Case 1

- 37 year-old M with alcohol use disorder presents to the ED with tremors, ataxia and inability to hold onto anything. He reported taking all of a recent medication he was prescribed to help him, “not drink.”
- He started taking the medication after picking it up, after a PCP visit on a Thursday evening. He liked the way it made him feel so he took some extra to sleep on Thursday night and then Friday morning, throughout the rest of the day Friday and into Saturday he finished the rest of the bottle taking a few capsules every couple of hours.
- He developed tremors and “twitches,” which progressed to the point where he couldn’t hold a glass of water and he wasn’t able to get out of a chair to get to the bathroom so he called for help.

Case 1 continued

- Exam: HR 88 bpm, BP 142/88 mmHg, RR 16 breaths-minute, Temp 36.8 C.
- Slight mydriasis with nystagmus
- Marked myoclonus and postural instability/truncal ataxia. Asterixis.
- Slurring speech.

- What is your diagnosis?

A patient with a movement disorder

GABAPENTANOIDS

"A Wolf in Sheep's Clothing"

Edwin A. Salsitz, M.D., DFASAM

Mount Sinai Beth Israel, NYC

No Disclosures

“All things are poisons, for there is nothing without poisonous qualities. It is only the **dose** which makes a thing poison.”

Philippus Aureolus Theophrastus Bombastus von Hohenheim, who published under the name **Paracelcus** was a Renaissance physician, botanist, alchemist, astrologer, and occultist. (1493—1541)

Gabapentin: FDA Approval

- 1993: Adjunctive Treatment for Partial Seizures
- 2000: Partial Seizures in Patients > 3y.o.
- 2002: Post Herpetic Neuropathy
- Never FDA Approved for Peripheral Diabetic Neuropathy
- Off Label: insomnia, anxiety, general pain, alcohol withdrawal, bi-polar, migraine, fibromyalgia, menopausal flashes
- 83—95% prescriptions are Off Label
- 2004-Pfizer: $420 million fine for off label promotion 
- $2 billion off label sales annually
- Not Scheduled

Pregabalin: FDA Approval

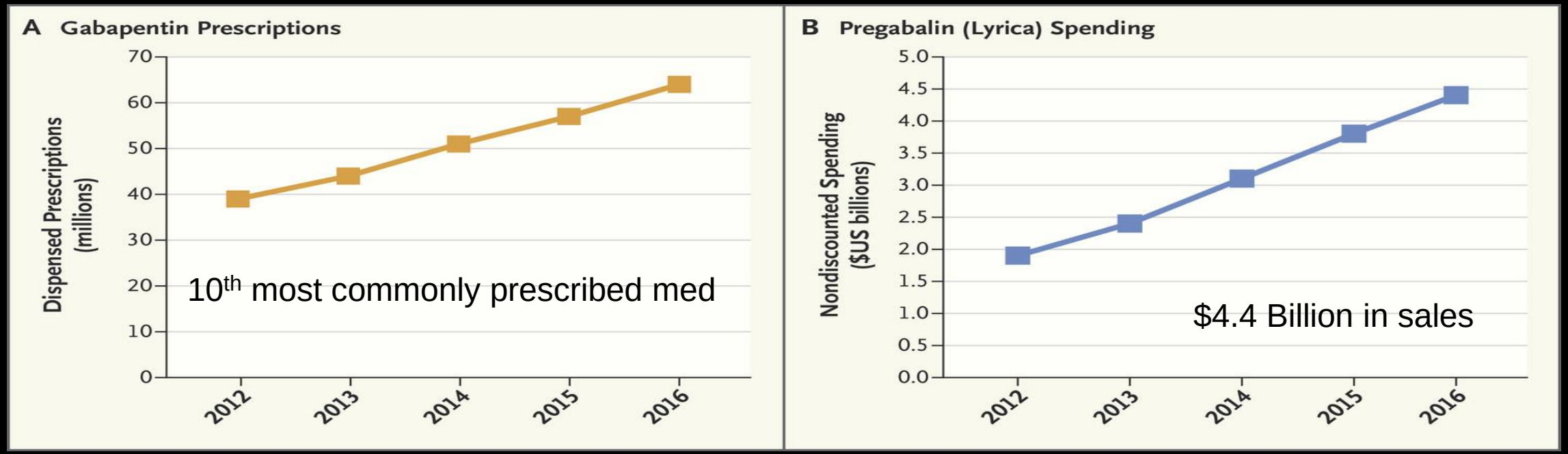
- 2005: Adjunctive Partial Seizures, Post Herpetic and Diabetic Peripheral Neuropathy, Spinal Cord Injury Neuropathy
- 2007: Fibromyalgia
- Europe: Generalized Anxiety Disorder
- 2012-Pfizer: Paid a Fine-$43M- for Promoting Off Label Use ☆
- 2016: $4.4 Billion Sales
- Schedule V: Potential for Abuse

Gabapentin Enacarbil: FDA Approval

- 2011: **Restless Legs Syndrome ?Dopaminergic Effect**
- 2012: Post Herpetic Neuralgia
- Pro-Drug → Gabapentin– 2X Bioavailability
- Extended Release/Long Acting: 600mg daily at 5PM
- Same Adverse Effects Profile as Gabapentin and Pregabalin

- 2012: Branded Once Daily Gabapentin Approved for Post Herpetic Neuralgia

Dispensed Prescriptions for Gabapentin and Nondiscounted Spending for Pregabalin, 2012–2016.

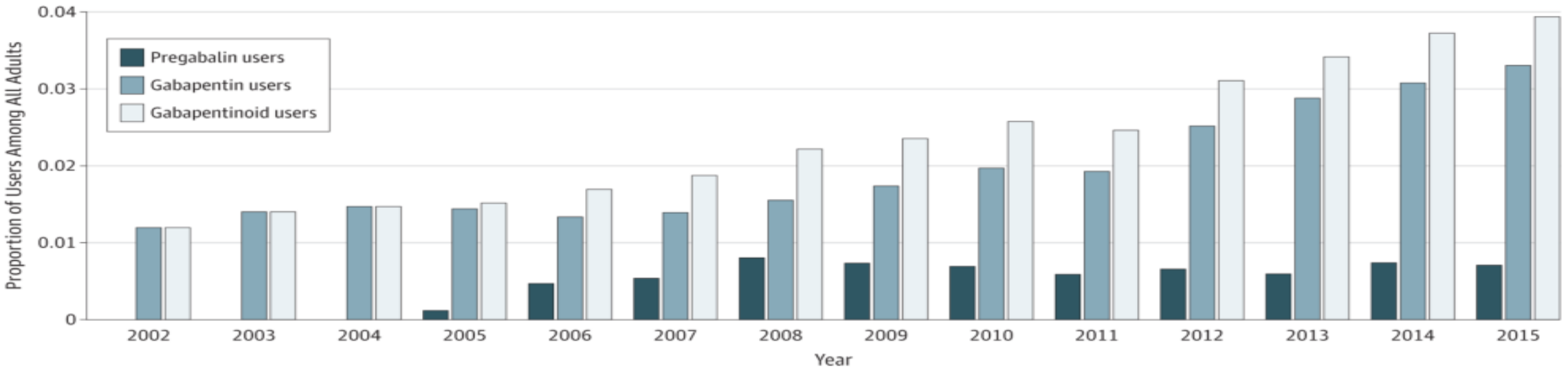


Goodman CW, Brett AS. N Engl J Med 2017;377:411-414.

The NEW ENGLAND JOURNAL of MEDICINE

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

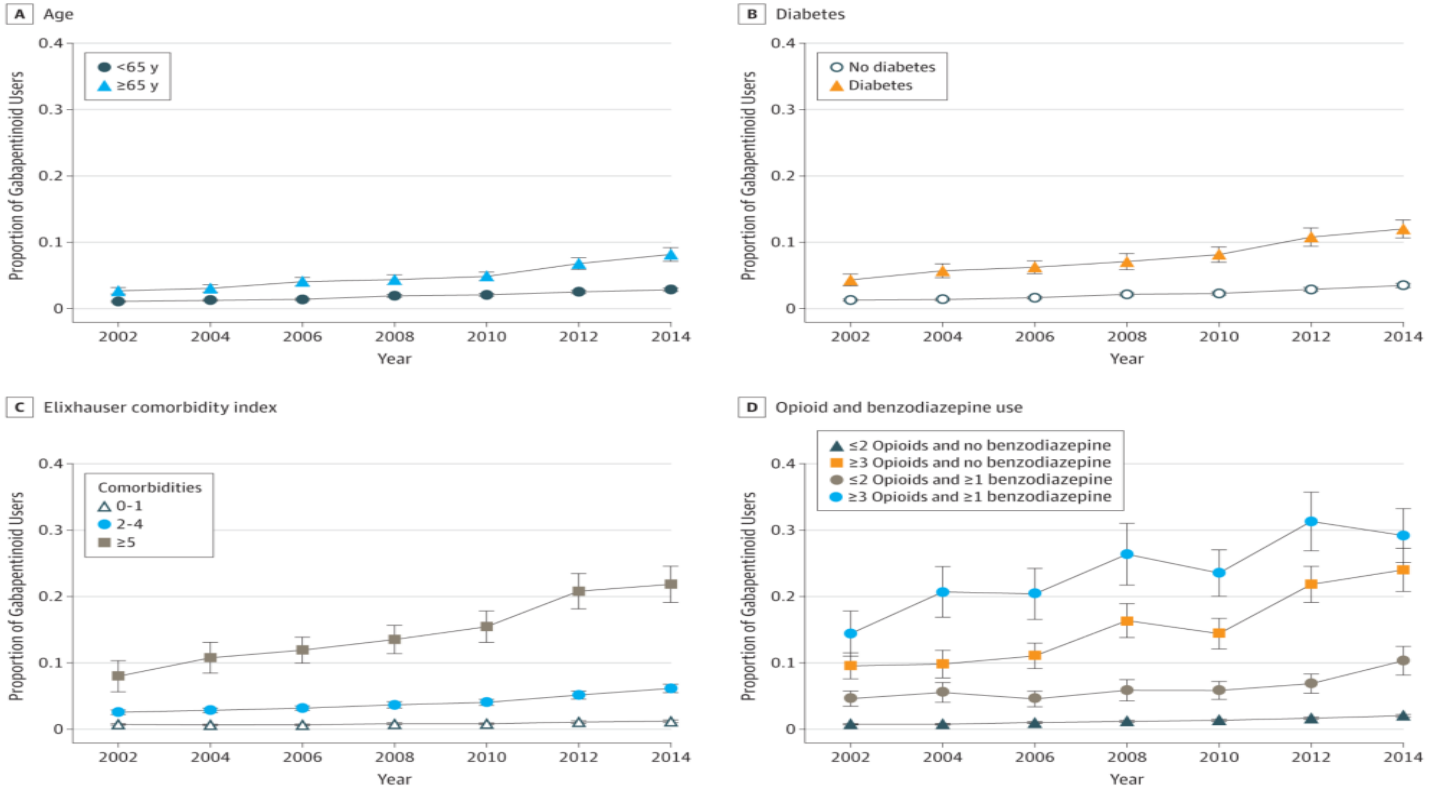
JAMA Intern Med. Published online January 02, 2018. doi:10.1001/jamainternmed.2017.7856



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.

