fronto-temporal MAJOR neurocognitive-disorder (behavioral variant)
Fronto-temporal dementia and primary progressive aphasia
Rapid progressive dementia
Symptoms Resolved or Improved
Symptoms Not Resolved
Patient or surrogate decision-maker gives informed consent for medications or ECT
Plan for placement
Institute behavioral & psychotherapeutic interventions D.I.C.E. protocol
Symptoms Not Resolved
Review evidence of prior medication interventions & response
Identify dementia subtypes & specific BPSD (e.g., Apathy in FTD)
Develop medication strategy to target BPSD
Symptoms Not Resolved
Assess capacity for medical decision-making: capacity LACKING
Symptoms Resolved or Improved
Symptoms Resolved or Improved

Choosing Wisely®
An initiative of the ABIM Foundation

Table 1. Behavior Management Techniques for Individuals With Dementia

Communication	• Smile • Positive tone • Calm manner/voice • One-step directions • Allow adequate time for responses
Redirection/ reassurance	• Acknowledge emotion • Simple distraction • Rest periods • Offer food or drink
Memory support	• Reminiscence therapy (photos/personal items) • Recorded familiar voices • Familiar environment
Sensory methods	**Visual** • Pictures of familiar things/people • Working in garden • Home-like environment **Auditory** • Play familiar music • Group music activities • One-on-one music activity **Olfactory** • Lavendar on pillow or lotion to skin for sleep disorders/anxiety • Diffusion of *Lavandula angustifolia* or sunflower for aggression/anxiety • Ylang, ylang, patchouli, rosemary, peppermint for BPSD • Taste • Offer simple choices • Finger foods **Tactile** • Brushing hair • Hand-under-hand technique • Hand massage • Stroking pets
Exercise	• Aerobic activities • Balance activities • Resistance activities • Walking • Chair exercise

Antipsychotics for primary BPSD

- Only one antipsychotic is FDA approved for agitation in AD (brexpiprazole (Rexulti®)
- All carry Black box warning
- All worsen cognition and lower the seizure threshold
- All carry risk of increased mortality and somnolence (dose dependent)
- Likelihood of harm vs help: for every 9-25 people helped there may be one death.
- Behaviors and medications used to treat BPSD are part of the morbidity of the disease.

Caregiver burden can improve when given a tool to manage difficult behaviors

Tampi, Rajesh, Behavioral and Psychological Symptoms of Dementia. Comprehensive review of geriatric psychiatry. 2017

Antipsychotics you will encounter

First generation

- Chlorpromazine (Thorazine)
- Haloperidol (Haldol)

Second generation

- clozapine (Clozaril®)
- aripiprazole (Abilify®)
- olanzapine (Zyprexa®)
- quetiapine (Seroquel®)
- risperidone (Risperdal®)
- brexpiprazole (Rexulti®)
- paliperidone (Invega®)
- cariprazine (Vraylar®)
- lurasidone (Latuda)
- ziprasidone (Geodon®)

	1st generation	2nd generation
A.K.A.	typical antipsychotics	atypical antipsychotics
MOA	Primarily block D2 receptors only	Primarily block D2 and 5HT2A receptors
Examples	• haloperidol • chlorpromazine	• aripiprazole • olanzapine • quetiapine • risperidone • clozapine
EPS	More likely to cause EPS (dystonia, akathisia, pseudoparkinsonism, and tardive dyskinesia)	Less likely to cause EPS and tardive dyskinesia (but can still occur)
Metabolic abnormalities	Less likely to have metabolic abnormalities	More likely to cause metabolic abnormalities (elevated glucose, lipids, and weight gain)

MOA = mechanism of action; D2 = dopamine-2 receptors; 5HT2A = serotonin 2A receptors; EPS = extrapyramidal symptoms

Risks: All Antipsychotics

Sedation-> pneumonia

Cognitive decline

Falls, fractures and other injuries

Lower seizure threshold

Risks: Most Antipsychotics

EPS (Extrapyramidal symptoms) (not quetiapine, clozapine, pimavanserin)

Metabolic complications: Olanzapine in particular

CVA: Olanzapine, Risperidone w/warning

Cardiovascular events: Olanzapine and Risperidone w/warning

VTE: evidence inconsistent

Hyperprolactinemia: Risperidone in particular

Neutropenia: Primarily Clozapine but ALL antipsychotics can cause

Antipsychotics and risk of death in patients with dementia

"The absolute effect of antipsychotics on mortality in elderly patients with dementia **may be higher than previously reported and increases with dose**."

Compared with respective matched nonusers		
Haloperidol	increased mortality risk of 3.8%	NNH of 26
Risperidone	increased mortality risk of 3.7%	NNH of 27
Olanzapine	increased mortality risk of 2.5%	NNH of 40
Quetiapine	increased mortality risk of 2.0%	NNH of 50

Risk of death is dose dependent with atypical antipsychotics (olanzapine, quetiapine, and risperidone).

Maust DT, et al. Antipsychotics, Other Psychotropics, and the Risk of Death in Patients With Dementia: Number Needed to Harm. *JAMA Psychiatry*. 2015;72(5):438–445

Severe agitated behaviors, acute setting

First Line: antipsychotics, used judiciously

- Haloperidol or risperidone can be used as the first-choice antipsychotic, unless the patient has Parkinson's Disease, Parkinsonism or Lewy body disease.
- If the patient has Parkinsonism (but does not have Parkinson's disease related dementia or Lewy body dementia), olanzapine can be used as first-choice antipsychotic.
- If the patient has Parkinson's disease related dementia or Lewy body dementia, quetiapine is usually the first -line agent, followed by clozapine (seek expert opinion).

Severe agitated behaviors, acute setting

Second Line: Valproic acid

- Valproic acid treatment of hyperactive or mixed delirium.
- Can start at 150-250 mg BID or TID.
- Avoid in patients with hepatic dysfunction. Monitor for platelets, ammonia, and liver enzymes.

