# MIGRAINE MANAGEMENT: PATIENTS WITH CHALLENGING CO-MORBIDITIES

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33rd Annual Internal Medicine Review
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# DISCLOSURES

NONE

# OVERVIEW

1

Use of estrogen in both young and older patients with migraine with visual aura

2

Available treatment options for migraine patients with liver disease

3

Available treatment options for migraine patients with kidney disease.

# CASE 1

- 49 yo woman with pmh significant for migraine with visual aura since her teens, anxiety, who initially presented to our clinic with episodic headaches.

She reports 2-4 headache days per month

Headaches are described as severe, throbbing, usually located on the left side, around her left eye, temple.

Headaches are associated with nausea, dizziness, light, sound and smell sensitivity.

# CASE 1

Headaches can last all day, but rarely overnight.

Visual auras are described as "rainbow prism" in both eyes lasting about 15 minutes.

Auras occur about once per month

- Exam is normal
- She is currently on Mirtazapine 7.5 mg for sleep and Clonazepam 0.25 mg as needed for anxiety
- She uses Ibuprofen to break her headaches but does not always find it effective.

# International Headache Society (IHS)


The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211.

# Migraine without aura diagnosis criteria


A. ≥5 attacks fulfilling criteria B-D
B. Attacks (untreated) last 4-72 hours
C. ≥2 of the following 4 characteristics
   - Unilateral location
   - Pulsating quality
   - Moderate or severe pain intensity
   - Aggravation by or causing avoidance of routine physical activity
D. During headache ≥1 of the following
   - Nausea and/or vomiting
   - Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis



International Headache Society. *Cephalalgia*. 2018;38(1):1-211.

# Migraine with aura diagnosis criteria

IHS Classification ICHD-3

A. ≥2 attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms:
- ❑ Visual
- ❑ Sensory
- ❑ Speech and/or language
- ❑ Motor
- ❑ Brainstem
- ❑ Retinal

C. At least three of the following six characteristics
- ❑ at least one aura symptom spreads gradually over ≥5 minutes
- ❑ two or more aura symptoms occur in succession
- ❑ each individual aura symptom lasts 5-60 minutes[1]
- ❑ at least one aura symptom is unilateral[2]
- ❑ at least one aura symptom is positive[3]
- ❑ the aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis

1. When for example three symptoms occur during an aura, the acceptable maximal duration is 3×60 minutes. Motor symptoms may last up to 72 hours.
2. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.
3. Scintillations and pins and needles are positive symptoms of aura

International Headache Society. *Cephalalgia*. 2018;38(1):1-211.

# CASE 1

Before we can discuss any treatment options, she has more information for us and some questions.

# CASE 1

She reports experiencing night sweats, difficulty sleeping for the last 5 years.

Her menstrual cycles are not as regular as they used to be.

She believes she is in perimenopause.

She also notes that she gained 30 lbs in the last few years.

- She would like to try hormone replacement therapy, but her PCP told her to check with neurology first.

# CAN MIGRAINE PATIENTS WITH VISUAL AURA BE ON HRT?

# WHICH OF THESE STATEMENTS IS CORRECT?

A. Hormone replacement therapy should only be offered to patients with migraine without aura

B. Progesterone only should be used for patient with migraine with aura

C. Migraine with aura is NOT an absolute contraindication for hormone replacement therapy including both estrogen and progesterone

# PERIMENOPAUSE

Perimenopause stage consists of the the period of 2-8 years prior to menopause in addition to the year after the end of menses.