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

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



Adverse Selection

☆

Gabapentinoid Use by Subgroups, 2002 Through 2015The figure identifies the proportion of gabapentinoid users among adults stratified by age (<65 vs ≥65 years), presence of diabetes, Elixhauser comorbidity index, and concomitant use of opioids (0-2 and ≥3 prescriptions) and benzodiazepines (any benzodiazepine prescription).

Drug Saf (2013) 36:55–62
DOI 10.1007/s40264-012-0006-6

ORIGINAL RESEARCH ARTICLE

Adverse Drug Reactions to Gabapentin and Pregabalin

A Review of the French Pharmacovigilance Database

Régis Fuzier · Isabelle Serres · Emmanuelle Guitton · Maryse Lapeyre-Mestre · Jean-Louis Montastruc · The French Network of Pharmacovigilance Centres

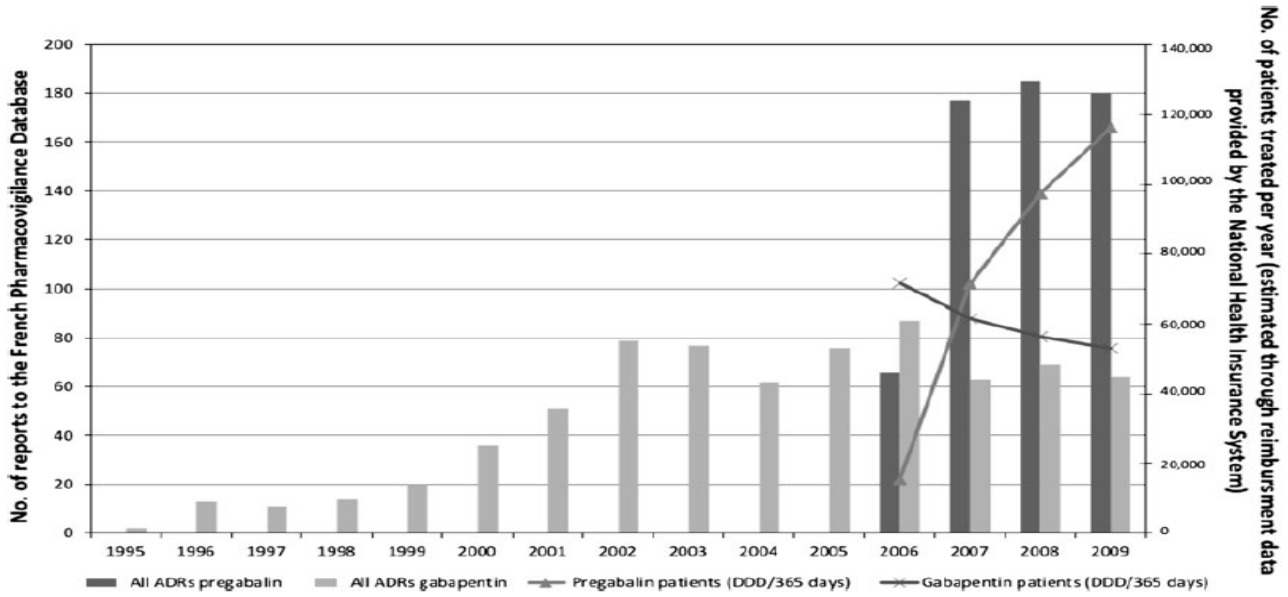


Fig. 1 Number of adverse drug reactions with gabapentin and pregabalin from 1995 to 2009, and number of patients treated by year, from 2006 to 2009. *ADRs* adverse drug reactions, *DDD* defined daily dose

Gabapentanoids: Pharmacokinetics

Gabapentin

- Low Lipophilicity
- **Cmax: 3-4 hours**
- **Zero Order-Saturable Absorption**
- **Bioavail: 60% at 900mg/33% at 3600mg**
- ½ Life= 5-7 hours: up to 132 hrs Renal
- Steady State: 24-48 hours
- No Metabolism: No CYP: No D/D Intx
- No Meal Adjustments

Pregabalin

- Low Lipophilicity
- **Cmax: 1 hour**
- **First Order-Linear Absorption**
- **Bioavail: >90% Not Dose Dependent**
- ½ Life= 5-7 hours: up to132 hrs Renal
- Steady State: 24-48 hours
- No Metabolism: No CYP: No D/D Intx
- No Meal Adjustments

Clinical Pharmacokinetics October 2010, Volume 49, Issue 10, pp 661–669
Howard N. Bockbrader, David Wesche Raymond Miller Sunny Chapel Nancy Janiczek Paula Burger

Pharmacokinetics

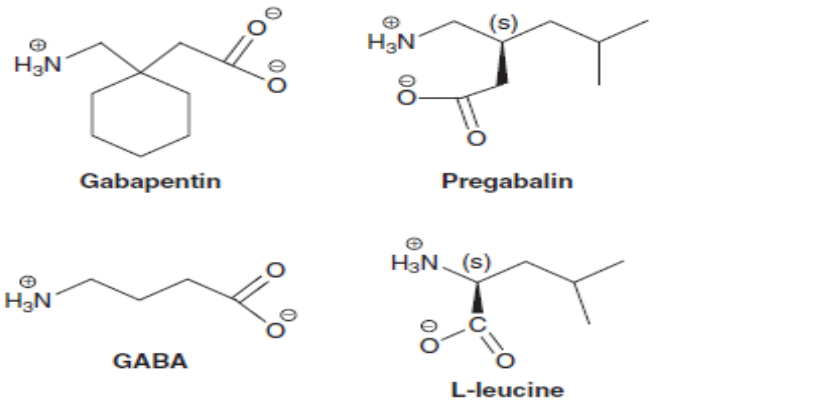


Fig. 1. Chemical structures of gabapentin, pregabalin, γ-aminobutyric acid (GABA) and L-leucine.

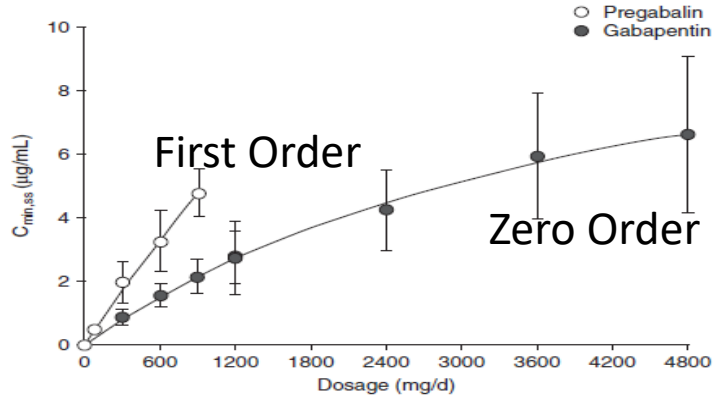


Fig. 2. Mean (± SD) steady-state minimum plasma drug concentration ($C_{min,ss}$) values in healthy subjects given pregabalin or gabapentin every 8 h.[14,20]

Clinical Pharmacokinetics October 2010, Volume 49, Issue 10, pp 661–669

Howard N. Bockbrader, David Wesche Raymond Miller Sunny Chapel Nancy Janiczek Paula Burger

Gabapentanoids: Absorption

Gabapentin

- Only LAT1* Transporter
- Only proximal small intestine
- CNS conc: 9-14% plasma conc.
- +Breast Milk=Plasma
- 50-75% not absorbed in 1800-4800 mg
- **↑ Absorption with Opioids→↓Small Bowel Motility**

Pregabalin

- LAT1* Transporter + unknown other
- Small intestine and Ascending Colon
- CNS conc: 10-30% plasma conc.
- +Breast Milk=Plasma
- **No Opioid Induced ↑Absorption**

- Gabapentin Enacarbil = Pregabalin

*LAT= Large Amino Acid Transport

Gabapentanoids: Metabolism/Excretion

- Metabolism: None
- No Hepatic Pharmacokinetic Dose Adjustments
- No Drug/Drug Interactions

- Excretion: 99% Renal Unchanged
- **Renal Dose Adjustments**
- Hemodialysis: ↓50% concentration

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Gabapentin Toxicity in Patients with Chronic Kidney Disease: A Preventable Cause of Morbidity

Ladan Zand, MD, Kevin P. McKian, MD, Qi Qian, MD

Department of Medicine, Division of Nephrology and Hypertension, Mayo Clinic College of Medicine, Rochester, Minn.

