THE TOXICOLOGY PANEL
-17TH NYSAM (VIRTUAL) CONFERENCE 2021

MODERATOR: TIMOTHY J. WIEGAND, MD, FACMT, FAACT, DFASAM

New York Society of Addiction Medicine

ACMT | American College of Medical Toxicology

NYSAM Virtual Annual Meeting February 5-6, 2021

PANELISTS

- JoAn Laes, MD
  - Addiction Medicine Faculty Hennepin County Medical Center, Minneapolis, MN
- Lewis Nelson, MD, FACMT
  - Chair, Department of Emergency Medicine, Rutgers New Jersey Medical School
- Jeanmarie Perrone, MD
  - Director of Division of Medical Toxicology & Penn Center for Addiction Medicine and Policy
- Ross Sullivan, MD
  - Director SUNY Upstate Emergency Bridge Clinic & Medical Director Helio Health, Syracuse, NY
- Paul Wax, MD, FACMT
  - Executive Director the American College of Medical Toxicology

CONFLICT OF INTEREST

NONE OF OUR SPEAKERS HAVE ANY CONFLICTS OF INTEREST TO DISCLOSE

CASE 1

- A 27 year-old M with history of opioid and sedative use disorder had been doing well in an outpatient treatment program with mix of counseling and treatment with buprenorphine/naloxone.
- He entered the program about 9 months prior after a 28 day combined detoxification/inpatient facility stay where he was transitioned from heroin/fentanyl ("10 bags/day") to the buprenorphine and "detoxified" from 2-4 mg alprazolam and/or 2-4 mg clonazepam daily.

CASE 1

- About 9 months into the program he is found sleeping at work by his boss and when awoke he is slurring his speech and has trouble walking.
- This was a job he'd lost prior to treatment but they had let him back in 3 months after starting in treatment after he demonstrated sobriety –he worked with his father in a recycling plant coordinating large shipments and sometimes picking up materials using heavy equipment and other machinery.
- He lives with his parents and they are quite upset about the incident but he states, "I wasn't using I was just tired!"

CASE 1

- The parents communicate with his counselor and he is brought in for a urine drug test –which initially tests positive for benzodiazepines but the confirmation is negative. He repeatedly denies use.

BENZODIAZEPINES W/CONF	See Below	50	ng/mL	2019-11-09 17:00	F

Confirmation testing was performed. See confirmation test results.

BENZODIAZEPINE LCM CON

ORDERING PROVIDER: TIMOTHY WIEGAND
STATUS: FINAL

COLLECTED: 2019-11-06 17:45
RECEIVED: 2019-11-07 16:01

Component	Result	Flag	Range	Units	Reported	Location
--NORDIAZEPAM	Negative		50	ng/mL	2019-11-09 17:00	F
--OXAZEPAM	Negative		50	ng/mL	2019-11-09 17:00	F
--LORAZEPAM	Negative		50	ng/mL	2019-11-09 17:00	F
--TEMAZEPAM	Negative		50	ng/mL	2019-11-09 17:00	F
--HYDROXYALPROAZOLAM	Negative		50	ng/mL	2019-11-09 17:00	F
--NITRAZEPAM	Negative		50	ng/mL	2019-11-09 17:00	F
--7-AMINOCLONAZEPAM	Negative		50	ng/mL	2019-11-09 17:00	F
--FLUNITRAZEPAM	Negative		50	ng/mL	2019-11-09 17:00	F
--TRIAZOLAM	Negative		50	ng/mL	2019-11-09 17:00	F
--FLURAZEPAM	Negative		50	ng/mL	2019-11-09 17:00	F
--MIDAZOLAM	Negative		50	ng/mL	2019-11-09 17:00	F
--ESTAZOLAM	Negative		50	ng/mL	2019-11-09 17:00	F

- This is about 4 months ‘pre-COVID-19’.

CASE 1

- The patient has good buprenorphine metabolite levels (norbup-cr 727 ng/mg Cr).
- The only other confirmed positive is THC at 37 ng/mg Cr).
- "From CBD tabs" started taking for insomnia.