Third Line: Benzodiazepines

- May be the preferred in Parkinson's disease and Lewy body dementia due to the lack of extrapyramidal side effects.
- Paradoxical agitation may precipitate or worsen delirium.
- Avoid IV use within 2h of IM Olanzapine due to risk of hypotension and cardiopulmonary depression.
- Lorazepam is the preferred Benzodiazepine in this patient population.

Lorazepam: 0.5 - 1 mg PO/IM /IV (start with lowest dose possible; onset of action 30 minutes) no dose maximum and can tailor to patient response.

Midazolam: 1 – 5 mg IM/IV (start with lowest dose possible; onset of action 20 - 30 minutes) reassess in 45 - 60 minutes; no dose maximum and can tailor to patient response

Agent	Dosing	Routes	Degree of Sedation	Risk of EPS	Dosing Adjustments	Adverse Effects
Haloperidol	Starting dose=0.25 – 0.5 mg (start 0.25 mg in most patients, reassess in 60 minutes then consider dose increase/2nd dose if 0.25 mg given initially; max dose = 30 mg/24 hours)	PO/IM/IV (IV has risk for QTc prolongation and Torsade's de Pointes)	Low	high	No renal or hepatic Adjustments required	Risk of EPS is high QTc prolongation Rising liver function test values Avoid in narrow-angle glaucoma Avoid in Underlying Parkinson's disease or Lewy body dementia
Risperidone	Starting dose=0.25 – 0.5 mg (start 0.25 mg in most patients, reassess in 60 minutes then consider dose increase/2nd dose if 0.25 mg given initially; max dose = 3mg /24 hours)	PO, Oral dissolving tablet	Low	High	Avoid in renal impairment	Slightly lower risk of EPS than haloperidol QTc prolongation
Olanzapine	Starting dose=2.5 – 5 mg (start 2.5 mg in most patients, reassess in 30 minutes then consider dose increase/2nd dose if 2.5 mg given initially; max dose = 20 mg /24 hours)	PO, Oral dissolving tablet and IM	Moderate	Moderate	No renal or hepatic Adjustments required	Fatal respiratory depression can occur when olanzapine and benzodiazepines are administered concomitantly. If necessary, olanzapine and benzodiazepines should be given at least 2 hours apart
Quetiapine	Starting dose=12.5 – 25 mg (start 12.5 mg in most patients, reassess in 60 minutes then consider dose increase/2nd dose if 12.5 mg given initially; max dose = 50 mg /24 hours)	PO	High	Low	No renal adjustments required; titrate slowly in hepatic impairment	QTc prolongation, orthostatic hypotension
Ziprasidone	Starting dose= 5 – 10 mg (start 5 mg in most patients, reassess in 60 minutes then consider dose increase/2nd dose if 5 mg given initially; max dose = 40 mg /24 hours)	PO, Oral dissolving tablet and IM	Very high	Low	No renal or hepatic adjustments required	Avoid in patients with prolonged QTc and those receiving other QTc-prolonging medications

Primary BPSD ambulatory setting

- Think of non-emergent behaviors as psycho-behavioral metaphors of classic psychiatric illness.
- Specify the behavior, attempt to cluster into a pattern that is roughly analogous to a drug responsive syndrome

BPSD analagous to	Class	Name and Dosages
Psychosis	Antipsychotics	Aripiprazole (Abilify): 2 mg-10 mg/day Olanzapine (Zyprexa): 2.5 mg-10 mg/day Quetiapine (Seroquel): 12.5 mg-100 mg/day Risperidone (Risperdal): 0.25 mg-2 mg/day
Depression/apathy	Antidepressants	Citalopram 10 mg-20 mg/day Escitalopram 5 mg-20 mg/day Mirtazapine 7.5-15 mg/day (geriatricians avoid higher doses) Sertraline 25 mg-100 mg/day
Hypomania/mania	Mood stabilizers	Carbamazepine: 200 mg-400 mg/day Divalproex sodium: 250 mg-1000 mg/day Oxcarbazepine: 300 mg-600 mg/day

Efficacy and side effect profiles:

- First line: Abilify or Risperdal
- Second line: Olanzapine
- Third line: Quetiapine
- Haldol-use for emergencies.

Tampi, Rajesh, Behavioral and Psychological Symptoms of Dementia. Comprehensive review of geriatric psychiatry. 2017

Commonly used antipsychotics

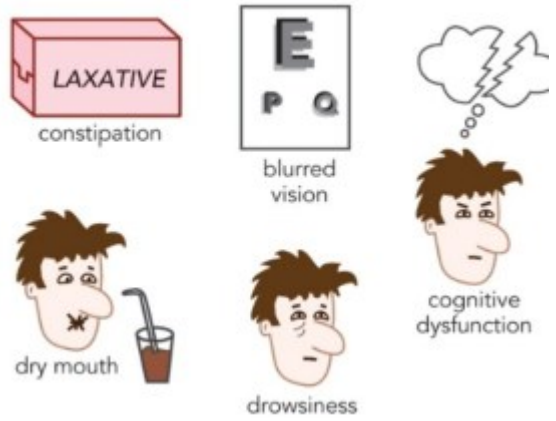
Available studies have demonstrated best effect/tolerability with Abilify and Risperdal

- **Risperdal-** effective for psychosis, agitation and overall BPSD
- **Aripiprazole-** effective for overall BPSD, less so for psychosis and agitation
- **Olanzapine-** effective for agitation, less for overall BPSD, equivocal for psychosis
- **Quetiapine-** consistently failed to outperform placebo for agitation, psychosis and overall BPSD
- **Haldol**-as effective as atypical antipsychotics for BPSD but has more safety concerns, typically is reserved for emergent situations

