ECHO Diabetes Opioids & Diabetes

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Pre-question

In people with diabetes, opioids

- A. Are the preferred treatment for painful diabetic neuropathy
- B. Have no impact on glycemia
- C. Can increase hyperglycemia
- D. Reduce the risk of hypoglycemia

Where Did It Hurt? Over Half of U.S. Adults Felt Pain in 2019

- 1. Any pain in the last 3 months: 58.9% of U.S. adults
- 2. Back pain in the last 3 months: 39%
- 3. Lower limb pain in the last 3 months: 36.5%
- 4. Upper limb pain in the last 3 months: 30.7%
- 5. Head pain in the last 3 months: 22.4%
- 6. Abdomen, genital or pelvic pain in the last 3 months: 9.8%
- 7. Tooth or jaw pain in the last 3 months: 9.2%

Notes: from the National Health Interview Survey, 2019 (n = 31,997). Source: National Center for Health Statistics, <u>NCHS Data Brief No. 415</u>, July 2021

Neuropathy pain is the most common pain associated with diabetes. However, PWD can have pain from many other causes and can use/ misuse opioids for a variety of reasons.

What do we need to be aware of when our patients with diabetes are taking opioids?

The Impact of Opioids on People with Diabetes

- PWD can suffer the effects that are common to opioid use, but with additional impact
 - Respiratory suppression → "found down" (hypoglycemia vs opioid OD or *both* see below)
 - Impaired driving/other functions impact on safety & self-care skills
 - Impaired perceptions neglected self-management
 - Sedative effect- impaired recognition of hypoglycemia
 - Endocrine effect
 - Hypogonadism exacerbate excess adiposity/bone loss (metabolic syndrome/fracture risk)
 - Glycemia increased hyper and hypoglycemia risks

Is any of this clinically relevant?

- Does Opioid Therapy Affect Quality of Care for Diabetes Mellitus? Adam J. Rose, et al The American Journal of Managed Care, April 2009, Volume 15, Issue 4
- For people with diabetes, chronic pain is a barrier to the completion of self-care activities such as taking medications, exercising, and pursuing a prudent diet.
- VA study specifically examined the effect of opioid therapy for chronic pain on the quality of care for unrelated chronic conditions, such as diabetes
- Conclusions: Chronic opioid therapy among patients within the Veterans Affairs system is associated with
 - slightly worse diabetes performance measures compared with patients who do not receive opioids.
 - patients receiving higher dosages of opioids had additional decrements in diabetes performance measures.

However, ...

The impact can be greater than diabetes performance measures ...

Impact of Opioids on the Endocrine System

Opioid receptors mediate the actions of endogenous and exogenous opioids and are present in the brain and throughout the body, including the endocrine organs, such as the adrenal cortex and the gonads

Effects include:

- Increase GH, TSH and prolactin
- Decrease LH, testosterone, estradiol, and oxytocin
- Hypogonadism
- An effect on the secretion of other pituitary hormones
- A decrease or increase of food intake
- Hyperglycemia
- Impaired insulin secretion

Additional studies have found:

- Blunted counterregulatory responses to hypoglycemia
- Induced hypoglycemia in people with & without diabetes (Tramadol & Methadone)

Opioid Induced Hypogonadism

- Common with all forms of opioids
 - Central hypogonadism (low LH and FSH)
 - Both men and women but more frequent in men
- Hypogonadism accelerates bone loss/osteoporosis
 - Low bone density & fracture risk is already increased in diabetes
 - Fracture risk increased by some diabetes medications & by hypoglycemia
- Hypogonadism leads to altered body composition with increased fat mass/ reduced muscle mass
 - Excess adiposity already a concern for both T2DM and T1DM
- Hypogonadism (especially in males) increases insulin resistance & metabolic syndrome

Opioid Induced Hyperglycemia

- Opioid administration leads to hyperglycemia and worsening diabetes.
 - The mechanisms that cause hyperglycemia appear to be
 - decreased insulin secretion
 - acting indirectly via the sympathetic nervous system
 - Additionally, hyperglycemia decreases the antinociceptive (pain blocking) properties of opioids.
 - More studies are needed to explore the interactions between opioids and insulin secretion/insulin resistance.