NORBUP/CREAT RATIO

ORDERING PROVIDER: TIMOTHY WIEGAND
STATUS: FINAL

COLLECTED: 2020-03-03 17:15
RECEIVED: 2020-03-04 16:09

Component	Result	Flag	Range	Units	Reported	Location
NORBUP/CREAT RATIO	727				2020-03-05 23:54	F

THCA/CREAT RATIO

ORDERING PROVIDER: TIMOTHY WIEGAND
STATUS: FINAL

COLLECTED: 2020-03-03 17:15
RECEIVED: 2020-03-04 16:09

Component	Result	Flag	Range	Units	Reported	Location
THCA/CREAT RATIO	37	A		ng/mg	2020-03-05 23:54	F

CASE 1 -QUESTIONS

- **Question:** What are your thoughts regarding this incident?

- **Question:** How do you interpret the toxicology results (BZD preliminary (+) & confirmatory (-)?

CASE 1

- The patient is confronted about "designer benzodiazepines" (which had become very common in illicit alprazolam tablets in particular in the region). He initially denies any knowledge of them but subsequently comments that he thinks some of the 'Xanax' he'd gotten in the past was actually some other type of benzodiazepine and appeared to be 'pressed' not really pharmaceutical grade tablets.
- He doesn't admit to current use though and for a week he is reported to be "acting normal" by his parents but then he misses group and his mother calls his counselor in a panic as she found him slumped over at the side of his bed, torso pressed to his knees head hanging down to the floor. She initially thought he wasn't breathing but when she rushed to his side she could hear his breath. She took a photo of him after trying to wake up him, only getting a groan, sending it to his counselor so she could see as well.

CASE 1

- After sending the photo she lifts him up into bed on his back and frequently checks on him over next few hours.
- About 5-6 hours later he wakes up but is groggy and slurring speech. He is irritable and denies use. He tries to get keys to his car but his mother had "hidden" them.
- He provides another UDS which is the same as the previous (good buprenorphine metabolites, preliminary positive BZD but confirmatory negative).

CASE 1

- The patient's mother tells his counselor "confidentially" that they had installed a 'tracking device' on his car since the episodes and that he appeared to be making one stop and then always running around the same routes after this stop –prior to his episodes of 'intoxication'. He reports he is driving for Uber and Grub hub since being fired from his job.
- Meds: sertraline, Valproic acid (500 mg PO BID), clonidine 0.1 mg PO BID PRN anxiety, buprenorphine/naloxone 8/2 mg SL BID
- The patient has a few more "groggy" episodes and during the holidays and on one day in particular is very disinhibited, "fell down the stairs at a family event and later fell asleep at the table during our family dinner." The patient blames it on his "meds not use!"
- His mother asks if his medications might be causing some of the "episodes" prior to the meeting involving patient and again also asks that we not disclose the tracking device.

CASE 1

- He is confronted about his driving pattern (parents) after a few more episodes of intoxication and some more photographs showing him unresponsive. After the first event his mother was given a Narcan® kit and advised to call 911 if she found him unresponsive or in similar state of intoxication (e.g. responds to voice but still quite sedated) and to use naloxone.
- At this point the patient admits he'd been getting some, "pressed 'Xanax'" from a guy but no longer has access to them. He is aware that it's, "not really 'Xanax' (alprazolam) but something the guy had been ordering over the Internet and "pressing into the bars". He mentions he is aware that there is quite a bit of this going around and it feels, "not quite like the alprazolam but close not as euphoric but 'stronger' if that makes sense."

CASE 1 – QUESTIONS

- **Question:** What types of treatments are available for sedative/benzodiazepine use disorder?

- **Question:** Does management of novel/synthetic benzodiazepine withdrawal differ from that of standard benzodiazepine withdrawal? What protocols do providers use?