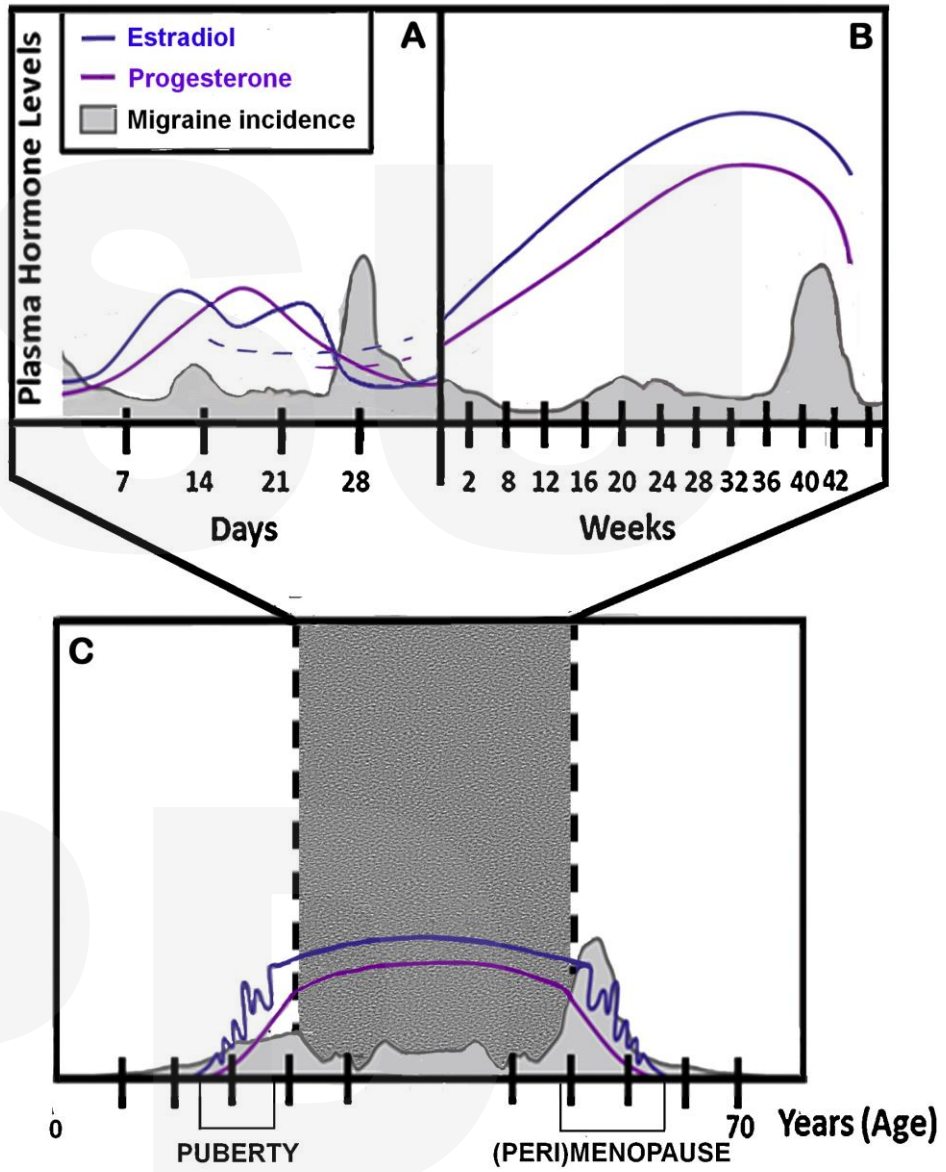
It is associated with symptoms associated with estrogen deficit due to a decline in ovaries' functions.

- Theses symptoms include:
  - night sweats
  - hot flashes
  - joint pain
  - vaginal dryness
  - sleep disturbances
  - decreased libido
  - irritability

Ibrahimi et al, 2014

# ESTROGEN FLUCTUATIONS AND MIGRAINE

Prevalence and frequency of migraines is affected by fluctuation in estrogen levels: puberty, pregnancy and menopause




Migraine incidence and female hormones during the menstrual cycle, pregnancy and a woman's life.

Ibrahimi et al, *Maturas,* 2014

# PERIMENOPAUSE

- STABILIZING ESTROGEN LEVELS SHOULD THEORETICALLY HELP MIGRAINES
- HRT (INCLUDING ESTROGEN) IS COMMONLY IN THIS PATIENT POPULATION TO CONTROL VASOMOTOR SYMPTOMS.

# MIGRAINE WITH AURA

Associated with an increased risk of ischemic stroke (~2-fold increase)

Concomitant use of oral contraceptive was associated with a ~7-fold increase of ischemic stroke

Smoking was associated with a ~9-fold increase of ischemic stroke

Spector et al. *Am J. Med.* 2010
MacClellan et al. *Stroke* 2007
Schürks et al. *BMJ* 2009

HOWEVER….