"In both humans and animal models, opioid administration leads to a metabolic state similar to diabetes as well as worsening diabetes by decreasing insulin secretion"

MORPHINE, OPIOID PEPTIDES, AND PANCREATIC ISLET FUNCTION

- Interaction of opiates with the endocrine pancreas:
 - The results of animal studies performed in vitro do not allow any conclusion to be drawn, because the effects of opioid peptides on pancreatic hormone release seem dependent on many variables, including the agent investigated, dose administered, concentration of glucose in the medium, and experimental procedure used.
 - Narcotic use disorder offers a model to evaluate the hormonal and metabolic effects of a chronically administered agent that binds and activates endogenous receptors.
 - In these subjects, it is possible to find *increased concentrations of glycosylated hemoglobin A1* and a *marked reduction of the acute insulin response* to intravenous glucose, but not to arginine, which suggests a *state of defective glucose recognition by pancreatic 6-cells during narcotic addiction*.
 - "Thus, the heroin addict, like patients with non-insulin-dependent diabetes, does not respond appropriately to glucose signals."

Blunted Counterregulatory Response to Hypoglycemia

- Recurrent and/or antecedent hypoglycemia and/or exercise causes blunting of protective counterregulatory responses, known as hypoglycemia-associated autonomic failure (HAAF) and exerciseassociated autonomic failure (EAFF)
 - Robust data point to a key role of the *endogenous opioid system* in the development of hypoglycemia-associated autonomic failure (HAAF) and exercise-associated autonomic failure (EAAF).
 - Opioid receptor activation induces HAAF in humans
 - Morphine induced an ~30% reduction in plasma epinephrine response together with reduced endogenous glucose production (EGP) and reduced hypoglycemia-associated symptoms

Tramadol Induced Hypoglycemia

- There have been several case reports describing **hypoglycemia induced by tramadol** and resolved upon its discontinuation
 - These incidences occurred in *both patients with and without diabetes*
 - Based on previous evidence from animal studies, tramadol induced hypoglycemia has been attributed to μ-opioid receptor agonist (MOR) agonism or serotonin modulation. Another possible etiology of hypoglycemia could be related to N-methyl-D-aspartate receptors (NMDAR) antagonism
 - Studies based on animal models have demonstrated that tramadol directly induced glucose utilization by hepatocytes and skeletal muscles via μ-opioid receptor activation.
 - Other animal studies have demonstrated the role of serotonin in glucose metabolism via insulin modulation
- Only methadone from the opioid cohort behaves similarly to tramadol and has an association with hypoglycemia

Tramadol Use and the Risk of Hospitalization for Hypoglycemia in Patients With Noncancer Pain

Clinical Pharmacy and Pharmacology | JAMA Internal Medicine | JAMA Network

- In a pharmacovigilance study, tramadol-induced hypoglycemia occurred rapidly after initiation—within 10 days of treatment.
 - In over 40% of the cases, there were no known risk factors, such as diabetes mellitus
 - Tramadol may induce hypoglycemia through its dual effects on μ opioid receptors and inhibitory activity on serotonin-norepinephrine reuptake.
- We found that tramadol use is associated with an increased risk of hospitalization for hypoglycemia, with the *risk highest around the time of treatment initiation*.
 - These results were corroborated in cohort and case-crossover analyses, which also associated tramadol use with a more than 3-fold increased risk of hospitalization for hypoglycemia.
 - Overall, these results remained robust in several secondary analyses, including among patients not using any antidiabetic drugs, as well as in sensitivity analyses.

Opioids not very effective for DPN pain

- Many endocrinologists avoid opioids altogether when it comes from pain specifically caused by diabetic neuropathy.
 - "By far and away, painful diabetic peripheral neuropathy (DPN) is the number one cause of diabetes-related pain ... It has been *recognized for decades that DPN does not respond well to opioids*." Timothy Graham MD – endocrinology Intermountain Health Utah
 - "Opioids are generally avoided in management of diabetic neuropathy. The risk of habituation is higher due to the chronic nature of the pain process. The preferred medications include pregabalin (Lyrica) and duloxetine (Cymbalta), which have FDA indications and low risk of dependence." Pedro Cazabon MD Ochsner Health Louisiana
- The chronic pain from diabetes also puts patients at risk of addiction if opioids are prescribed.
 - "When using opioids, it becomes difficult to tell what is the medication requirement due to pain and what is the requirement due to dependence."