CASE 1 –EXAMPLE PHENOBARBITAL PROTOCOL

- Phenobarbital 130 mg is administered as 'test' dose in patient thought to be sedative dependent (whether benzodiazepines, pregabalin, gabapentin or baclofen) if concern for withdrawal symptoms (or presented in withdrawal and stabilized but need to "taper" anticipated. If no sedation proceed with:
  - Day 1: 130 mg PO (or IV) q 4 hours x 6.
  - Day 2: 130 mg PO (or IV) q 6 hours x 4.
  - Day 3: 130 mg PO (or IV q 8 hours x 3.
- If any sedation hold and reassess if sedation (or slurred speech, ataxia) persist d/c protocol no further doses needed.
  - Clonidine 0.1 mg PO QID adjunctively PRN anxiety
  - Valproic acid 500 mg PO BID 2-4 weeks for sub-acute mood stabilization (less anxiety and insomnia) similar to use in ambulatory EtOH w/d protocols

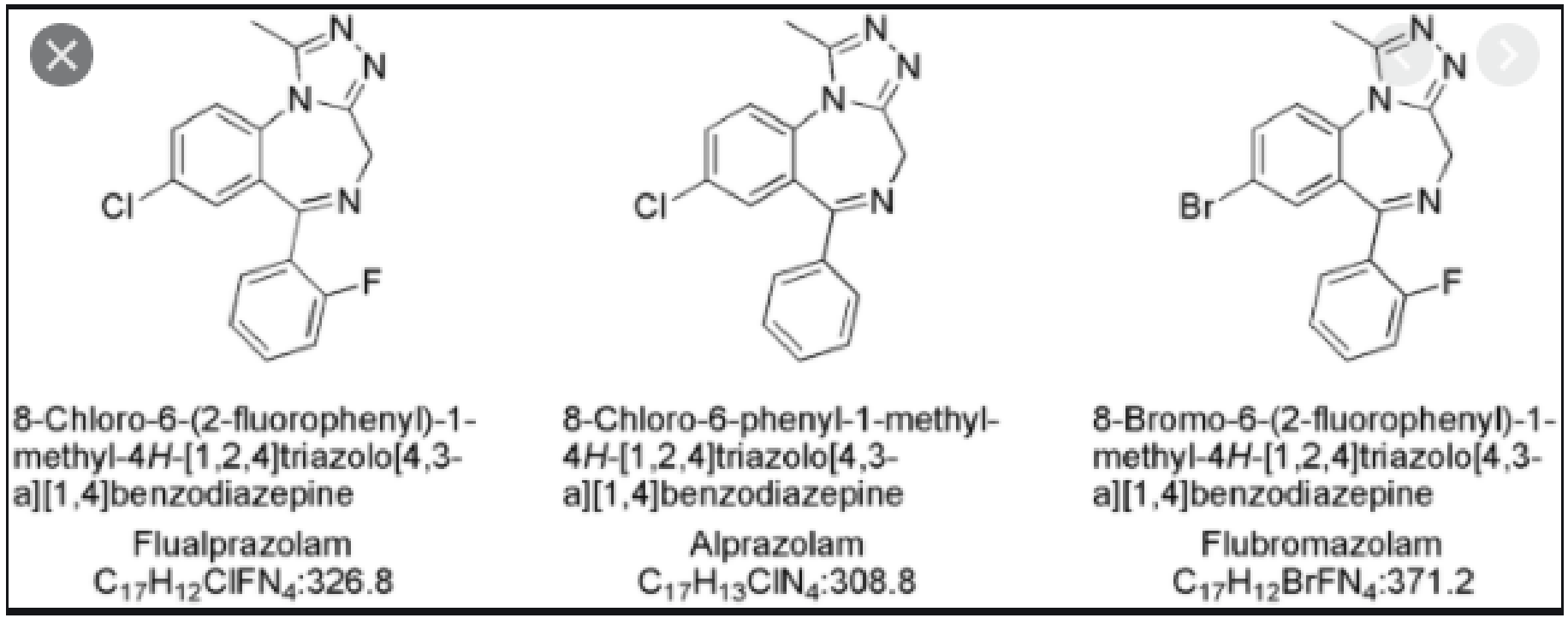
CASE 1 -QUESTIONS

- **Question:** What types of substances have been found in counterfeit alprazolam/'Xanax' bars?
- **Question:** What is the state of the 'designer benzodiazepine market in the US and availability?
- **Question:** How frequently is this coming up in your practice?