Anticholinergic effects of antipsychotics

Antipsychotic	Clinical anticholinergic effects
Clozapine	++++
Thioridazine	++++
Chlorpromazine	++++
Methotrimeprazine	++++
→ Olanzapine	+++
Loxapine	++
→ Quetiapine	++
Fluphenazine	+
Flupenthixol	+
→ Haloperidol	+
→ Risperidone	+

Impaired concentration
Confusion
Attention deficit
Memory impairment



Lieberman JA 3rd. Managing anticholinergic side effects. Prim Care Companion J Clin Psychiatry. 2004;6

Dopamine receptor effects of antipsychotics:
List below is in descending order of potency at dopamine receptor

Agents	Dopamine D_{2L}
Perphenazine	1.4
→ Risperidone	3.3
Aripiprazole	3.4
→ Haloperidol	4
Ziprasidone	4.8
→ Olanzapine	11
Chlorpromazine	19
Loxapine	71.4
→ Quetiapine	160
Clozapine	180

Most anti-dopaminergic: avoid in Parkinson's disease

Least anti-dopaminergic: preferred in Parkinson's disease

Receptor	D2				M1	α1	5-HT2
	EPS/TD	Dyslipidemia	Weight gain/T2DM	Elevated prolactin	Anticholinergic effects	Orthostatic hypotension	QTC prolongation	
*First generation**								
chlorpromazine	+	+++	+++	++	+++	+++	+++	
haloperidol	+++	+	+	+++	+/-	-	++ (+++ if IV)	
fluphenazine	+++	+	+	+++	+/-	-	+/-	
*Second generation**								
aripiprazole	+	-	+	-	-	-	+/-	++
asenapine	++	-	++	++	-	+	++	+++
brexpiprazole	+	+	+	+/-	+/-	+/-	+/-	++
lurasidone	++	+/-	+/-	+/-	-	+	+/-	++
olanzapine	+	++++	++++	+	++	+	++	+++
paliperidone	+++	+	+++	+++	-	++	++	+++
pimavanserin	+/-	-	+	-	+	++	+	
quetiapine	+/-	+++	+++	+/-	++	++	+++	+
risperidone	+++	+	+++	+++	+	+	++	++++
ziprasidone	+	+/-	+/-	+	-	+	+++ (BBW!)	++
clozapine	+/-	++++	++++	+/-	+++	+++	++	

EPS/TD = extrapyramidal symptoms/tardive dyskinesia; T2DM = type 2 diabetes mellitus

Antipsychotics: “Pick your poison”

Which antipsychotic is least likely to cause issues in the patient?

-Movement disorders existing or predisposition to them?

(avoid haldol/risperidone)

-Urinary retention (avoid olanzapine/quetiapine)

-Otherwise high anticholinergic burden (caution with olanzapine/quetiapine)

Leverage side effects/properties:

-Behaviors at night/sundowning= Seroquel = anticholinergic properties

-Olanzapine=weight loss/anorexia=metabolic side effects (weight gain)

-Abilify=longer half life; patients who intermittently refuse meds

Second generation antipsychotic key facts

Zyprexa/Olanzapine-Metabolic Effects; reports of death when combined with benzos

Geodon/Ziprasidone and **Haldol/Haloperidol**-qtc prolongation

Abilify/Aripiprazole-no qtc prolongation

Seroquel/Quetiapine-least effective for all BPSD (according to existing studies)

Risperdal/Risperidone- hyperprolactinemia

Rexulti/Brexpiprazole-only FDA approved medication for agitation in setting of dementia (controversy)

Nuplazid/Pimavanserin-only FDA approved medication for Parkinson's Psychosis (action restricted to serotonin 2A receptor)-no EPS potential

Risperdal/Risperidone-only antipsychotic specifically studied/demonstrated to reduce wandering (1 mg TDD) (Cipriani et. al 2014)

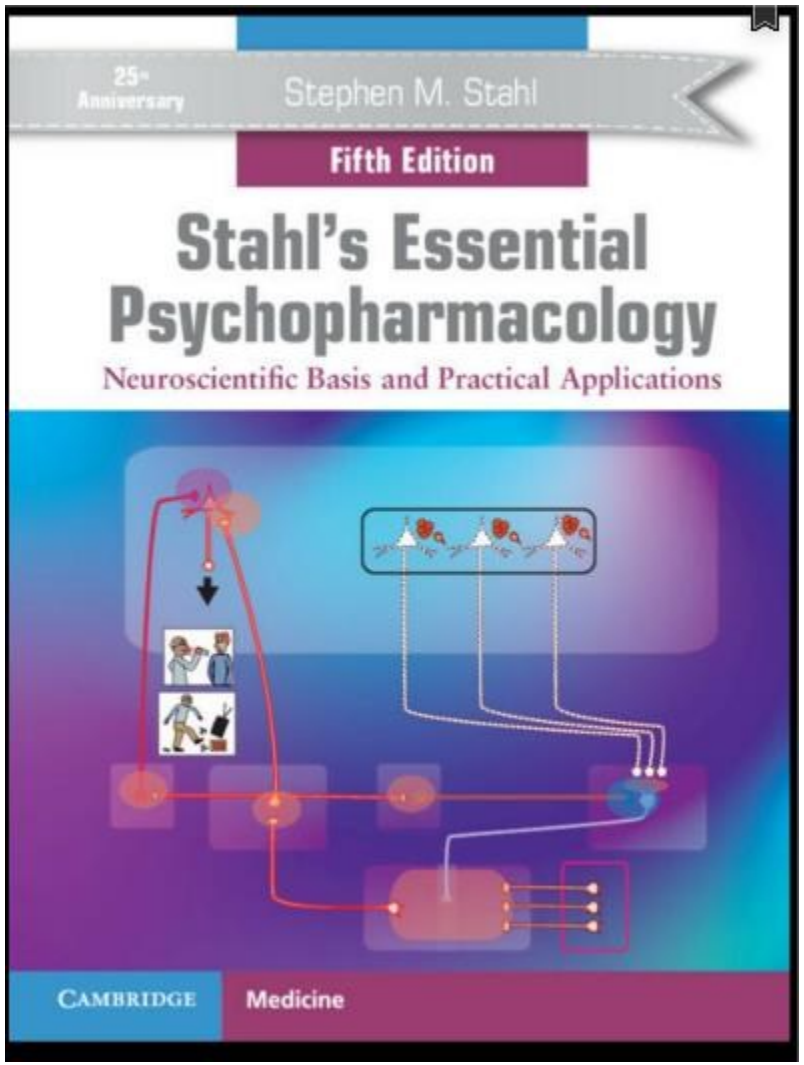
Avoid antipsychotics (RUN!)

