

CLINICAL PRACTICE

Gabapentin abuse: A case presentation on how to manage this growing concern

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ABSTRACT

Gabapentin was first approved by the US Food and Drug Administration in 1993 as an adjunct treatment of epilepsy. In 2004, an additional indication of pain associated with post-herpetic neuralgia was added. Misuse of gabapentinoids dates back to 2010 while surging recently to the tenth most commonly prescribed medication in 2016. Abuse can be as high as 65% for even those who legally obtained the medication through a prescription. It is used off-label up to 95% of the time despite limited evidence of its efficacy particularly with multiple pain types. The surge in misuse can be attributed not only to off-label use but also an assumption of no abuse potential coupled with clinicians seeking alternative treatment options to the opioids. More common side-effects include sedation, dizziness, and cognitive difficulties. However, even normal dosing can produce side-effects similar to other addictive substances including: euphoria, talkativeness, and increased energy (opioids); sedation (opioids, benzodiazepines); and dissociation (hallucinogens). In fact, a few states including Kentucky, Ohio, and West Virginia will or have already added gabapentin to the controlled substance rosters even though no federal designation is in place. Identified risks for gabapentin misuse in the literature are limited with the exception of a history of or current substance abuse, particularly opioids. Unfortunately, gabapentin is often co-prescribed with opioids leading to a heightened risk of opioid-related mortality. Clinicians must understand that gabapentin is not effective for a variety of pain conditions nor is a routine substitute for opioids. In addition, close monitoring practices often associated with opioids and benzodiazepines (i.e., regular monitoring for aberrant drug taking behaviors, limits on supply, guarded dose titration) should be applied to that of gabapentin.

Key Words: Gabapentin abuse, Pain management, Off-label use, Fibromyalgia, Anxiety, Opioids

1. INTRODUCTION

Gabapentin was first approved by the US Food and Drug Administration (FDA) in 1993 as an adjunct treatment of epilepsy.^[1] In the next decade, the United Kingdom expanded the indications for gabapentin to include anxiety while also giving credence to its use in neuropathic pain.^[2] In 2004, the US FDA also approved gabapentin for treatment of pain associated with post-herpetic neuralgia.^[1] Recently the Centers for Disease Control and Prevention, through

guidelines, have advised clinicians to consider alternative drug classes to opioids for pain, including use of gabapentinoids as a first-line treatment for neuropathic pain.^[3]

Misuse of gabapentinoids dates back to 2010 through data obtained in population-based studies involving prisoners and persons attending addiction treatment.^[2] Since this time gabapentin has dramatically risen in 2016 to the tenth most commonly prescribed medication in the US.^[3] This resulted in 64 million prescriptions, an almost 75% increase since

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2012.^[3] The surge in use and misuse of gabapentin can be attributed to a number of factors: FDA expanding the number of indications;^[3] unclear mechanism of action and assumptions of no abuse potential leading to increased off-label use;^[1] clinicians desperately seeking alternatives to opioids in the treatment of multiple pain types;^[3] decreased availability of prescription opioids;^[4] relatively inexpensive;^[1] and illegal marketing by Warner-Lambert (now Pfizer) of gabapentin as an off-label use for multiple pain types resulting in a fine of \$420 million.^[1,3] Gabapentin misuse in the general population is estimated to be 1%; however, this increases to 40%-65% among those with prescriptions. It is also estimated that 15%-22% of the opioid abuse population misuses gabapentin.^[1] Some qualitative data suggest that gabapentin is being misused along with prescription opioids and that gabapentin and heroin are being combined for the synergistic effects of collective use. Law enforcement has determined that such misuse scenarios are promoting current gabapentin diversion.^[5]

2. CASE PRESENTATION

Mary Smith is a middle-aged female who has been under medical management by her primary care provider (PCP) for fibromyalgia over the last six years. During that time, she has had two major depressive episodes but denies depressive symptoms for more than two years resulting in a discontinuation of her sertraline (antidepressant). Approximately eight weeks ago, she sought treatment from her PCP for reports of pain exacerbation associated with her fibromyalgia along with anxiety on most days and sleep disturbance. At the time, the PCP continued her hydrocodone (opioid) and added gabapentin for the additional complaints. Gabapentin was initiated at 100 mg three times daily and rapidly titrated to 600 mg three times daily over a two week timeline.

Mrs. Smith presents to the PCP today with her husband. He reports a deterioration in her condition over the last week including symptoms of dizziness and cognitive difficulties, along with memory problems. He comments that she ran out of her gabapentin prescription early and went to the urgent treatment center for a refill of this medication. It is confirmed that she has the expected number of pills remaining of her hydrocodone prescription. Assessment findings including new-onset dizziness, cognitive difficulties, and memory problems raised suspicion she was potentially abusing her gabapentin prescription. This was confirmed through both self-disclosure and behavior of seeking medication refills sooner from another provider. In order to avoid possible withdrawal symptoms as documented in the literature,^[1] her gabapentin was tapered over two weeks as agreed upon by Mrs. Smith and her husband. Phone consultation was placed

with Mrs. Smith's mental health clinician for follow-up care recommendations. Based on her history of depression, anxiety, sleep disturbance, and fibromyalgia, the mental health specialist recommended adding duloxetine to her pain treatment regimen as a therapeutic substitute for gabapentin since duloxetine has shown improvements with these issues.^[6] Her as-needed hydrocodone was continued as there was no determination of abuse with this medication. Follow-up visits to the office demonstrated a resolution of neurological symptoms paralleled with a reduction in reported pain, anxiety, and sleep problems.