CASE 1 –DESIGNER BZD BACKGROUND

- Designer benzodiazepines have appeared as Novel Psychoactive Substances since 2007.
- As of 2020/21 at least 29 designer benzodiazepines have been detected through various surveillance systems (e.g. European Monitoring Center for Drugs and Drug Addiction (EMCDDA) and forensic laboratory detection in the United States (e.g. NMS lab surveillance).
- Variety of potencies, duration of effect and sold as tablets, powders, capsules, on blotter paper, in liquids and as counterfeit forms of known benzodiazepines (e.g. alprazolam/Xanax®)
- Etizolam and flu-alprazolam have been sold as 'pressed alprazolam' and phenazepam (very long acting benzodiazepine) and clonazolam (sold to users as clonazepam and ordered directly through Internet vendors).
- Complications often due to user misinterpretation of potency, duration of effect and other factors, "I thought it was like 'Xanax' and only lasted a few hours!" of, "I thought if I took a similar dose to what I do with clonazepam I'd be all right!"

CASE 1 EXAMPLE OF BENZODIAZEPINE ANALOGUE STRUCTURE



CASE 1

- Patient's parents report a month of his doing quite well -he's keeping appointments and then he has a call with his provider (phone) where his speech is thick and slurred. He is brought in for a UDS and denies taking any benzodiazepines (including synthetic/designer).

- BZD preliminary negative but the panel shows…?

CASE -1

- Pregabalin positive and he admits he "found some old caps from a prescription he'd "forgotten about."
- Case ongoing and is regularly now pregabalin positive –less episodes of severe intoxication but still having impairment noted frequently.

BENZODIAZEPINES W/CONF	Negative	50	ng/mL	2020-07-17 11:12	F

GABAPENTIN

ORDERING PROVIDER: TIMOTHY WIEGAND
STATUS: FINAL

COLLECTED: 2020-07-13 16:20
RECEIVED: 2020-07-14 20:08

Component	Result	Flag	Range	Units	Reported	Location
GABAPENTIN	Negative		500	ng/mL	2020-07-17 11:12	F

PREGABALIN

ORDERING PROVIDER: TIMOTHY WIEGAND
STATUS: FINAL

COLLECTED: 2020-07-13 16:20
RECEIVED: 2020-07-14 20:08

Component	Result	Flag	Range	Units	Reported	Location
PREGABALIN	>12000	A	500	ng/mL	2020-07-17 11:12	F

CASE 2

"Nothing is right anymore!"

CASE 2

- A 27 year-old male calls an area outpatient treatment program 2 days after leaving a detox facility where he'd left AMA, "because I cannot wait long enough to get enough time for the buprenorphine to work without causing precipitated withdrawal."
- He's left the detox twice in two weeks even though there are supportive medications including diazepam, clonidine, and hydroxyzine among other medications. The regimen of induction there is to wait either > 24 hours from last use and for COWS > 10 OR when the patient is demonstrating/reporting some symptoms of w/d and feels appropriate to start (with on-call provider consent).
- The first dose is 2/0.5 mg buprenorphine/naloxone and 2nd 4/1 mg one hour later followed by another 4/1 mg later that same day. Additional doses at discretion of provider on day 1.

CASE 2

- The patient reports 2-3 bundles of heroin IV daily and has been doing so now for 6 months with prior use/relapse/sobriety episodes for > 5 years.
- For the last 6 months he has had an active Rx for buprenorphine/naloxone during much of this time but has not been able to resume it –about two months into the relapse he reported waiting 36-48 hours at home and that an 8/2 mg dose, "nearly killed me."

CASE 2

- **Question:** Fentanyl is a short-acting opioid. Why are reports of precipitated withdrawal occurring 36-48 hours after individuals with prolonged and heavy use report cessation? What are panelists experience with precipitated withdrawal during buprenorphine initiation during the era of fentanyl-adulterated heroin?

- **Question:** How would panelists initiate buprenorphine or otherwise help this patient?

CASE 2

- The patient is counseled about reasons/risks of precipitated withdrawal with buprenorphine induction in heavy fentanyl users and he is intrigued about a description of "micro induction" that the clinic is offering through telemedicine support (with observed doses) and one on-site visit if he is willing.
- He agrees to try the protocol which entails taking 1/16th of a 2/0.5 mg film (125 micrograms) SL after he picks up the prescription from the pharmacy via an observed dose visit (use via Doxy.me). He reported use about 3 hours prior to the dose ("2-3 bags").
- The protocol involves: 1/16th (125 mcg) SL q 6 hours x 4 → 1/8th (250 mcg) SL q 6 hours x 4 → 1/4th (500 mcg) SL q 6 hours x 4 → ½ (1/0.25 mg) SL q 6 hours x 4 → 2/0.5 mg SL q 6 hours x 4 → 8/2 mg SL BID/TID if symptoms. Clonidine 0.1 mg 1-2 PO QID adjunctively. Instructed that he can still use throughout but to try and cut down in particular if he is "feeling better" and if goes > 12 hours from no use can accelerate the induction process.