Risks were shown in younger patients ( < 45yo)

Combined Oral Contraceptive- high dose of estrogen (≥ 50 µg of ethinyl estradiol )

Sacco et al. *J Headache and Pain* 2012

Headache

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doi: 10.1111/head.12960
Published by Wiley Periodicals, Inc.

# Review Articles

## Hormonal Contraceptives and Migraine With Aura—Is There Still a Risk?

Anne H. Calhoun, MD, FAHS

**Unnecessary confusion still surrounds the use of combined hormonal contraceptives (CHCs) in the setting of migraine with aura (MwA). Clearing this confusion is a key issue for headache specialists, since most women with migraine have menstrual-related migraine (MRM), and some CHCs can prevent this particularly severe migraine. Their use, however, is still restricted by current guidelines due to concerns of increased stroke risk – concerns that originated over half a century ago in the era of high dose contraceptives. Yet studies consistently show that stroke risk is not increased with today's very low dose CHCs containing 20-25 μg ethinyl estradiol (EE), and continuous ultra low-dose formulations (10-15 μg EE) may even reduce aura frequency, thereby potentially decreasing stroke risk.**

**This article clarifies the stroke risk of CHCs and examines their impact on migraine. It also examines how stroke risk is altered by the estrogen content of the CHC, by contributing factors such as smoking, age and hypertension, and by aura frequency. And finally, it puts these risks into a meaningful context with a risk/benefit assessment.**

**Key words: aura, hormonal contraceptive, migraine, stroke risk**

(*Headache* 2017;57:184-193)

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Stroke

RESEARCH ARTICLE | Originally Published 9 August 2007 |

Check for updates

# Probable Migraine With Visual Aura and Risk of Ischemic Stroke: The Stroke Prevention in Young Women Study

Leah R. MacClellan, PhD, Wayne Giles, MD, John Cole, MD, Marcella Wozniak, MD, Barney Stern, MD, Braxton D. Mitchell, PhD, and Steven J. Kittner, MD | AUTHOR INFO & AFFILIATIONS

Stroke • Volume 38, Number 9 • https://doi.org/10.1161/STROKEAHA.107.488395

***Methods***— Using data from a population-based, case-control study, we studied 386 women ages 15 to 49 years with first ischemic stroke and 614 age- and ethnicity-matched controls. Based on their responses to a questionnaire on headache symptoms, subjects were classified as having no migraine, probable migraine without visual aura, or probable migraine with visual aura (PMVA).

# FREQUENCY OF VISUAL AURA & LIFETIME DURATION AFFECT STROKE RISK

**TABLE 3. Effect of Severity, Frequency, and Duration of PMVA on Stroke Risk (OR and 95% CI)**

| | Cases With PMVA/Cases Without Migraine | Controls With PMVA/Controls Without Migraine | OR (95% CI)* | OR (95% CI)† |
|---|---|---|---|---|
| Frequency | | | | |
| ≤12 per year | 65/206 | 111/360 | 1.1 (0.7–1.6) | 0.9 (0.6–1.4) |
| >12 per year | 80/206 | 64/360 | 2.2 (1.5–3.3) | 1.7 (1.1–2.8) |
| Severity‡ | | | | |
| Nonsevere | 78/206 | 97/360 | 1.5 (1.0–2.2) | 1.3 (0.8–1.9) |
| Severe | 64/206 | 77/360 | 1.4 (0.9–2.1) | 1.1 (0.7–1.8) |
| Lifetime duration§ | | | | |
| >12 years | 62/206 | 68/360 | 1.5 (1.0–2.3) | 1.2 (0.8–1.9) |
| 1–12 years | 52/206 | 92/360 | 1.0 (0.6–1.5) | 0.7 (0.5–1.2) |
| <1 year | 17/206 | 5/360 | 6.8 (2.4–20.0) | 8.3 (2.6–25.7) |