Trends in Pain Medication Initiation Among Patients With Newly Diagnosed Diabetic Peripheral Neuropathy, 2014-2018

Jungwei Fan, PhD; Molly Moore Jeffery, PhD; W. Michael Hooten, MD; Nilay D. Shah, PhD; Rozalina G. McCoy, MD, MS JAMA Netw Open. 2021;4(1):e2035632. doi:10.1001/jamanetworkopen.2020.35632 January 28, 2021

- Diabetic peripheral neuropathy (DPN) affects approximately half of people living with diabetes.
- Approximately half of patients with DPN have pain resulting in debility, disability, and impaired quality of life.
- Clinical guidelines recommend use of anticonvulsants, antidepressants (serotoninnorepinephrine reuptake inhibitors, tricyclic antidepressants), or topical analgesics for painful DPN owing to their demonstrated efficacy and safety in this context.
- The study examined initiation of pain medication among adults with newly diagnosed DPN.
- Results: Overall, 43.8% patients initiating therapy were prescribed opioids compared with 42.9% who were prescribed guideline-recommended medications.

Such high rates of opioid use by patients with DPN, a lifelong pain syndrome, are concerning because safer effective treatment options are available.

Trends in Pain Medication Initiation Among Patients With Newly Diagnosed Diabetic Peripheral Neuropathy, 2014-2018 – Medscape discussion

- For painful neuropathic pain, duloxetine [Cymbalta], pregabalin [Lyrica], and gabapentin [Neurontin] are the most effective pain medications based on multiple studies and extensive experience using them
 - Despite these meds being first line, prescriptions for opioids as a first-line treatment for painful diabetic peripheral neuropathy (DPN) outnumbered those for other medications between 2014 and 2018, even though the former is not recommended, new research indicates.
- "When a patient comes with severe pain, I think there's that kind of gut feeling that if the pain is severe, I need to give opioids." senior author Rozalina G. McCoy, MD, an endocrinologist and primary care clinician at the Mayo Clinic in Rochester, Minnesota
- What's more, she noted, "Evidence is emerging for other harms, not only the potential for dependency and potential overdose, but also the *potential for opioid-induced hyperalgesia*. Opioids themselves can cause chronic pain. When we think about using opioids for chronic pain, we are really shooting ourselves in the foot. We're going to harm patients."

That's true even for severe DPN pain or painful exacerbations, she added.

- "There's a myth that opioids are the strongest pain meds possible...," she explained.
- The American Diabetes Association DPN guidelines essentially say as much, advising opioids only as a tertiary option for refractory pain, she observed.

Diabetic Neuropathy: A Position Statement by the American Diabetes Association

https://care.diabetesjournals.org/content/40/1/136

Pain Management - Recommendations

- Consider either pregabalin or duloxetine as the initial approach in the symptomatic treatment for neuropathic pain in diabetes. A
- Gabapentin may also be used as an effective initial approach, taking into account patients' socioeconomic status, comorbidities, and potential drug interactions. B
- Although not approved by the U.S. Food and Drug Administration, tricyclic antidepressants are also
 effective for neuropathic pain in diabetes but should be used with caution given the higher risk of serious
 side effects. B
- Given the high risks of addiction and other complications, the use of opioids, including tapentadol or tramadol, is not recommended as first- or second-line agents for treating the pain associated with DSPN.
 E

Trends in Pain Medication Initiation Among Patients With Newly Diagnosed Diabetic Peripheral Neuropathy, 2014-2018 – Medscape discussion

Dr. McCoy Offers Clinical Pearls for Treating Pain in DPN - Individualize treatment for painful DPN – "you maximize benefit if you use one drug to treat multiple things"

- "I tend to use duloxetine if the patient also has a mood disorder including depression or anxiety, because it can also help with that."
- "Gabapentin can also be helpful for radiculopathy or for chronic low back pain. It can even help with degenerative joint disease like arthritis of the knees."
- "Gabapentin can cause drowsiness, which makes it ideal for a patient with insomnia but much less so for a long-haul truck driver. Duloxetine doesn't cause sleepiness. Pregabalin can, but less so than gabapentin."
- All three of the recommended medications are generic now, although pregabalin still tends to be more expensive, she noted.

Summary

- In addition to risks common to all persons who use opioids
 - Opioid use can impair diabetes self-management
 - Opioid use can cause hypogonadism which, among other things, can worsen insulin resistance and metabolic syndrome
 - Opioid use can cause/worsen hyperglycemia, likely due to impaired insulin secretion
 - Opioid use can reduce awareness of hypoglycemia via a sedative effect and by blunting the autonomic response to hypoglycemia
 - Tramadol and Methadone can cause hypoglycemia in people with or without diabetes
 - Opioids are not the recommended treatment of painful diabetic neuropathy
 - The recommended agents are usually more effective & can be individualized

Post-question

In people with diabetes, opioids

- A. Are the preferred treatment for painful diabetic neuropathy
- B. Have no impact on glycemia

C. Can increase hyperglycemia

D. Reduce the risk of hypoglycemia