Table 5 Symptoms of Gabapentin Intoxication, Corresponding Serum Gabapentin Concentration, and Hospital Admission

	Group II **eGFR<90**	Group III **Dialysis Patients**
No. of Symptomatic Patients	33	7
Symptoms[a,b,c]	Reduced consciousness (13,[a] 21.9 ± 1.29,[b] 4[c]) Unsteady gait or ataxia (9,[a] 31.7 ± 4,[b] 0[c]) Dizziness and weakness (8,[a] 29.5 ± 3.84,[b] 1[c]) Myoclonus (8,[a] 29.9 ± 5.71,[b] 0[c]) Confusion (5,[a] 23.0 ± 0.49,[b] 2[c]) Tremulousness and asterixis (5,[a] 42.6 ± 3.84,[b] 1[c])	Reduced consciousness (6,[a] 59.6,[b] 6[c]) Unsteady gait or ataxia (1,[a] 25.0,[b] 1[c])

[a]No. of patients with the symptom.
[b]Corresponding serum gabapentin value.
[c]No. of hospital admissions.

730 patients-(1998-2007) who had a serum gabapentin level recorded, and outcome known

The American Journal of Medicine
Volume 123, Issue 4, April 2010, Pages 367-373

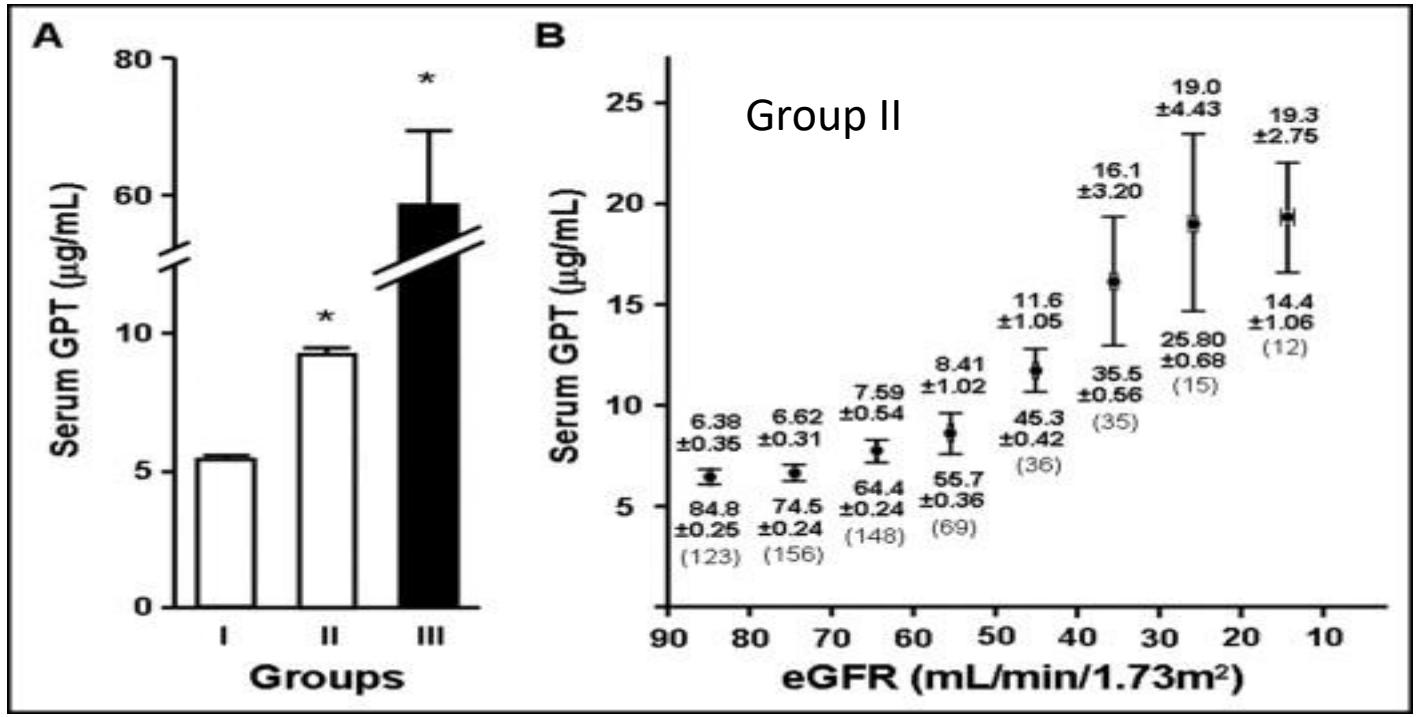


Figure 1. (A) Patients with kidney dysfunction exhibited a higher level of serum gabapentin. The serum gabapentin elevations seemed to be proportional to the severity of kidney dysfunction. Group III patients receiving dialysis had the highest mean serum gabapentin level, 58.8 ± 10.2 µg/mL, compared with those in groups I (estimated glomerular filtration rate > 90 mL/min/1.73 m2) and II (estimated glomerular filtration rate < 90 mL/min/1.73 m2 and without dialysis): 5.52 ± 0.35 µg/mL and 8.38 ± 0.32 µg/mL, respectively, P < .01 (1-way analysis of variance). (B) Patients in group II were stratified at decremental estimated glomerular filtration rates, and their corresponding serum gabapentin concentrations were collected and plotted. Serum gabapentin concentrations progressively escalated with the decline of estimated glomerular filtration rate. The numbers above individual dots are serum gabapentin concentration values, the numbers below individual dots are the corresponding estimated glomerular filtration rates, and the numbers in parentheses are the number of patients. GPT = gabapentin; eGFR = estimated glomerular filtration rate

The American Journal of Medicine
Volume 123, Issue 4, April 2010, Pages 367-373

Gabapentanoids: Mechanism of Action

- High Affinity Binding to the α2δ protein subunit of voltage gated Calcium channels in CNS/peripheral neuronal tissues
- ↓ Ca influx→ ↓ excitatory neurotransmitter release
- Chemical analogue of GABA: No binding at $GABA_A$ or $GABA_B$ receptors
- Indirect ↑ in Brain GABA-- ?↓ Glutamatergic Tone
- ? ↓ release of Substance P and other pro nociceptive peptides
- ? Indirect activation of dopaminergic reward circuitry
- GBPT: W/D similar to EtOH/Benzo. Rx Benzo or GBPT

Gabapentanoids: Evidence of Effectiveness
Cochrane Reviews Pain Studies

- Migraine Prophylaxis: No Evidence
- PHN and DPN: Moderate Evidence: 20% ↓ Pain, 1-2 pts on VAS
- Post-Op Pain: Weak Evidence
- Fibromyalgia: GBPT-NE, PGL-↓Pain in 10-15%
- Chronic Post-Op Pain: No Evidence
- Nociceptive Pain: No Evidence

Morphine, Gabapentin, or Their Combination for Neuropathic Pain

Ian Gilron, M.D., Joan M. Bailey, R.N., M.Ed., Dongsheng Tu, Ph.D., Ronald R. Holden, Ph.D., Donald F. Weaver, M.D., Ph.D. and Robyn L. Houlden, M.D.

N Engl J Med
Volume 352;13:1324-1334
March 31, 2005

The NEW ENGLAND JOURNAL of MEDICINE

Study Overview

- In a randomized trial, the combination of morphine and gabapentin led to better pain control than either agent alone in patients with diabetic neuropathy or postherpetic neuralgia
- The dose of each agent was lower when used in combination than when used alone
- Adverse effects were not more severe with the combined formulation
- These findings suggest that treatment with the combined formulation of morphine and gabapentin for neuropathic pain is superior to treatment with either agent alone

Original Article

Trial of Pregabalin for Acute and Chronic Sciatica

Stephanie Mathieson, M.Chiro., Christopher G. Maher, Ph.D., Andrew J. McLachlan, Ph.D., Jane Latimer, Ph.D., Bart W. Koes, Ph.D., Mark J. Hancock, Ph.D., Ian Harris, Ph.D., Richard O. Day, M.B., B.S., M.D., Laurent Billot, M.Sc., M.Res., Justin Pik, M.B., B.S., Stephen Jan, Ph.D., and C.-W. Christine Lin, Ph.D.

N Engl J Med
Volume 376(12):1111-1120
March 23, 2017

The NEW ENGLAND JOURNAL of MEDICINE

Study Overview

- In a randomized trial involving patients with sciatica, the antiepileptic drug pregabalin, at a dose of up to 600 mg per day, was no more effective than placebo in reducing pain or disability over the course of 8 weeks and resulted in a higher incidence of adverse events.

RESEARCH

Anticonvulsants in the treatment of low back pain and lumbar radicular pain: a systematic review and meta-analysis

Oliver Enke MBBS MSc, Heather A. New MBBS MPH, Charles H. New MBBS, Stephanie Mathieson PhD, Andrew J. McLachlan PhD, Jane Latimer PhD, Christopher G. Maher PhD, C.-W. Christine Lin PhD

■ Cite as: *CMAJ* 2018 July 3;190:E786-93. doi: 10.1503/cmaj.171333

ABSTRACT

BACKGROUND: The use of anticonvulsants (e.g., gabapentin, pregabalin) to treat low back pain has increased substantially in recent years despite limited supporting evidence. We aimed to determine the efficacy and tolerability of anticonvulsants in the treatment of low back pain and lumbar radicular pain compared with placebo.

METHODS: A search was conducted in 5 databases for studies comparing an anticonvulsant to placebo in patients with nonspecific low back pain, sciatica or neurogenic claudication of any duration. The outcomes were self-reported pain, disability and adverse events. Risk of bias was assessed using the Physiotherapy Evidence Database (PEDro) scale, and quality of evidence was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE). Data were pooled and treatment effects were quantified using mean differences for continuous and risk ratios for dichotomous outcomes.

RESULTS: Nine trials compared topiramate, gabapentin or pregabalin to placebo in 859 unique participants. Fourteen of 15 comparisons found anticonvulsants were not effective to reduce pain or disability in low back pain or lumbar radicular pain; for example, there was high-quality evidence of no effect of gabapentinoids versus placebo on chronic low back pain in the short term (pooled mean difference [MD] −0.0, 95% confidence interval [CI] −0.8 to 0.7) or for lumbar radicular pain in the immediate term (pooled MD −0.1, 95% CI −0.7 to 0.5). The lack of efficacy is accompanied by increased risk of adverse events from use of gabapentinoids, for which the level of evidence is high.