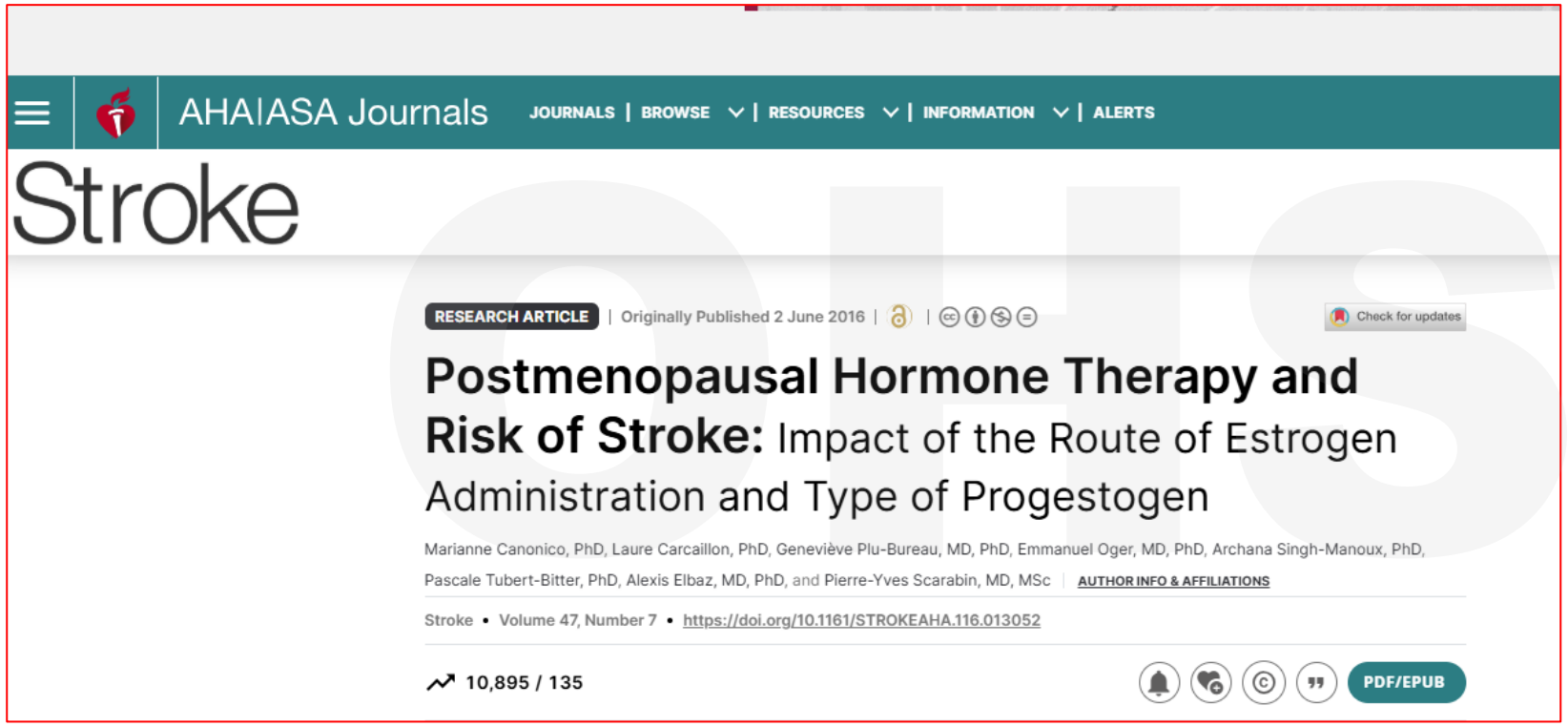
*Adjusted for study period, age, race, and geographic region.
†Adjusted for study period, age, race, geographic region, smoking, diabetes, hypertension, MI, and OC use.
‡Three cases and 1 control with missing data.
§Fourteen cases and 10 controls with missing data. Index date was stroke date for cases and within 1 week of interview date for controls.