- In Parkinson’s Disease or Parkinsonism (Seroquel OK)
- In patients with Lewy Body Dementia or Parkinson’s Dementia- (donepezil has some evidence)
- In patients with existing Tardive Dyskinesia or drug induced parkinsonism
- In patients with a history of catatonia
- In patients with Frontotemporal Dementia (not studied)

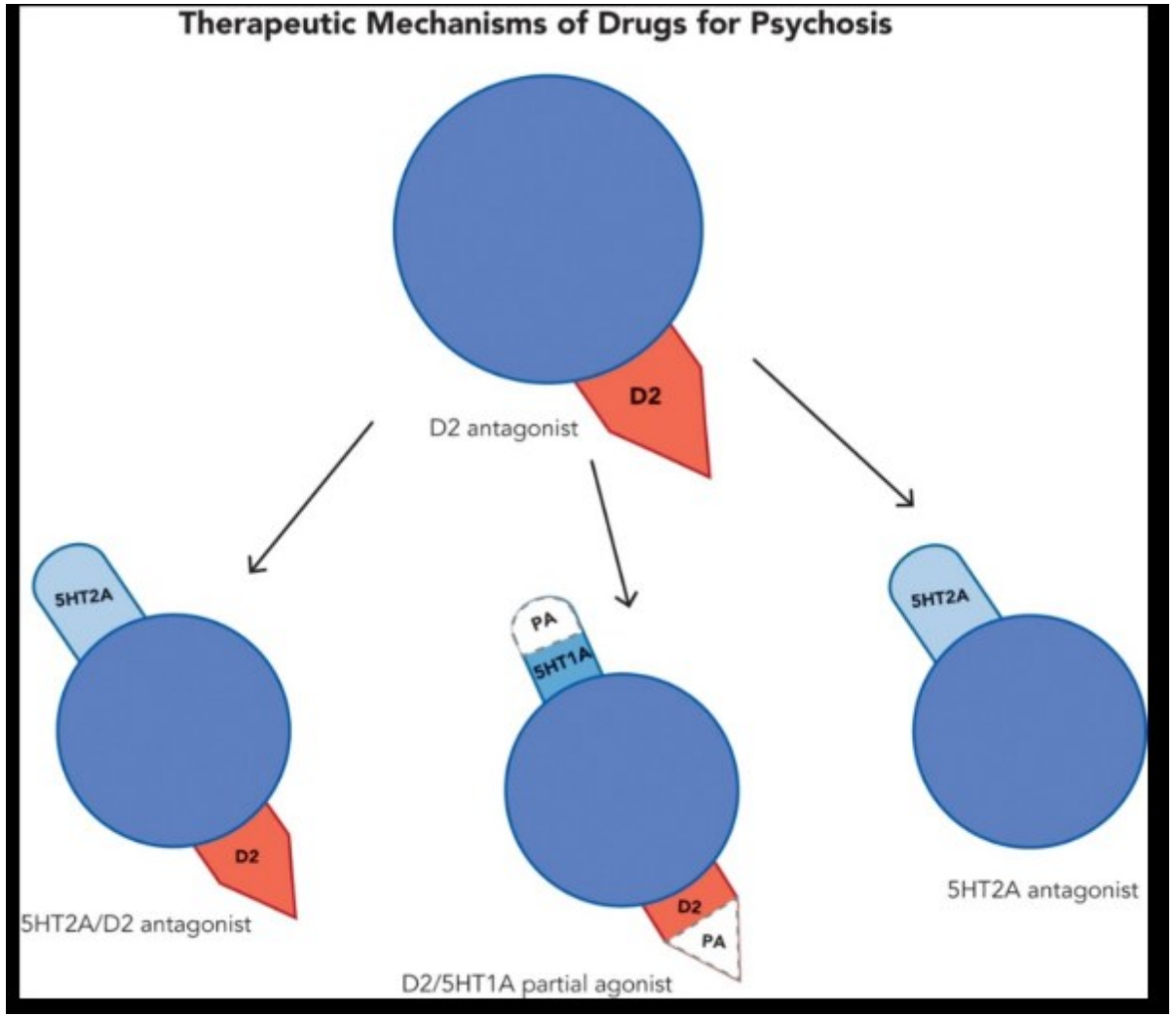
In the extreme...

	GABA-Deficient state (withdrawal/deficiency)	Dopamine-Deficient state (blockade)
Feature	**Malignant Catatonia (MC)**	**Neuroleptic Malignant Syndrome (NMS)**
Cause	Various medical, neurological, or psychiatric conditions	Antipsychotic medications (including typical and atypical)
Symptoms	- Stupor, mutism, catalepsy, waxy flexibility, negativism, posturing, pyrexia, autonomic dysfunction, rigidity, increased CPK levels - May include hyperthermia, unstable blood pressure, tachycardia, and cyanosis	- Altered mental status, muscle rigidity, hyperthermia, autonomic instability, and leukocytosis
Diagnostic	History of underlying illness or condition, presence of catatonic symptoms	History of antipsychotic medication use
Treatment	Benzodiazepines, ECT, and treatment of underlying cause	Discontinuation of offending antipsychotic, supportive care, and potentially dantrolene or bromocriptine