INTERPRETATION: There is moderate- to high-quality evidence that anticonvulsants are ineffective for treatment of low back pain or lumbar radicular pain. There is high-quality evidence that gabapentinoids have a higher risk for adverse events. **Protocol registration:** PROSPERO-CRD42016046363

*

Gabapentanoids: Adverse Effects Therapeutic Use

- Dizziness
- Sedation/Somnolence
- Dry Mouth
- Peripheral Edema
- Blurred Vision
- Confusion
- Myoclonus
- Respiratory Depression
- Dystonia
- Choreoathetosis
- Ataxia
- **Dose Dependent: Reversible**

Gabapentin Therapy of Hiccups

Dennis F Thompson, Krista G Brooks

300---1200mg divided daily

Request

What is the efficacy of gabapentin in the treatment of persistent hiccups?

Response

BACKGROUND

Hiccups (also referred to as hiccoughs or singultus) are described as an abrupt inspiration resulting from a sudden, involuntary contraction of the diaphragm. The glottis then abruptly closes to produce the characteristic sound of a hiccup.[1] Most individuals experience benign, short-term hiccups sometime during their lifetime. Hiccups that continue for more than 2 days are termed *persistent*; hiccups occurring for more than 1 month are termed *intractable*.[2] Persistent or intractable hiccups are often associated with an underlying organic or psychogenic cause. Classification of persistent or intractable hiccups may be based on underlying organic or psychogenic causes.[3] Only when these causes are ruled out is it appropriate to classify hic-

OBJECTIVE: To determine whether gabapentin is effective in the treatment of persistent or intractable hiccups.

DATA SOURCES: A search of MEDLINE (1966-March 2013) using the MeSH search terms gabapentin, hiccups, and hiccups/drug therapy was performed. Additional databases searched included Web of Science (1945-March 2013) and International Pharmaceutical Abstracts (1970-March 2013) using the text words gabapentin and hiccups. Bibliographies of relevant articles were reviewed for additional citations.

STUDY SELECTION AND DATA EXTRACTION: All data sources were considered for inclusion. Preference was given for articles written in English, although one abstract in German was used.

DATA SYNTHESIS: Because of the low incidence of persistent or intractable hiccups, few if any controlled clinical trials are conducted on the efficacy of drug treatment. Therefore, most of the data involve case reports or case series. We evaluated 17 case reports and 2 case series involving gabapentin therapy for persistent or intractable hiccups. Therapeutic outcomes with gabapentin were positive in all cases, with temporal evidence suggesting an effect, but outcomes often were obscured by combination therapy and comorbidities in some cases. Case reports suggest that gabapentin might be useful as a second-line agent in patients undergoing stroke rehabilitation or in the palliative care setting where chlorpromazine adverse effects are undesirable. Gabapentin was very well tolerated, with only a few minor adverse effects.

CONCLUSIONS: Gabapentin has a similar body of evidence as other pharmacotherapeutic agents used to treat hiccups. Gabapentin is well tolerated and should be considered as a second-line agent in selected patients.

Ann Pharmacother 2013;47:897-903.

Published Online, 13 May 2013, *theannals.com*, doi: 10.1345/aph.1S018

Adverse Effects
Therapeutic Use

Table 3 Type of adverse drug reactions reported for gabapentin and pregabalin

Type of ADRs	Total ($n = 1333$)	Gabapentin ($n = 725$)	Pregabalin ($n = 608$)
Neuropsychiatric	425 (31.9)	211 (29.1)	214 (35.2)
Hepatic	122 (9.2)	90 (12.4)	32 (5.3)
Cutaneous	105 (7.9)	69 (9.5)	36 (5.9)
Haematological	99 (7.4)	57 (7.9)	42 (6.9)
Allergic	76 (5.7)	53 (7.3)	23 (3.8)
Digestive	53 (4.0)	26 (3.6)	27 (4.4)
Cardiorespiratory	61 (4.6)	25 (3.4)	36 (5.9)
Blurred vision	40 (3.0)	22 (3)	18 (3)
Related pregnancy	19 (1.4)	17 (2.4)	2 (0.3)
Oedema	55 (4.1)	17 (2.4)	38 (6.2)
Electrolytic	23 (1.7)	16 (2.2)	7 (1.2)
Renal	43 (3.2)	14 (1.9)	29 (4.8)
Muscular	27 (2.0)	9 (1.2)	18 (3)
Weight gain	33 (2.5)	8 (1.1)	25 (4.1)
Administration error	14 (1.1)	7 (1)	7 (1.2)
Sexual disorder	11 (0.8)	5 (0.7)	6 (1)
Other	127 (9.5)	79 (10.9)	48 (7.8)

Data are expressed as n (%)

Table 4 Main characteristics of neuropsychiatric adverse drug reactions

Characteristics of neuropsychiatric ADRs	Gabapentin ($n = 211$)	Pregabalin ($n = 214$)
Age (y)	63 ± 20	65 ± 18
Sex ratio (male:female)	1:1.1	1:2.1
Seriousness	111 (53)	103 (49)
Outcome[a]		
Recovery with no sequelae	152 (73.4)	161 (76.3)
Not yet recovered	39 (18.8)	17 (8.1)
Unknown	7 (3.4)	17 (8.1)
Related death	1 (0.5)	0 (0)
Other	8 (3.9)	16 (7.5)
Imputability score		
Possible	146 (69.2)	150 (70.1)
Probable	58 (27.5)	46 (21.5)
Likely	7 (3.3)	17 (7.9)
Very likely	0 (0)	1 (0.5)
Type of ADRs (n)	391	511
Somnolence	41 (10.5)	49 (9.6)
Confusion	28 (7.2)	43 (8.4)
Dizziness	25 (6.4)	40 (7.8)
Falls	0 (0)	21 (4.1)
Trembling	0 (0)	19 (3.7)
Hallucination	16 (4.1)	0 (0)
Agitation	11 (2.8)	0 (0)
Aggressiveness	8 (2.0)	4 (0.8)
Other	262 (67.0)	335 (65.6)

Data are expressed as mean ± SD or n (%)

ADRs adverse drug reactions

[a] Four sets of data are missing in the gabapentin group and three in the pregabalin group

Drug Safety (2013), 36: 55-62

Received: 23 January 2019 | Revised: 14 March 2019 | Accepted: 17 March 2019

DOI: 10.1111/jcpt.12840

CASE REPORT

WILEY Journal of Clinical Pharmacy and Therapeutics

A rare case of a gabapentin-induced cardiomyopathy

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Email: katie.tellor@stlcop.edu

Summary

What is known and objective: Gabapentin, a γ-aminobutyric acid derivative, is used for the treatment of partial onset seizures, postherpetic neuralgia, diabetic neuropathy and a host of other neurological disorders.

Case description: A 44-year-old woman with spinal stenosis was prescribed gabapentin for pain. Two months after initiating therapy, she was diagnosed with a new-onset non-ischaemic cardiomyopathy with an ejection fraction of 36% measured on a transthoracic echocardiogram.

What is new and Conclusion: A patient with suspected gabapentin-induced cardiomyopathy is reported. However, to date, gabapentin therapy has not been associated with risk of the developing a cardiomyopathy.

KEYWORDS
adverse effect, cardiomyopathy, cardiovascular disease

What Is Trypophobia?

MPR > News > Patient's Trypophobia Linked To Treatment With Gabapentin

Diana Ernst, RPh

February 05, 2018

Patient's Trypophobia Linked to Treatment With Gabapentin

A case published in the *Journal of Clinical Psychopharmacology* describes a patient who developed trypophobia reversibly associated with the medication gabapentin.

The 67-year-old woman was being treated with gabapentin 1800mg/day for paresthesia which had developed 5 years prior without any obvious triggers. While the treatment was effective, it led the patient to develop trypophobia, "a feeling of aversion or fear in response to visual images of arrays of small holes." Specifically, the patient had reported fear associated with traffic lights (which led to driving impairment), certain television images (eg, insect eyes), shower heads, and pictures of lotus flowers.

Trypophobia is often discussed on the Internet but has only recently been documented in the literature

Robakis, *Journal of Clinical Psychopharmacology* • Volume 38, Number 2, April 2018

LETTER TO THE EDITORS

Trypophobia Associated With Gabapentin
A Case Report

To the Editors:

Trypophobia, a feeling of aversion or fear in response to visual images of arrays of small holes, has been discussed extensively on the general Internet but only recently begun to be documented in the medical literature.[1–7] It has been estimated that about 16% of the population is susceptible.[1] There is no previous report of trypophobia, or any specific phobia, arising as a side effect of medication. The present report discusses a case of trypophobia reversibly associated with treatment with gabapentin.

CASE REPORT

Ms B was a 67-year-old woman who had situational anxiety and depression in the context of a chronic burning and itching paresthesia in a cape-like distribution over her arms and shoulders. The paresthesia had arisen without obvious triggers when she was aged 62. She had no history of psychiatric illness prior to that time. Electromyography and nerve conduction studies were negative, but no other explanation for the paresthesia was discovered.

The patient had initially been treated with gabapentin by her primary care physician, in doses up to 1800 mg per day. The gabapentin was effective in treating the paresthesia but was associated with the new onset of trypophobia. Her other medical history, besides the paresthesia, included diabetes type 2, hypertension, hyperlipidemia, and cataracts. She had had a distant history of migraines in her 30s, with nausea and photophobia but no visual aura. She did not have any history of psychiatric symptoms before the onset of the paresthesia. At presentation, her other medications included aspirin, glimepiride, lisinopril, metformin, simvastatin, and alprazolam, which she had been given by her outside neurologist to address the trypophobia.

Ms B's trypophobia was characterized most prominently by fear, less so disgust or revulsion. She denied any changes to her vision. She found the light-emitting diode arrays in traffic lights particularly upsetting, to the point that she became unable to drive while taking doses of gabapentin greater than 900 mg per day. She also found certain stimuli on the television frightening (eg, large clear images of insect eyes). Other triggers included the shower head, pictures of lotus flowers, and the holes in pitted sliced olives. She recognized that these fears were irrational. When invited to look at trypophobic stimuli in the clinic to quantify her distress, she declined, stating that it would be too upsetting for her.