3. IMPLICATIONS FOR CLINICAL PRACTICE

3.1 Gabapentin (Neurontin)

Gabapentin is a gamma-aminobutyric acid (GABA) analog that does not bind to GABA receptors. However, it increases GABA and decreases glutamate. In addition, it does not bind to benzodiazepine, opioid, or cannabinoid receptors.^[1] Its mechanism of action is still unclear for its indications,^[1,4] but it is believed to affect calcium channels which regulate a number of neurotransmitter levels^[4] and potentially reduces the release of pain-related peptides.^[1]

Prescription dosing parameters of gabapentin show it can be safely managed in a dose range of 800-1,800 mg/day with typical starting doses being less than 400 mg/day while implementing rapid titration. The drug manufacturer maintains dosing can still be safe in doses as high as 3,600 mg/day but no additional benefit has been observed above 1,800 mg/day in clinical trials. Even with normal dosing, some reports have demonstrated a variety of subjective experience side effects comparable to that of other addictive substances including: euphoria, talkativeness, and increased energy (opioids); sedation (opioids, benzodiazepines); and dissociation (hallucinogens).^[1] In addition to sedation and dizziness, cognitive difficulties may occur as more common side effects.^[3] There have also been reported cases of persons experiencing tolerance with the need of dose titration for therapeutic benefit and withdrawal symptoms on abrupt medication discontinuation.^[1]

3.2 Associated risks

Despite no evidence in robust efficacy of gabapentin in off-label use,^[3] it is often used off-label 83%-95% of the time a prescription is written to treat a variety of non-indicated conditions including: insomnia, non-neuropathic pain conditions, drug and alcohol addiction, anxiety, bipolar disorder, borderline personality disorder, menopausal conditions, vertigo, pruritic disorder, and migraines.^[1] Clinical observations indicate fewer than 20% of patients with non-indicated diagnoses achieve substantial pain relief with the use of

gabapentin.^[2] In fact, discrete diagnoses such as fibromyalgia achieve only a 10%-20% improvement in pain rating on a ten point scale.^[2] Even so gabapentin prescriptions have soared in large part due to the historical perspective that there is no abuse potential. However, more recent data demonstrates almost one-third of gabapentin abusers maintain their use is for recreational purposes.^[4] In fact, a cohort population in rural Kentucky represented a 2,950% increase in the misuse of gabapentin since 2008.^[4] Reports indicate misuse can be as high as 65% even for those who legally obtained a prescription.^[1] The driving force for misuse typically develops from one of three aspects: recreational (to get high or replace other drugs as a cheaper alternative); self-harm; or self-medicate for pain or to treat withdrawal symptoms from other drugs.^[1]

Identified risks for gabapentin misuse in the literature are limited with the exception of a history of or current substance abuse particularly opioids.^[1] Unfortunately, gabapentin is often co-prescribed with opioids leading to a 49% increased risk of dying from an opioid overdose.^[7] This is believed to occur from increased gabapentin absorption by opioid slowing of the gastrointestinal tract resulting in increased respiratory depression. Compounding the problem is that benzodiazepines are often additionally co-prescribed for anxiety and/or sleep disturbances further exacerbating the respiratory depression.^[1] One study reports that among individuals taking prescribed opioids in concert with gabapentin, were at an appreciably heightened risk of opioid-related mortality.^[7] As such, it is quite important to not only understand the abuse risks associated with gabapentin but also how best to communicate such risks to both clinical providers and patients. In addition, close monitoring practices often associated with opioids and benzodiazepines (i.e., regular monitoring for aberrant drug taking behaviors, limits on supply, guarded dose titration) should be applied to that of gabapentin.^[8]

3.3 Additional considerations

Additional considerations for the prescribing clinician is understanding that pain management encompasses more than just pharmacotherapy. It should not be assumed that in and

of itself gabapentin is efficacious for most pain syndromes or is an appropriate substitute for opioids. At times, referral for cognitive behavioral therapy, physical therapy, and/or multidisciplinary pain practices may be warranted. In addition, realistic goals may not include complete elimination of pain but assisting patients to a level of coping and functionality.^[3]

4. DISCUSSION

Prescribers must not reason that gabapentin is an effectual method for the management of various pain conditions nor as a routine substitute for opioids.^[3] While it may be possible that gabapentinoids provide a potentially more innocuous non-opioid treatment modality, further examination is essential to more confidently characterize their proper place as analgesics. As there have been a myriad of authenticated occasions of gabapentin misuse, even in light of it being deemed as a medication assisted therapy go-to for those with other addictions, it is imperative that clinicians scrutinize drug-seeking behaviors to evaluate one's risk for abuse of gabapentin.^[9] Some purport that the most favorable means to contest gabapentin abuse is federal regulations and nationwide incorporation into prescription drug monitoring and reporting programs. In fact, a few states including Kentucky, Ohio, and West Virginia will or have already added gabapentin to the controlled substance rosters even though no federal designation is in place.^[10] More generally, solutions promoted by other studies include mediations by pharmaceutical companies, better-quality detection and oversight of gabapentin misusers by prescribers, various socioeconomic approaches, and development of available substance abuse treatment.^[11] While it has been employed by some patients to leverage the effects of opioids, further elevating concerns for misuse, gabapentin used within therapeutic doses may offer numerous benefits for some patients.^[12] Nevertheless, responsible clinicians will always be mindful of gabapentin's abuse potential through careful consideration of its suitability to be prescribed.

CONFLICTS OF INTEREST DISCLOSURE

The authors declare that there is no conflict of interest.

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