For a deeper understanding of pharmacology



Targeting Dopamine and Serotonin Receptors for Psychosis, Mood, and Beyond: So-Called "Antipsychotics"



Therapeutic mechanisms of drugs for psychosis. The first mechanism identified to treat psychosis was **Dopamine 2 (D2) antagonism.** Today there are many agents with additional mechanisms including **D2 antagonism combined with serotonin (5HT) 2A antagonism**, **D2 partial agonism combined with serotonin 1A (5HT1A) partial agonism**, and **serotonin 2A (5HT2A) antagonism.**

First generation

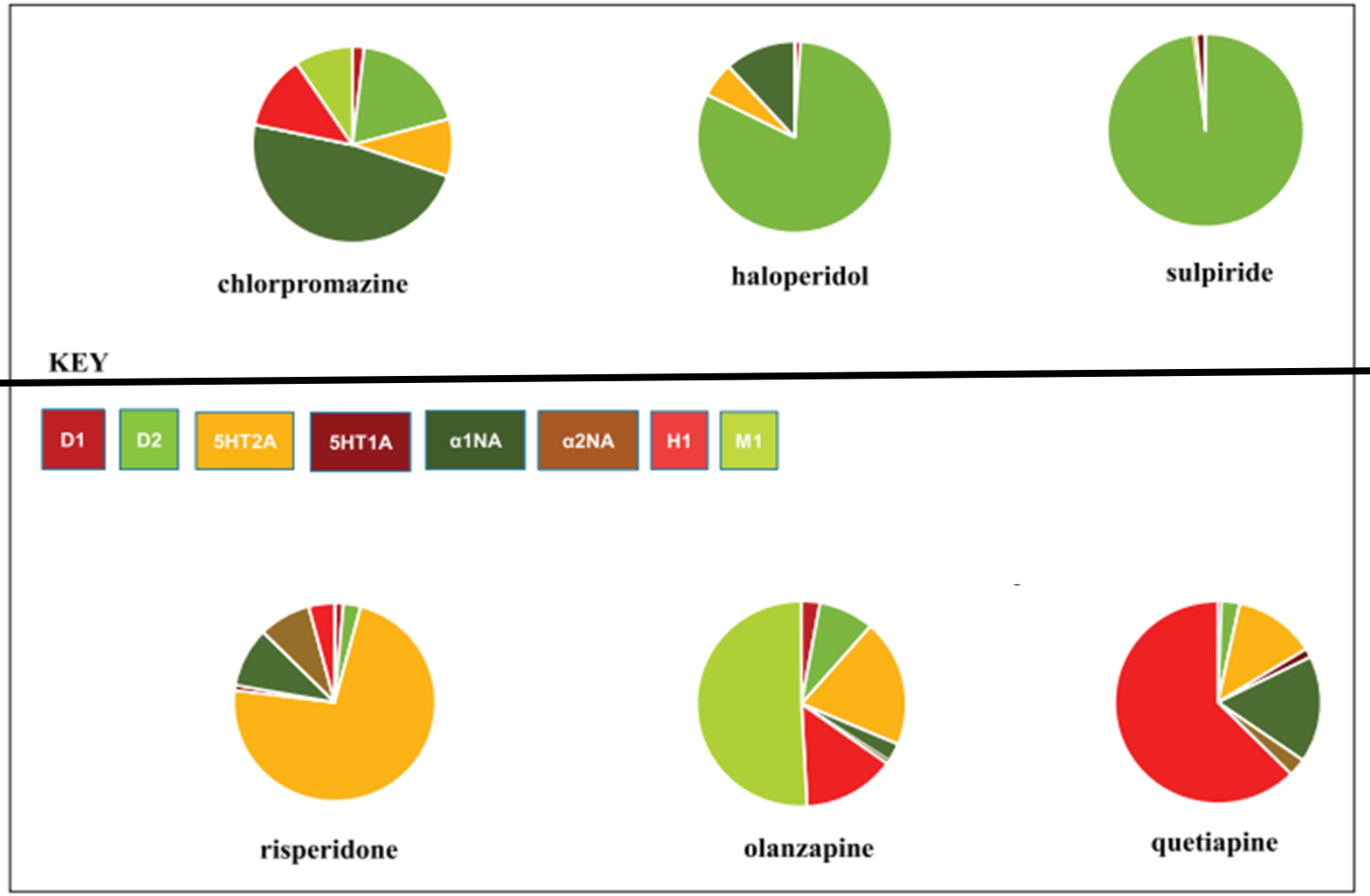
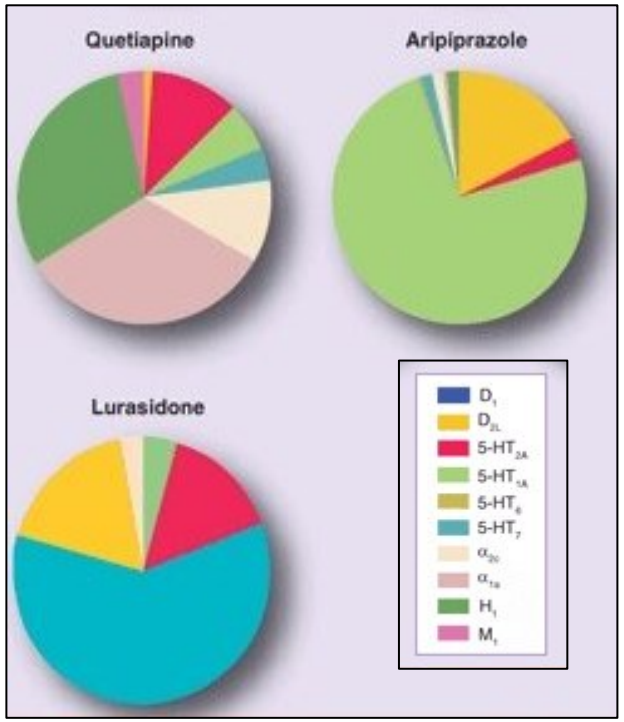


Figure 1. Antipsychotic drugs: schematic representation of some receptor-binding profiles (percentages of total binding: for method of calculation, see Hyttel et al., 1984 and Goldstein, 2000).