Frequency of aura associated with stroke risk
Date of onset of aura also associated with stroke risk

# YOUNGER PATIENTS WITH VISUAL AURA

- No absolute contraindication to estrogen
  - Low estrogen formulation (10-25 μg of EE)
  - Monitor visual aura (less risk < 1/m)
  - Lifetime duration (avoid within the first year of diagnosis)

# HOW ABOUT OUR PATIENT (49 YO) IN PERIMENOPAUSE?



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Stroke

RESEARCH ARTICLE | Originally Published 2 June 2016 | Check for updates

# Postmenopausal Hormone Therapy and Risk of Stroke: Impact of the Route of Estrogen Administration and Type of Progestogen

Marianne Canonico, PhD, Laure Carcaillon, PhD, Geneviève Plu-Bureau, MD, PhD, Emmanuel Oger, MD, PhD, Archana Singh-Manoux, PhD, Pascale Tubert-Bitter, PhD, Alexis Elbaz, MD, PhD, and Pierre-Yves Scarabin, MD, MSc | AUTHOR INFO & AFFILIATIONS

Stroke • Volume 47, Number 7 • https://doi.org/10.1161/STROKEAHA.116.013052

10,895 / 135 PDF/EPUB

**Methods—**

We set up a nested case–control study of ischemic stroke (IS) within all French women aged 51 to 62 years between 2009 and 2011 without personal history of cardiovascular disease or contraindication to hormone therapy. Participants were identified using the French National Health Insurance database, which includes complete drug claims for the past 3 years and French National hospital data. We identified 3144 hospitalized IS cases who were matched for age and zip code to 12 158 controls. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI).

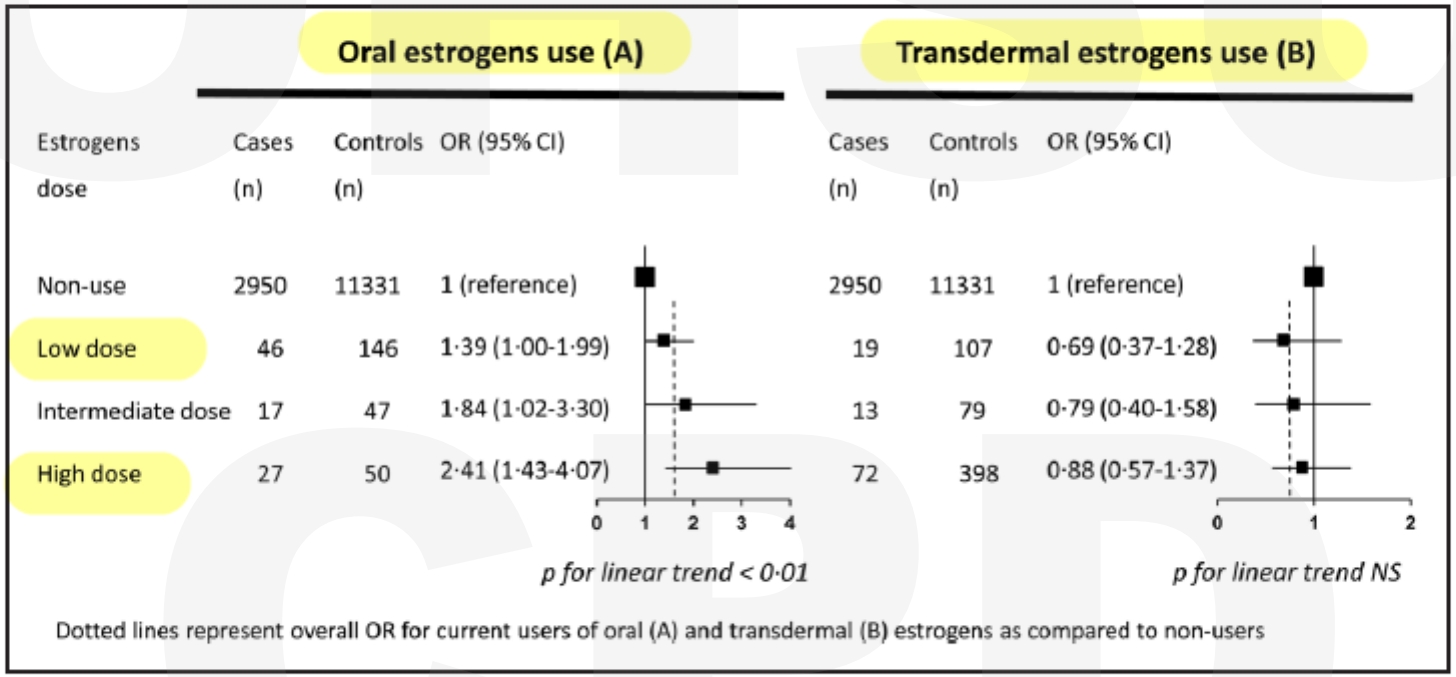


**Figure 2.** Odds ratios of ischemic stroke according to estrogen dose by route of administration. Dotted lines represent overall OR for current users of oral (**A**) and transdermal (**B**) estrogens compared with nonusers. CI indicates confidence interval; and OR, odds ratio.