CASE 2

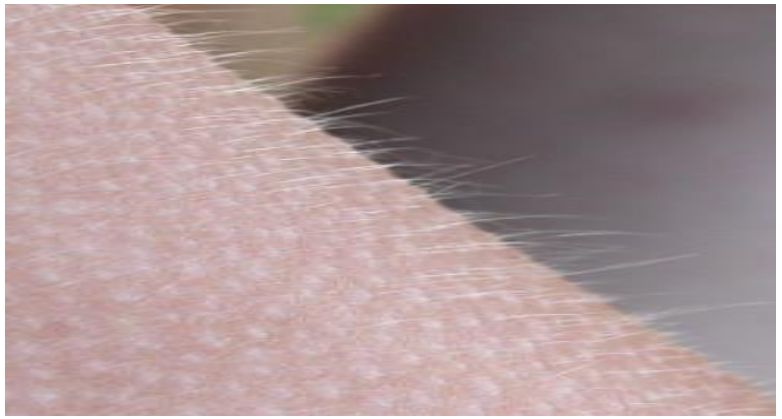
- **Question:** Can panelists describe the use of buprenorphine micro induction in initiation of buprenorphine and different settings it is utilized?
- **Question:** Thoughts/comments on the use of micro induction in the outpatient setting? Do panelists have any particular tips/protocols?

CASE 2

- The patient does another observed dose on day 2 and day 3 and on day 4 presents for an on-site UDS reporting no fentanyl for > 12-16 hours and he was taking the 8/2 mg films. "I was a little worried but after the first 1/16th didn't do anything even though it was only a few hours earlier I'd used a few bags and then the next day I took an 1/8th literally about an hour after using I realized it was going to work."
- UDS pos buprenorphine and fentanyl preliminary (pending confirmation/quantification) and patient currently treated with 8/2 mg SL BID buprenorphine/naloxone and topiramate 50 mg PO BID (intermittent cocaine use) the topiramate is 'off-label' use for cocaine craving.

CASE 2

- **Question:** If the patient had presented to the ED during his precipitated withdrawal episodes where he'd taken an 8/2 mg film 36-48 hours after stopping fentanyl but felt "severe precipitated withdrawal," how would panelists treat the precipitated withdrawal?



CASE 2 EXAMPLE PRECIPITATED WITHDRAWAL PROTOCOL

- After onset of precipitated withdrawal symptoms reassure the patient and options include:
  - Clonidine 0.1 mg 1-2 PO QID PRN (dose to 1.2 mg/day limited only by HR/BP) –well tolerated if ppt w/d.
  - **Resume buprenorphine quickly dose 2/0.5 mg SL q 1 hours until starting to feel better than increase to 8/2 mg SL 1-2 additional doses.**
- Adjunctive meds (depending on severity):
  - Hydroxyzine 50 mg 1-2 PO QID PRN anxiety/restlessness
  - Ondansetron 4 mg PO/IV q 8 hours PRN nausea
  - If severe* precipitated withdrawal diazepam 5-10 mg PO early after w/d and then use clonidine and diazepam

CASE 3

- A 35 year-old M is sent to the Emergency Department after he was admitted to a local detoxification facility as he is found ataxic and with, "twitches and tremors," about 8 hours after admit when he was normal earlier and at intake. He had been in his room for about an hour and was encountered by an assistant at the facility as he was attempting to walk from his room to the bathroom.
- He was admitted for the treatment of opioid withdrawal (to initiate buprenorphine and link back to outpatient treatment). He had an active prescription for buprenorphine/naloxone but hadn't been taking it and didn't bring it with him to the facility. He described taking: gabapentin, bupropion, clonidine and quetiapine at the admission evaluation but hadn't brought those either.