At intake, Ms B was started on duloxetine at 20 mg per day. This was initially very helpful for the paresthesia, and she was able to reduce her dependence on gabapentin. She had a period of a few days where she was able to avoid using gabapentin altogether, and during this period of time the trypophobia was noticeably reduced. However, after several days, the paresthesia began to recur in the afternoon, and she began taking the gabapentin again to compensate. The trypophobia then returned, along with the impairment to her driving. The duloxetine was titrated up to a dose of 40 mg 3 times per day, at which level she no longer needed gabapentin, and during this time the trypophobia was absent.

Six months after her original presentation, she stopped taking duloxetine because her insurance company refused coverage, and her paresthesia rapidly returned. She restarted gabapentin and found that the trypophobia again recurred, with attendant limitation of her driving. Ultimately the insurance company agreed to cover the duloxetine at a reduced dose of 30 mg twice per day. At this dose, she needed to take supplemental doses of gabapentin at 300 mg up to once per day. With this amount of gabapentin, the trypophobia was absent or very minimal and did not interfere with her daily functioning.

We obtained verbal consent from the patient to publish the case report.

DISCUSSION

Trypophobia has only recently been begun to be discussed in the medical literature. A search of PubMed and Google Scholar turned up only 7 unique English-language citations,[1–7] of which the first was published in 2013. This study found a prevalence of 16% in its unselected sample population.[1] A symptom scale has been devised,[2] which evinced good construct validity and instrument reliability. Unfortunately, this symptom scale could not be used to evaluate Ms B because she refused to look at trypophobia-inducing images; this seems to constitute a limitation on the use of the scale for evaluation of the most severely affected individuals.

All of the existing literature regards trypophobia as an enduring characteristic. Indeed, the present article appears to be the first report of any specific phobia that is reversibly associated with a medication. Other instances of reversible, medication-associated anxiety disorders have been reported, including panic attacks associated with oral contraceptives[8] and social phobia associated with haloperidol,[9] but induction of a specific phobia by a medication does not appear to have been documented previously. However, application of the Naranjo Adverse Drug Reaction Probability Scale[10] to this case yielded a score of 8, indicating that gabapentin was highly probable as a cause of the trypophobia.

It is notable that the medication involved in this case, gabapentin, is often used off-label for the treatment of anxiety and has some documented efficacy in the treatment of social phobia[11] and panic disorder.[12] Gabapentin targets the α2δ subunit of the voltage-sensitive calcium channel,[13] a component which enhances calcium flux through the channel[14] and potentiates excitatory synaptogenesis.[15] In animal models, this subunit is upregulated on a short time scale after exposure to anxiety-provoking stimuli.[16] Binding of gabapentin to α2δ reduces calcium flux through the channel and impairs the calcium-dependent release of monoamine neurotransmitters,[17,18] which are typically involved in unusual states. This effect is dependent on the availability of the α2δ-1 subunit,[19] which suggests that paradoxical anxiogenic effects, as seen in Ms B, could potentially be related to individual differences in the expression patterns of the α2δ-1 subunit.

This does not, however, explain the unusual and intriguing specificity of the effect observed in Ms B. It is worth noting that different specific phobias have been found to be associated with somewhat distinct patterns of metabolic activation in the brain.[20] For example, levels of activation in the anterior cingulate and anterior insula differentiate spider phobia from blood-injection-injury phobia, and prefrontal and orbitofrontal activation is higher in snake phobia than in dental phobia.[20] These findings might suggest that individual variations in the expression level and distribution of calcium channel subunits could play a role in determining susceptibility to the gabapentin-associated development of specific phobias. Future research investigating the potential correlations between individual calcium channel complements and susceptibility to specific phobias may help to

Trypophobia, a feeling of aversion or fear in response to visual images of arrays of small holes, has been discussed extensively on the general Internet but only recently begun to be documented in the medical literature. It has been estimated that about **16% of the population is susceptible**. **There is no previous report of trypophobia, or any specific phobia, arising as a side effect of medication.**

The patient had initially been treated with gabapentin by her primary care physician, In doses up to 1800 mg per day. The gabapentin was effective in treating the paresthesia but was associated with the new onset of trypophobia.

Ms B's trypophobia was characterized most prominently by fear, less so disgust or revulsion. She denied any changes to her vision. **She found the light-emitting diode arrays in traffic lights particularly upsetting, to the point that she became unable to drive while taking doses of gabapentin greater than 900 mg per day. She also found certain stimuli on the television frightening (e.g., large clear images of insect eyes). Other triggers included the shower head, pictures of lotus flowers, and the holes in pitted sliced olives.** She recognized that these fears were irrational. When invited to look at trypophobic stimuli in the clinic to quantify her distress, she declined, stating that it would be too upsetting for her.

OO☹PS

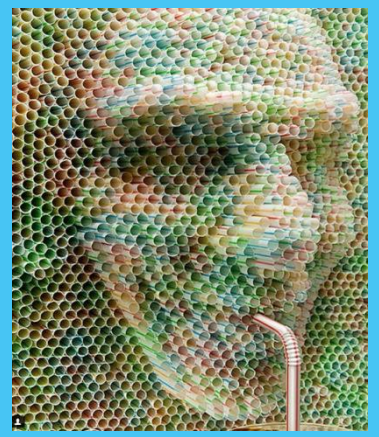
To: Salsitz, Edwin
Cc:
Subject: [EXTERNAL] Trypophobia

As a sufferer, I can tell you this is real. You can't say figure 3 isn't a bit creepy. I really enjoyed your talk anyway.
https://www.buzzfeed.com/philippjahner/do-you-have-trypophobia?utm_term=.mmKZBOPRL#.tbkQP5jJD









Gabapentanoids: Addiction Pharmacotherapy

- Acute Alcohol Withdrawal Syndrome
- Protracted Alcohol Withdrawal Syndrome
- Cocaine: Negative Study

Research

Original Investigation

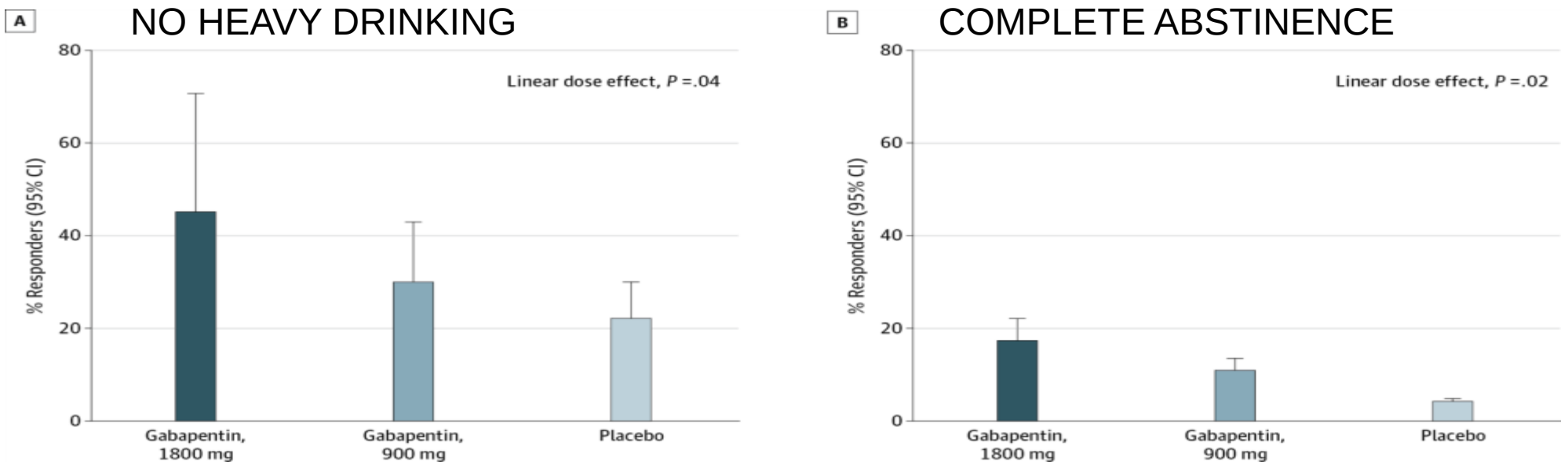
Gabapentin Treatment for Alcohol Dependence
A Randomized Clinical Trial

Barbara J. Mason, PhD; Susan Quello, BA, BS; Vivian Goodell, MPH; Farhad Shadan, MD; Mark Kyle, MD; Adnan Begovic, MD

JAMA Intern Med. 2014;174(1):70-77.

From: **Gabapentin Treatment for Alcohol Dependence: A Randomized Clinical Trial**

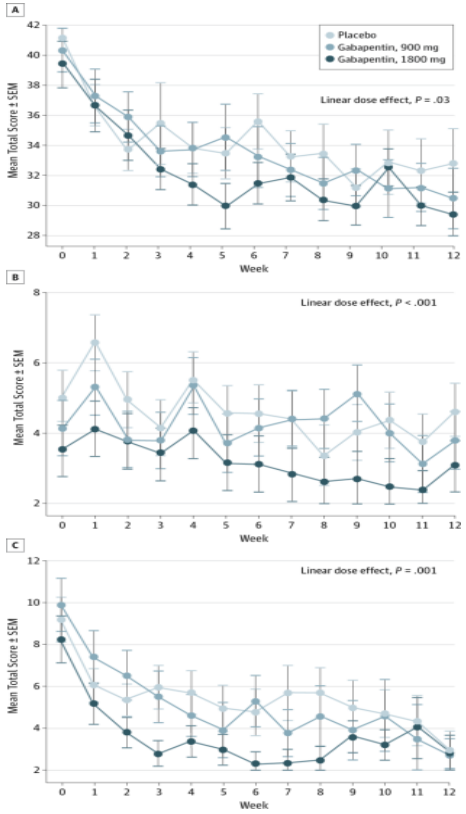
JAMA Intern Med. 2014;174(1):70-77. doi:10.1001/jamainternmed.2013.11950



Gabapentin Effects on Rates of No Heavy Drinking and Complete Abstinence During the 12-Week Study in the Intention-to-Treat Population A, No heavy drinking; B, complete abstinence. Error bars indicate 95% confidence intervals (N = 150).