Second generation



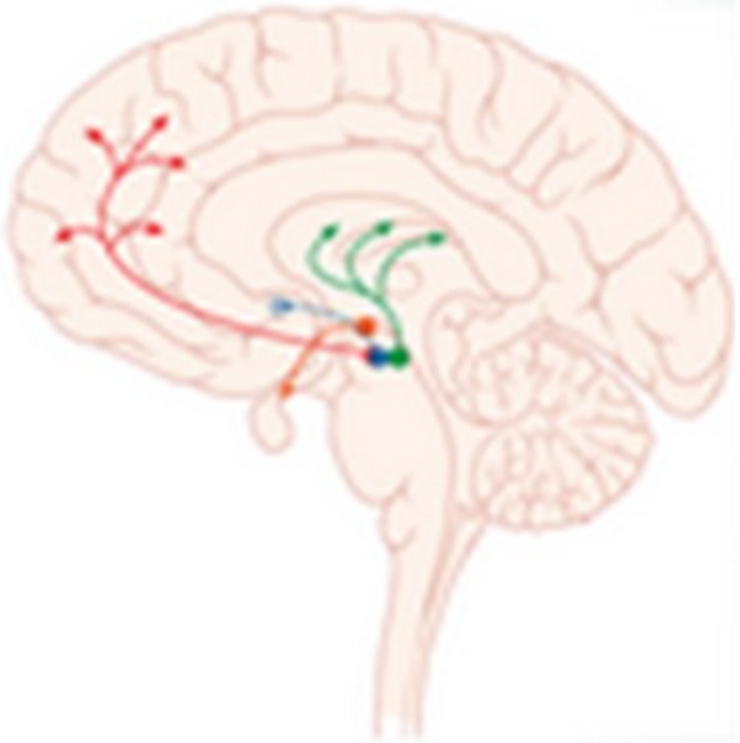
Dopaminergic pathways

Primary target

- Mesolimbic pathway (positive symptoms)

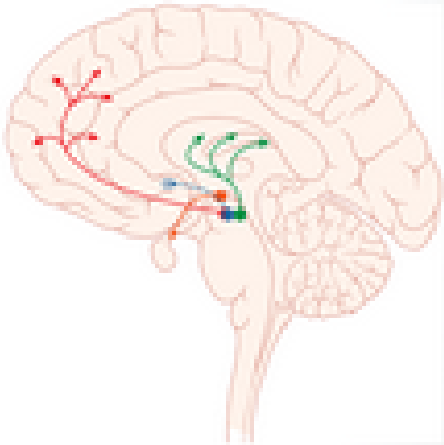
Side effects

- Mesocortical pathway (negative symptoms)
- Nigrostriatal pathway (EPS and TD)
- Tuberoinfundibular pathway (hyperprolactinemia)



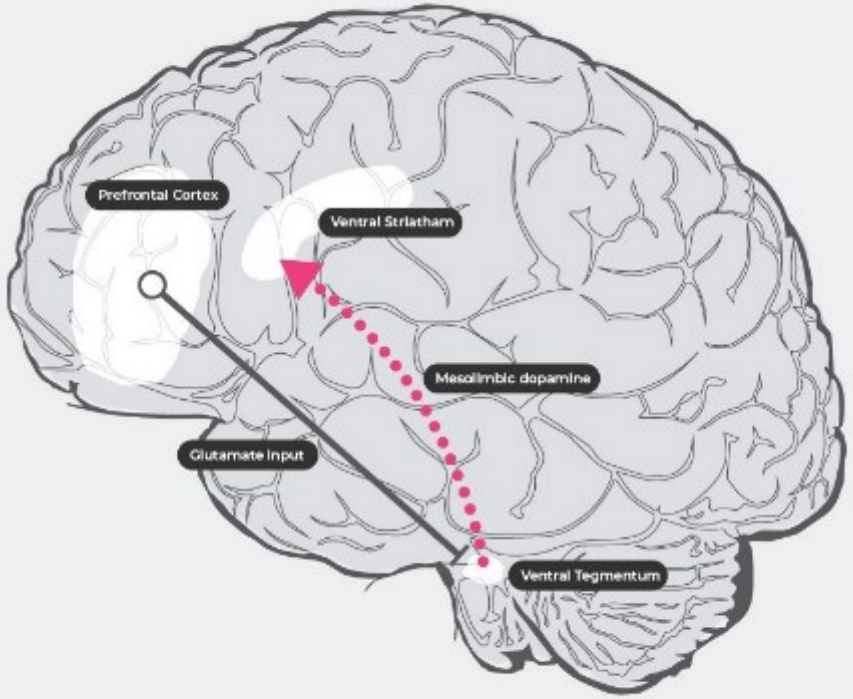
Target to reduce psychosis:
Reducing dopamine in the mesolimbic pathway

- Mesolimbic pathway (positive symptoms)
- Mesocortical pathway (negative symptoms)
- Nigrostriatal pathway (EPS and TD)
-Tuberoinfundibular pathway (hyperprolactinemia)