CASE 3

- In the ED the patient is somnolent but interactive. He is having myoclonic jerks of the upper and lower extremities. When asked to hold his arms up, "as if doing a push up in the air," he has asterixis and postural instability. He is unable to lift a cup shaking it as it is lifted from the table immediately spilling water.
- The detox sends notes indicating no medications were provided other than two nicotine lozenges and one 0.1 mg clonidine tablet about 4 hours prior to his being found ataxic and "twitching."
- ED vitals: Temp 36.5 C, HR 88 bpm, BP 136/88 mmHg, RR 20 breaths-minute.
- Other exam: pupils mid range and he is not diaphoretic. Stigmata of IVDU on extremities but no obvious cellulitis or abscess.

CASE 3

- **Question:** What is your diagnosis or differential diagnosis for this patient?

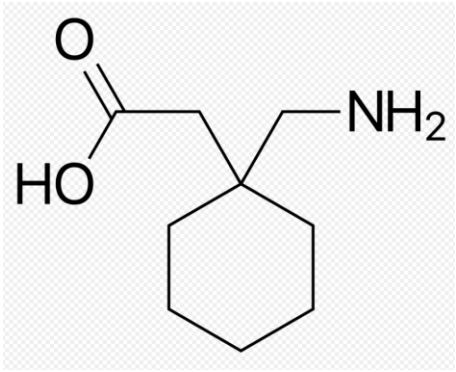
CASE 3

- The patient is known to the on-call Medical Toxicologist and he reports he, "is one of the most adept 'body stuffers', I've ever met." He also relates that the patient has been known to misuse gabapentin (in fact the ED provider is able to locate several prior encounters related to gabapentin intoxication and one related to seizures after insufflation of crushed bupropion).
- Several mixed gabapentin and heroin/fentanyl overdoses (each while being Rx'd buprenorphine but not taking it).
- The patient is given a small dose of lorazepam (0.5 mg IV) and admitted to the hospital for monitoring and initiation of buprenorphine if he doesn't clear before opioid withdrawal develops. If he clears and can return within 24 hours he can return to the detoxification facility for initiation per their policy (or resubmit name to admission list if after 24 hours).

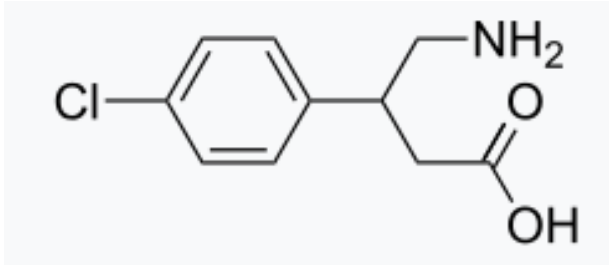
CASE 3

- **Question:** What drugs are collectively known as "gabapentinoids" and why are they most commonly misused by patients with opioid use disorder diagnosis?