From: **Gabapentin Treatment for Alcohol Dependence: A Randomized Clinical Trial**

JAMA Intern Med. 2014;174(1):70-77. doi:10.1001/jamainternmed.2013.11950



CRAVING

SLEEP

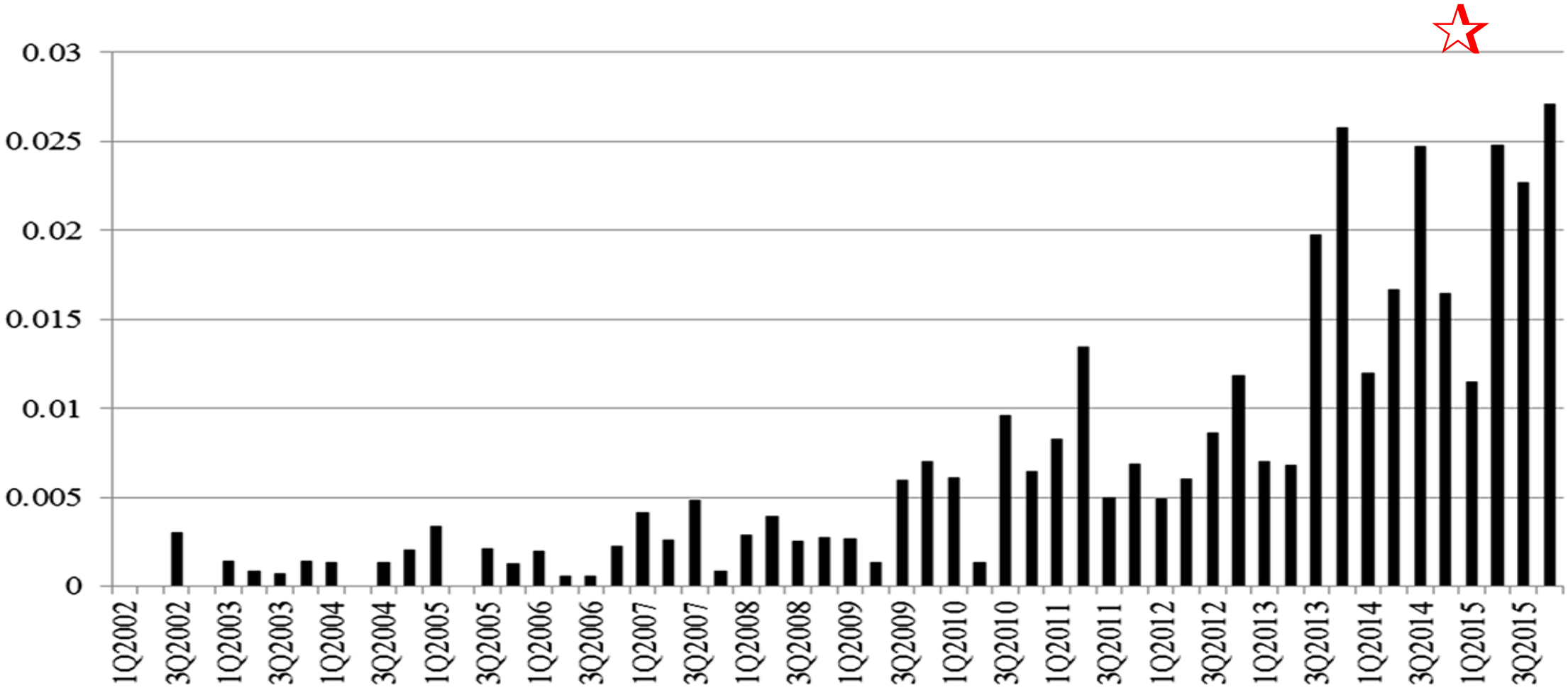
MOOD

Gabapentin Effects on Standardized Measures of Craving, Sleep, and Mood During the 12-Week Study in the Intention-to-Treat PopulationA, Alcohol Craving Questionnaire; B, Pittsburgh Sleep Quality Index; C, Beck Depression Inventory II. Error bars indicate SEM (N = 150).

Gabapentanoids: Misuse

- Supra-Therapeutic Doses of Prescribed or “Illicit”
- Intranasal and Intravenous Route
- 2nd Most Diverted Drug in Prison (#1 Tramadol)
- Low Street Cost: $1.00 in Kentucky: $1—10 in USA
- ~1% Misuse in General Population: 15—65% Misuse in SUD
- OUD +/- MAT With OAT Highest Rate of Misuse

Law enforcement-derived data on gabapentin diversion and misuse, 2002-2015: Per 100,000 population



Pharmacoepidemiology and Drug Safety
PDS-16-0304.R2, 10 MAY 2017 DOI: 10.1002/pds.4230
http://onlinelibrary.wiley.com/doi/10.1002/pds.4230/full#pds4230-fig-0001

The American Journal on Addictions, 24: 173–177, 2015

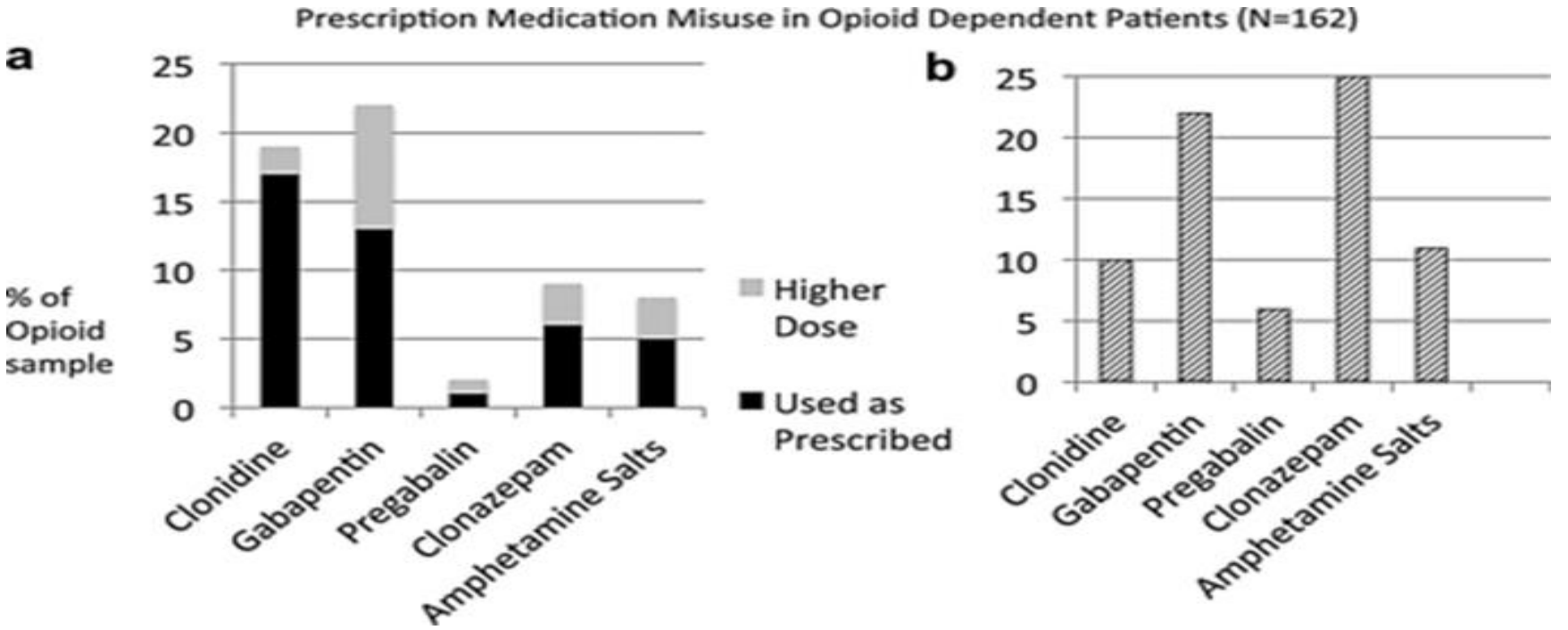
ISSN: 1055-0496 print / 1521-0391 online
DOI: 10.1111/ajad.12159

Prescription Medication Misuse Among Opioid Dependent Patients Seeking Inpatient Detoxification

Timothy Wilens, MD,[1,2] Courtney Zulauf, BA,[1] Denece Ryland, RN,[2] Nicholas Carrellas, BA,[1] Isela Catalina-Wellington, RN, BSN[2]

[1]Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts
[2]Bay Cove Human Services, Andrew House Detoxification Center, Quincy, Massachusetts

N= 162



Misusing
No Rx
High Dose

European Addiction Research

Eur Addict Res 2014;20:115–118
DOI: 10.1159/000355268

Gabapentinoid Abuse in Order to Potentiate the Effect of Methadone: A Survey among Substance Misusers

Colin R.W. Baird[a] Pauline Fox[b] Lesley A. Colvin[a]

[a]University of Edinburgh and [b]Lothian Substance Misuse Service, Western General Hospital, Edinburgh, UK

Table 1. Summary of questionnaire responses about drug use by patients attending the SMS

Substance Misuse Service

Drugs used by respondents (n = 129)	Prescribed	Non-prescribed
Gabapentin	9 (7%)	25 (19%)
Pregabalin	2 (1.5%)	4 (3%)
Methadone	102 (79%)	19 (15%)
Benzodiazepines	54 (42%)	61 (47%)
Buprenorphine	4 (3%)	2 (2%)
Cannabis	N/A	55 (43%)
Heroin	N/A	7 (5%)

All on Rx methadone

Gabapentanoids: Intoxication

- Euphoria
- Boost Methadone and Buprenorphine
- Sedation/Relaxation/Calmness
- Improved Sociability
- To Treat Withdrawal from Opioids, Alcohol, Benzodiazepines
- ↑ Energy
- ↑Sleep

Gabapentanoids: Overdose Deaths

- Uncommon Even With High Doses
- Most Often in Combination With Other CNS Depressants: Primarily Opioids (alcohol, benzodiazepine, SSRIs, quetiapine)
- Fatal Overdose 49% higher in Opioid/Gabapentin vs Opioid
- Gabapentin Dose Related
- 15—22% of OUD on MAT Misusing Gabapentanoids

JOURNAL OF FORENSIC SCIENCES

J Forensic Sci, September 2011, Vol. 56, No. 5
doi: 10.1111/j.1556-4029.2011.01798.x
Available online at: onlinelibrary.wiley.com

CASE REPORT

PATHOLOGY/BIOLOGY; TOXICOLOGY

Owen Middleton,[1] *M.D.*

Suicide by Gabapentin Overdose

ABSTRACT: Gabapentin is an antiepileptic drug that is prescribed for both FDA-approved and multiple off-label conditions, and has a relatively safe side-effect profile. Rare cases of overdose-related adverse effects have been reported in the literature. Described herein are the circumstances and autopsy findings of a 62-year-old woman with a history of depression, whose death was caused by intentional ingestion of excess gabapentin. The postmortem peripheral blood gabapentin concentration as determined by high-performance liquid chromatography/tandem mass spectroscopy was 88 μg/mL. Previously reported cases of individuals surviving gabapentin overdoses are discussed and compared with this case. Based on a review of the available literature, this appears to be the first published report of a death due solely to gabapentin toxicity.