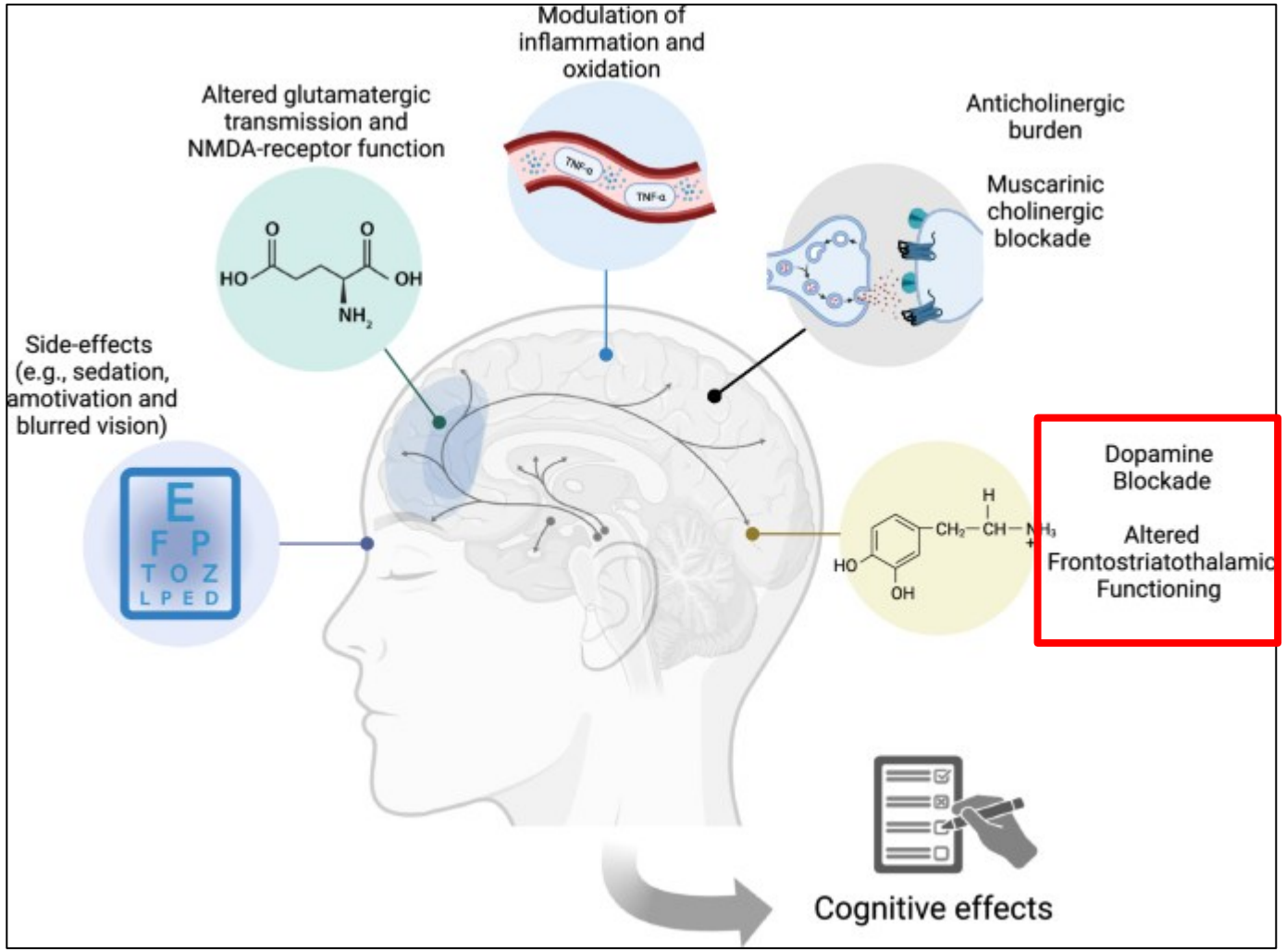


Dopamine Hyperfunction[1-3]

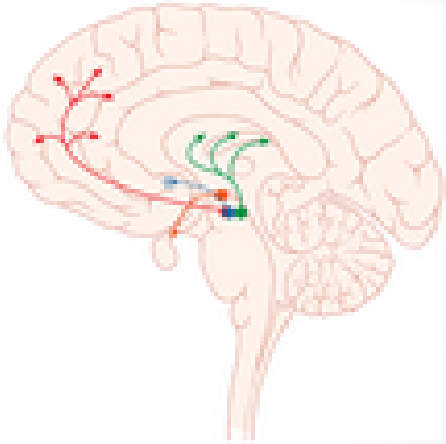
Positive Symptoms



“Cost of doing business”: Cognitive decline from dopamine blockade (D2 receptor in mesolimbic system)



- Mesolimbic pathway (positive symptoms)
- Mesocortical pathway (negative symptoms)
- Nigrostriatal pathway (EPS and TD)
-Tuberoinfundibular pathway (hyperprolactinemia)



“Cost of doing business”: **Movement disorders (EPS)** from D2 blockade in nigrostriatal pathway

Acute Dystonia
- Onset: hours to days
- Characteristics: severe muscle spasms with pulling or twisting of the head, neck, eyes, or trunk

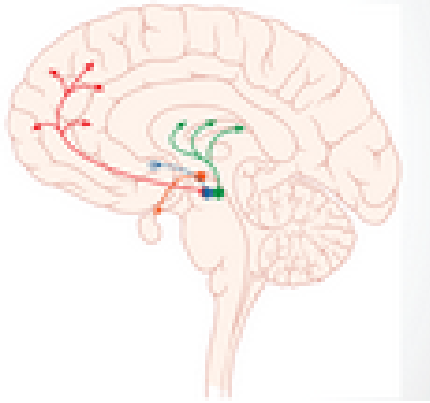
Acute Akathisia
- Onset: days to weeks
- Characteristics: fidgeting, restlessness, foot tapping, shuffling, shifting weight, rocking

Tardive Dyskinesia
- Onset: weeks to years
- Characteristics: tongue protrusion, chewing, lip pursing, grimacing, blinking, rocking, foot tapping, “piano-playing” with fingers