GABAPENTINOIDS EITHER ARE GABA-B AGONISTS OR ALPHA-2-DELTA LIGANDS

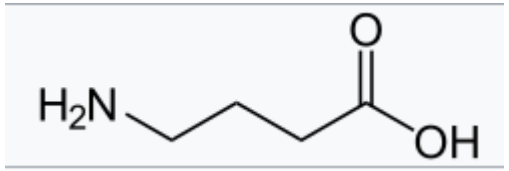


- Gabapentin structure
- Pregabalin structure

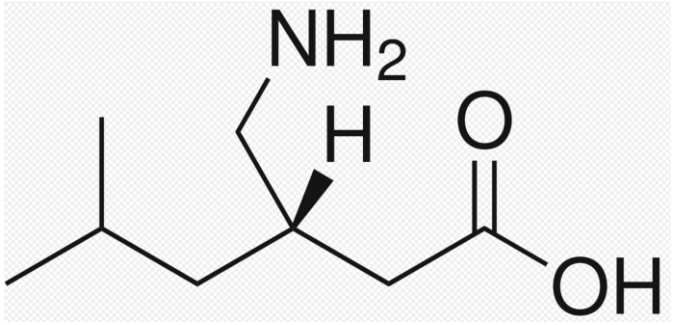


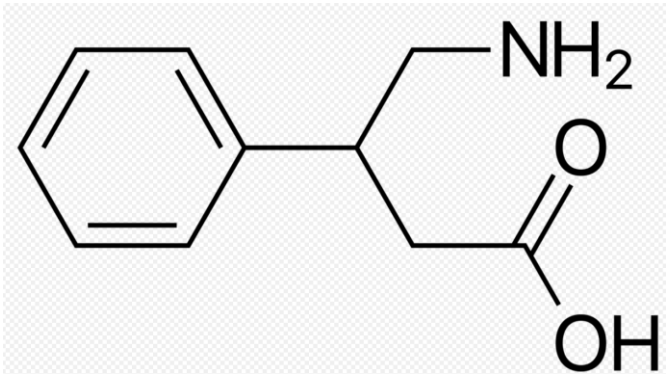
baclofen structure

phenibut structure



GABA structure





CASE 3

- The following AM the patient has minimal myoclonic jerks he is blaming the days prior issues on the lack of his continuation of "prescribed" gabapentin. He reports taking 900 mg PO QID for "nerve pain," and that if he doesn't have this continued he will have worsening withdrawal symptoms.
- He has exaggerated shaking on close assessment (more when examined than when simply discussing his presentation from bedside). He is mildly clammy and has hyperactive bowel sounds. He is offered buprenorphine but wants to delay another > 12 hours, "to avoid precipitated withdrawals."

CASE 3

- **Question:** Have panelists treated patients with gabapentin withdrawal (or other 'gabapentinoid')? If so what symptoms have predominated and what treatments employed?

CASE 3 –GABAPENTINOID WITHDRAWAL

- Depending on amount/duration used onset of withdrawal usually 7-12 hours after last dose –similar to other sedative withdrawal: anxiety, neuropsychiatric symptoms, somatic symptoms, confusion, abnormal movements.
- Variability depending on if GABA-B agonist or alpha-2-delta Calcium channel activity (gabapentin and pregabalin)
- Cross-tolerance with other GABAergic agents (e.g. phenobarbital, benzodiazepines, propofol*)
- ? Treat with taper vs phenobarbital (depends on the patient and use pattern also severity)
- Valproic acid may be useful adjunctively (or as primary if lower level dependence) 250-500 mg PO BID (VPA is indirectly GABAergic)

CASE 3

- The patient is noted to be resting in between nursing and other provider visits during the day. He is not resumed on gabapentin (felt that he has more 'binge' use rather than regular daily use). He ultimately decides to return to the detoxification facility before 24 hours to keep his bed after nursing discovers him holding a small baggie with capsules inside (which he flushes before it can be obtained) –he'd been sitting on the toilet holding the baggie with the door slightly ajar when nursing entered.
- The provider that had been prescribing him gabapentin is called and informed about the prior (numerous) gabapentin overdoses (often mixed with opioids/heroin) and misuse of bupropion.
- Valproic acid had been suggested for the detox to initiate at 500 mg PO BID if anxiety or insomnia without gabapentin (and in the past during prior (other patient) episodes of gabapentin withdrawal had been utilized for 2-4 weeks after using a 3 day phenobarbital protocol employed for general sedative (benzodiazepine) detoxification (130 mg PO q 4 hours x 6 day 1, 130 mg PO q 6 hours x 4, 130 mg PO q 8 hours x 3 then d/c if any sedation hold and reassess if held twice then d/c) by the toxicology/addiction CL service for this hospital.

CASE 3

- **Question:** Any final comments on the use, intoxication from or treatment of withdrawal or even use disorder related to gabapentin?

SELECT REFERENCES

- Greenblatt HK, Greenblatt DJ. Designer Benzodiaepines: A Review of Published Data and Public Health Significance. Clin Pharmacol Drug Dev. 2019 Apr;8(3): 266-269. pmid: 30730611.
- Huhn AS, Hobelmann GJ, Oyler GA, Strain EC. Protracted renal clearance of fentanyl in persons with opioid use disorder. Drug Alcohol Dependence. 2020 Sep 1; 214: 108147. PMID: 32650192.
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- Mersfelder TL, Nicholas WH. Gabapentin: Abuse, Dependence, and Withdrawal. Ann Pharmacother. 2016 Mar; 50(3):229-33. PMID: 26721643.

Q&A