Postmortem Gabapentin = 88ug/ml. High Therapeutic = 2.6ug/ml

PLOS | MEDICINE

October 3, 2017

RESEARCH ARTICLE

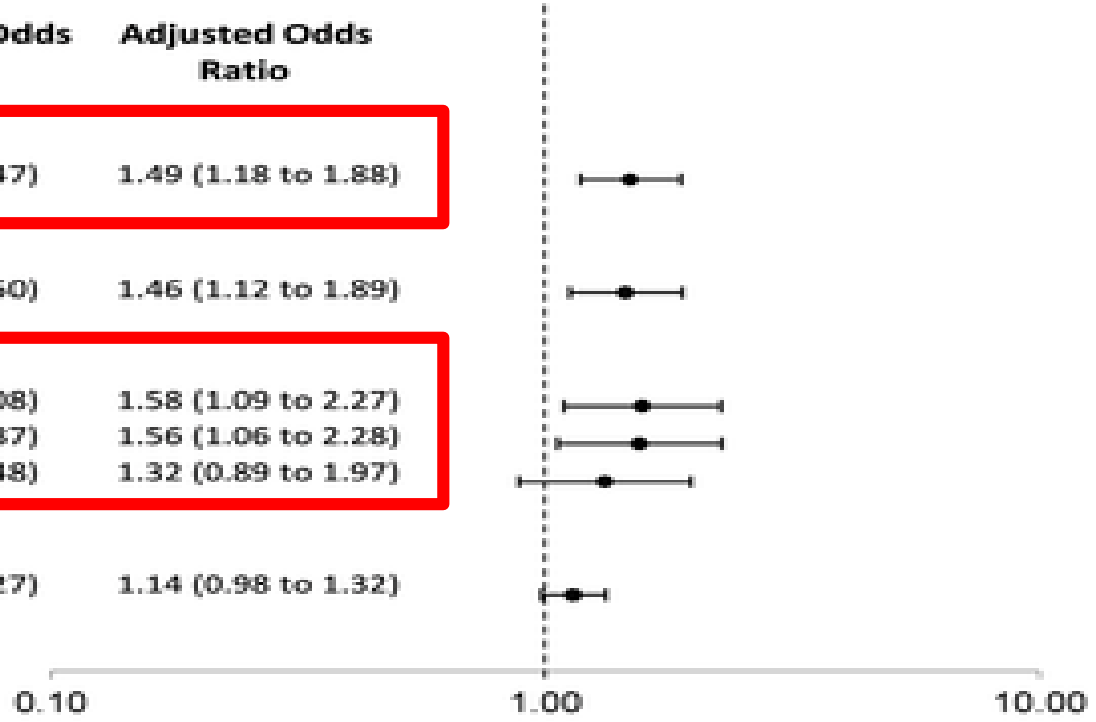
Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case–control study

Tara Gomes[1,2,3,4]*, David N. Juurlink[2,3,5,6], Tony Antoniou[1,2,7], Muhammad M. Mamdani[1,2,3,4,6,8], J. Michael Paterson[2,3,9], Wim van den Brink[10]

Fig 2. Association between co-prescription with gabapentin and opioids and opioid overdose.

1997--2013

	No. Exposed Cases	No. Exposed Controls	Unadjusted Odds Ratio	Adjusted Odds Ratio
***Primary Analysis**:*				
Recent Gabapentin Use	155 (12.3%)	313 (6.8%)	1.99 (1.61 to 2.47)	1.49 (1.18 to 1.88)
Sensitivity Analysis: Overlapping Gabapentin Use*				
Gabapentin Overlapping Index	121 (9.6%)	240 (5.2%)	1.98 (1.56 to 2.50)	1.46 (1.12 to 1.89)
Secondary Analysis: Gabapentin Dose **				
High Dose	57 (4.5%)	101(2.2%)	2.20 (1.58 to 3.08)	1.58 (1.09 to 2.27)
Moderate Dose	57 (4.5%)	111 (2.4%)	2.05 (1.46 to 2.87)	1.56 (1.06 to 2.28)
Low Dose	41 (3.3%)	101 (2.2%)	1.70 (1.17 to 2.48)	1.32 (0.89 to 1.97)
Neutral Exposure†:				
Recent NSAID Use	480 (38.2%)	1647 (35.7%)	1.11 (0.98 to 1.27)	1.14 (0.98 to 1.32)



*1,256 cases and 4,619 controls; Reference Group: no gabapentin use
** Low dose: <900mg/day; moderate dose: 900-1799mg/day; high dose: ≥1800mg/day; Reference Group: no gabapentin use
† Reference Group: no NSAID use

Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, et al. (2017) Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case–control study. PLOS Medicine 14(10): e1002396. https://doi.org/10.1371/journal.pmed.1002396
http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002396

PLOS | MEDICINE

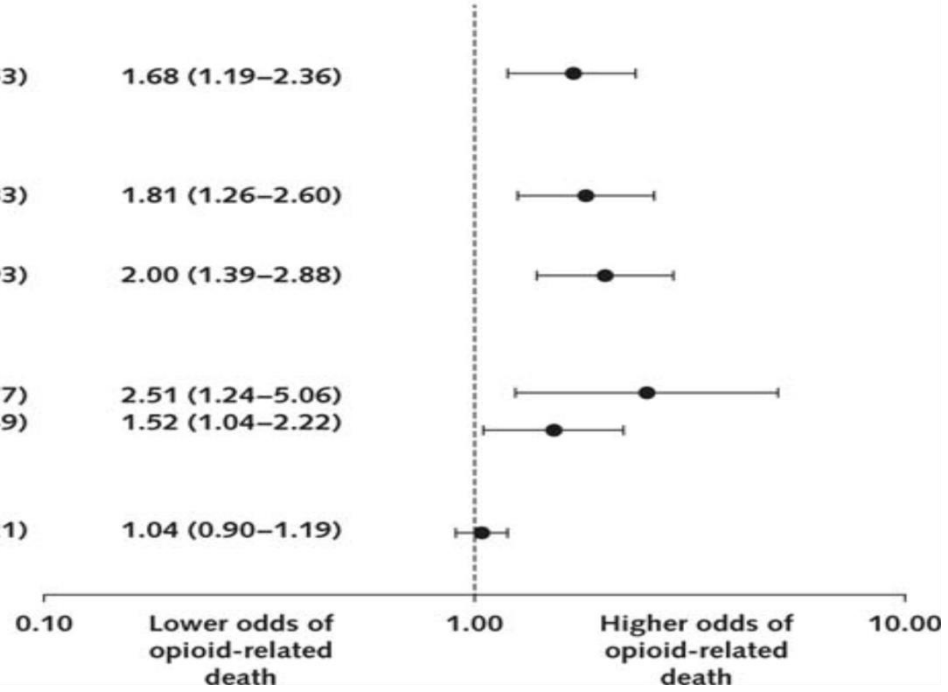
Annals of Internal Medicine®

From: Pregabalin and the Risk for Opioid-Related Death: A Nested Case–Control Study

Ann Intern Med. 2018;169(10):732-734. Tara Gomes, MHSc, PhD

1997--2016

	Exposed Case Patients, *n* (%)	Exposed Control Participants, *n* (%)	Odds Ratio (95% CI) Unadjusted	Odds Ratio (95% CI) Adjusted
Primary analysis*				
Recent pregabalin exposure†	69 (4.9)	153 (3.0)	1.85 (1.36–2.53)	1.68 (1.19–2.36)
Sensitivity analysis				
Overlapping gabapentinoid use*				
Pregabalin overlapping index	60 (4.2)	121 (2.4)	2.03 (1.45–2.83)	1.81 (1.26–2.60)
Matching on other CNS depressant use‡				
Recent pregabalin exposure	59 (4.9)	116 (3.0)	2.05 (1.44–2.93)	2.00 (1.39–2.88)
Secondary analysis: Pregabalin dose analysis§				
>300mg High dose‖	17 (1.2)	25 (0.5)	3.02 (1.58–5.77)	2.51 (1.24–5.06)
<300mg Low or moderate dose¶	52 (3.7)	128 (2.5)	1.74 (1.22–2.49)	1.52 (1.04–2.22)
Neutral exposure**				
Recent NSAID exposure	531 (34.5)	1830 (35.9)	1.07 (0.95–1.21)	1.04 (0.90–1.19)



Gabapentanoids: Withdrawal

- Similar to Alcohol and Benzodiazepines
- Delirium tremens
- Status Epilecticus After Stopping GBP 8000 mg daily
- Catatonia
- Treatment: Benzodiazepines or Gabapentanoids
- Gabapentanoids Should be Tapered, Not Stopped Abruptly

Effective May 7, 2018, the New Jersey Division of Consumer Affairs adopted amendments to the New Jersey **Prescription Monitoring Program(NJPMP)** rules to require New Jersey licensed pharmacies and registered out-of-State pharmacies to electronically **transmit information to the Division about prescriptions dispensed for gabapentin.** The recognition of gabapentin as a drug of concern stems from national prescription and overdose data. New Jersey is joining a growing list of states who have already begun to monitor gabapentin use, including those that have scheduled the medication at the state level.