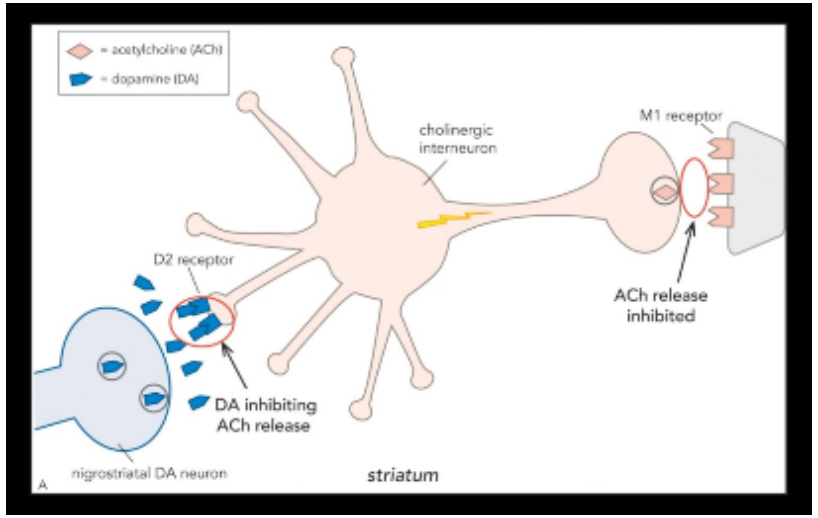
Acute Onset: Hours to Days ← Hyperkinetic: Excessive, Abnormal Movements / Hypokinetic: Slow, Insufficient Movements → Tardive Onset: Months to Years

Parkinsonism
- Onset: weeks to years
- Characteristics: tremor, bradykinesia (slow, insufficient movements), reduced blinking or facial expression, rigidity, flexed posture, shuffling gait

- Mesolimbic pathway (positive symptoms)
- Mesocortical pathway (negative symptoms)
- Nigrostriatal pathway (EPS and TD)
- Tuberoinfundibular pathway (hyperprolactinemia)

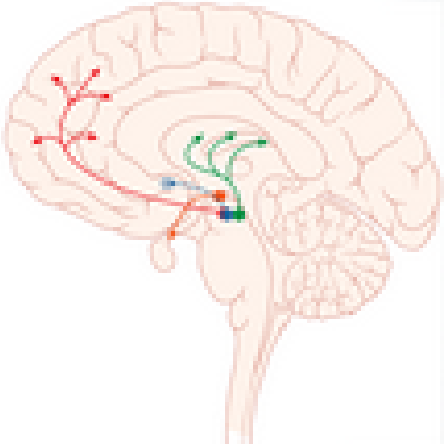


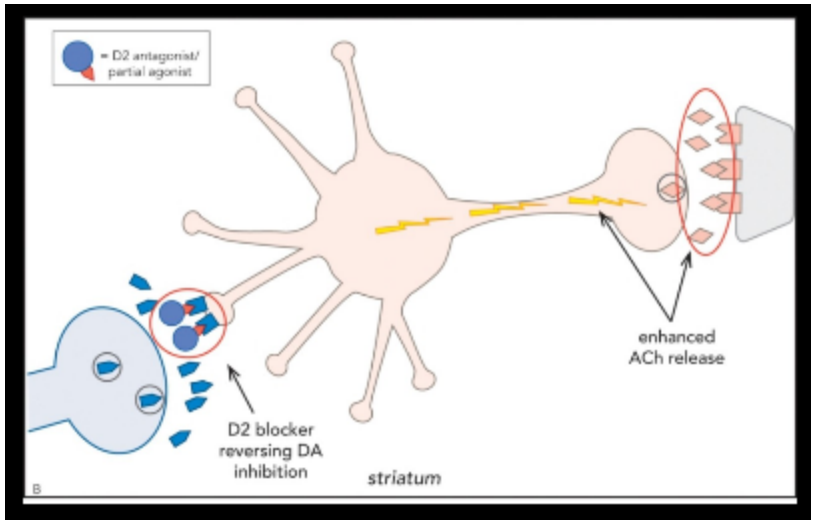
Propensity to cause EPS: Haldol>Risperidone>Aripiprazole>Olanzapine>Quetiapine/Pimavanserin



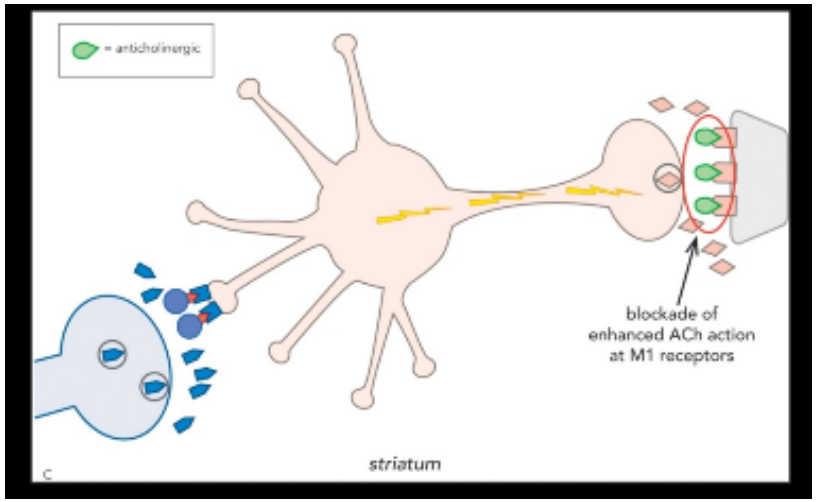
Reciprocal relationship of Dopamine and Acetylcholine: Dopamine binding in NS pathway suppresses Acetylcholine

- Mesolimbic pathway (positive symptoms)
- Mesocortical pathway (negative symptoms)
- Nigrostriatal pathway (EPS and TD)
-Tuberoinfundibular pathway (hyperprolactinemia)





Dopamine blockade, Acetylcholine increased, **mechanism of drug induced parkinsonism**



Dopamine blocked, M1 receptor blocked, normal balance restored and **reduced drug induced parkinsonism**

Olanzapine and Quetiapine

Thank you for your attention!