Studies have shown **that gabapentin prescribing in the United States has increased 49% over the past five years resulting in 64 million prescription dispensations in 2016**. Additionally, the prevalence of gabapentin abuse in the general population is only 1.2%, but increases to a staggering **15% - 22% amongst opioid users**; likely a direct result of the potentiating effects caused by combination therapy. In New Jersey, over the past two years, the **presence of gabapentin in post-mortem toxicology reports increased by more than 1,000% overall and by more than 3,000% in the opioid-use subgroup.**

Consistent with the Director's statutory authority, the proposed amendments require pharmacies to transmit information to the NJPMP about each prescription dispensed for gabapentin**. The Director believes that the monitoring of prescriptions issued for gabapentin is warranted in light of growing concerns about the use of gabapentin for purposes other than those authorized under Federal law and the potential side effects associated with the misuse of this medication. Prescribers are encouraged to reference the NJPMP prior to issuing a prescription for gabapentin in order to make the most informed decision relating to treatment.**

Ohio and Michigan

“All things are poisons, for there is nothing without poisonous qualities. It is only the **dose** which makes a thing poison.”

Philippus Aureolus Theophrastus Bombastus von Hohenheim, who published under the name **Paracelcus** was a Renaissance physician, botanist, alchemist, astrologer, and occultist. (1493—1541)

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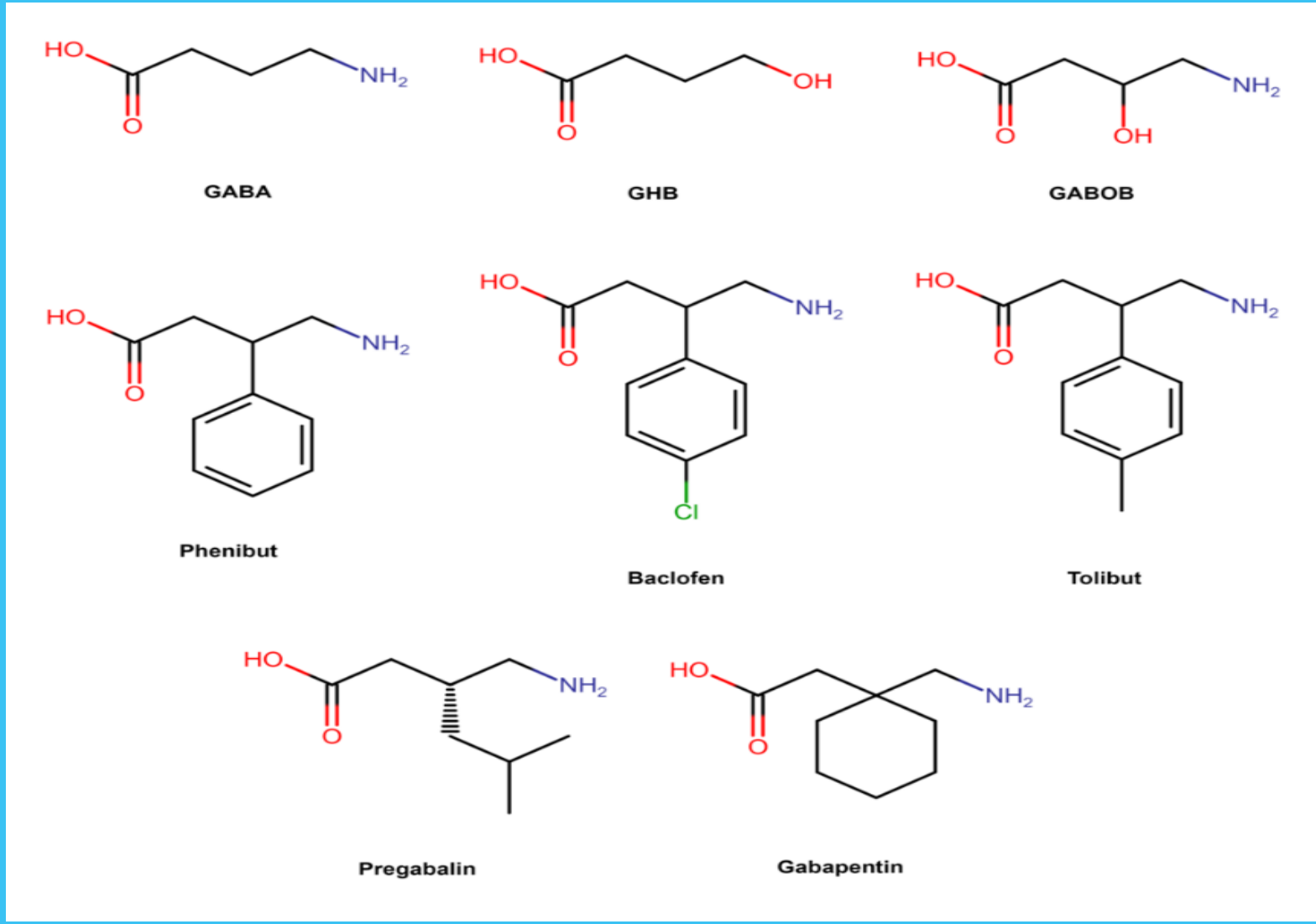
Home / Products / Phenibut HCL

Phenibut HCL

Phenibut (1) History

- $\beta - \boldsymbol{phenyl} - \gamma - amino\boldsymbol{but}yric\ acid$
- GABA analogue
- Synthesized in Russia in the 1960s
- Brand Names: Anvifen, Fenibut, Noofen
- Marketed for medical use in Russia, Latvia, Ukraine and Kazakhstan. Controlled only in Australia
- Widely available on the Internet as a supplement and nootropic(Cognitive Enhancement)
- Indications: anxiety, insomnia, depression, AUD, alcohol withdrawal, PTSD, stuttering in children,
- Soviet Cosmonauts Used in the Apollo-Sojuz Flight(1975)

Molecular Structures of Phenibut and Analogues



Phenibut (2) Pharmacology

- Full Agonist at GABA-B Receptor (Baclofen)
- Binding to the α2δ protein subunit of voltage gated Calcium channels in CNS/peripheral neuronal tissue→↓ Ca influx→ ↓ excitatory neurotransmitter release: same MOA as the Gabapentanoids
- Onset of Action 2-4 hrs: Peak Effect 6 hours
- Elimination ½ Life ~ 5 hours
- Urinary Excretion Unchanged
- Therapeutic Dose 250-500mg/day: Misuse 1-3 gms
- Reports of Rectal Administration with Rapid Onset of Action—30 minutes

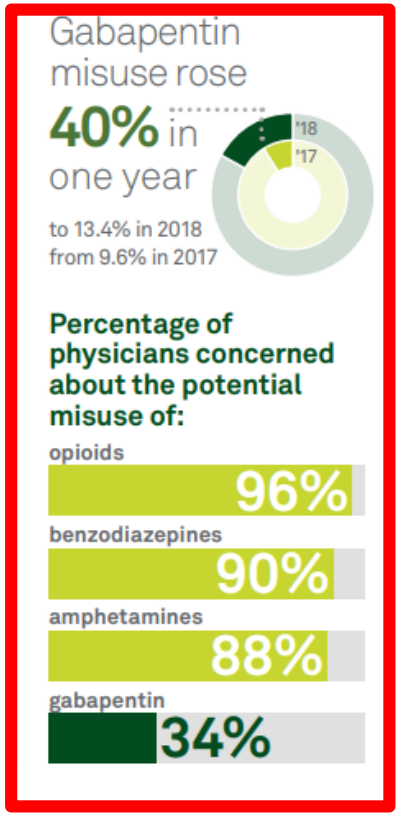
Finding 4: Gabapentin is emerging as an alternative pain therapy to opioids — just as misuse and illicit use increase

Gabapentin, an anticonvulsant that can be used to relieve neuropathic pain, is a non-opioid pain treatment that may be prescribed as an alternative to opioids for managing chronic pain. When taken alone and as prescribed, there is little potential for misuse or addiction. However, when a person takes gabapentin with other medications, such as muscle relaxants, opioids, or anxiety medications, it can produce a high.

While physicians may think of gabapentin as a less risky alternative to opioids, rates of misuse are surging. Laboratory data from Quest Diagnostics show that non-prescribed **gabapentin misuse rose 40% in one year** — to 13.4% in 2018 from 9.6% in 2017. This makes gabapentin the most commonly misused prescription drug in 11 states and in the top three drug groups in an additional 10 states.

Despite the increase in misuse rates, physicians are turning to gabapentin and are relatively less concerned about its potential for misuse:

- **78%** say that in an effort to avoid prescribing opioids, they often prescribe gabapentin to their patients with chronic pain
- **85%** have prescribed gabapentin in the past six months for chronic pain vs. **62%** who have prescribed opioids for chronic pain in the same time frame
- **63%** believe less than 10% of patients prescribed gabapentin misuse it



For more information about Quest Diagnostics, visit **www.QuestDiagnostics.com**

Quest Diagnostics™

Gabapentanoids: Conclusions

- Significant Misuse Among Patients with SUDs, Primarily OUD Receiving Methadone or Buprenorphine Maintenance.
- Significant Adverse Effects With Therapeutic Doses, and Increased Adverse Effects With Supra-Therapeutic Doses
- Must Adjust for Renal Function
- Full Recovery From Adverse Effects Is The Rule
- Death Is Rare, But Increased In Combination With Opioids
- Gabapentin Bioavailability ↓ With Increasing Dose
- Weak Evidence For Off Label Pain Treatment
- ? Should Gabapentanoids Be Listed On PDMPs (e.g. Ohio, NJ)
- ? Add Gabapentanoids To Drug Toxicology Screens