Transdermal estrogen seems to be the safest option for hormone therapy

# TRANSDERMAL VS ORAL ESTROGEN

- Oral estrogen has a prothrombic effect- passes through the liver and increases increase prothrombotic substances like clotting factors VII, IX, or fibrinogen.

- Transdermal estrogen enters blood stream directly, bypasses the liver and consequently does not affect clotting factors.

***Progesterone-necessary if patients has intact uterus (to prevent endometrial growth can happen with unopposed estrogen)

# WHICH OF THESE STATEMENTS IS CORRECT?

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C. Migraine with aura is NOT an absolute contraindication for hormone replacement therapy including both estrogen and progesterone

# CASE 1

- 49 yo woman with pmh significant for migraine with visual aura since her teens, anxiety, who reports 2-4 migraine per month.
- She uses Ibuprofen to break her headaches but does not always find it effective.
- She is currently on Mirtazapine 7.5 mg for sleep and Clonazepam 0.25 mg as needed for anxiety

# ACUTE TREATMENT OF MIGRAINE

## Effective

- Triptans: Sumatriptan, Rizatriptan, Eletriptan, Naratriptan, Zolmitriptan,Frovatriptan, Almotriptan
- Ergotamines: Dihydroergotamine nasal spray, IV DHE
- Gepants (calcitonin gene-related peptide receptor antagonists): Ubrogepant, Rimegepant, Zavegepant
- Lasmiditan
- NSAIDs OTC: aspirin, ibuprofen, naproxen, combination analgesics
- Prescription NSAIDs: celecoxib oral solution, diclofenac

## Probable Effective

- NSAIDs: ketoprofen, IV and IM ketorolac
- Ergotamine/caffeine
- Antiemetics: prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide
- IV Magnesium

Ailani J et al. The American Headache Society consensus statement: update on integrating new migraine treatments into clinical practice. Headache 2021;61(7):1021–1039

# CASE 1: ADDITIONAL INFORMATION

- Social history: works as a teacher in middle school
- Does not smoke or uses drugs
- Drinks 4-6 glasses of wine per evening, since graduate school
- ➔ Liver disease?

# LIVER DISEASE: CHILD-PUGH CLASSIFICATION

- Class A: Normal liver function (5-6 pts)
- Class B: Reduced liver function (7-9 pts)
- Class C: Severe liver dysfunction (10-15 pts)

| Parameter | Points assigned | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Ascites | Absent | Slight | Moderate |
| Bilirubin | <2 mg/dL (<34.2 micromol/L) | 2 to 3 mg/dL (34.2 to 51.3 micromol/L) | >3 mg/dL (>51.3 micromol/L) |
| Albumin | >3.5 g/dL (35 g/L) | 2.8 to 3.5 g/dL (28 to 35 g/L) | <2.8 g/dL (<28 g/L) |
| Prothrombin time (seconds over control) or | <4 | 4 to 6 | >6 |
| INR | <1.7 | 1.7 to 2.3 | >2.3 |
| Encephalopathy | None | Grade 1 to 2 | Grade 3 to 4 |

*Uptodate.com*

# WHICH OF THESE STATEMENTS IS CORRECT IN PATIENTS WITH LIVER DISEASE?

A. Triptans should not be offered to patients with liver disease

B. Ergotamines are safe to use in patients with liver disease

C. Gepants such as Ubrogepant may be used in patients with liver disease

# Migraine Management in Medically Complex Patients: a Narrative Review

Review | Published: 29 July 2024

Volume 24, pages 423–438, (2024) Cite this article



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Megan A. Hird & Claire H. Sandoe

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**Table 1** Acute migraine treatment dose recommendations in renal, hepatic, and cardiovascular disease

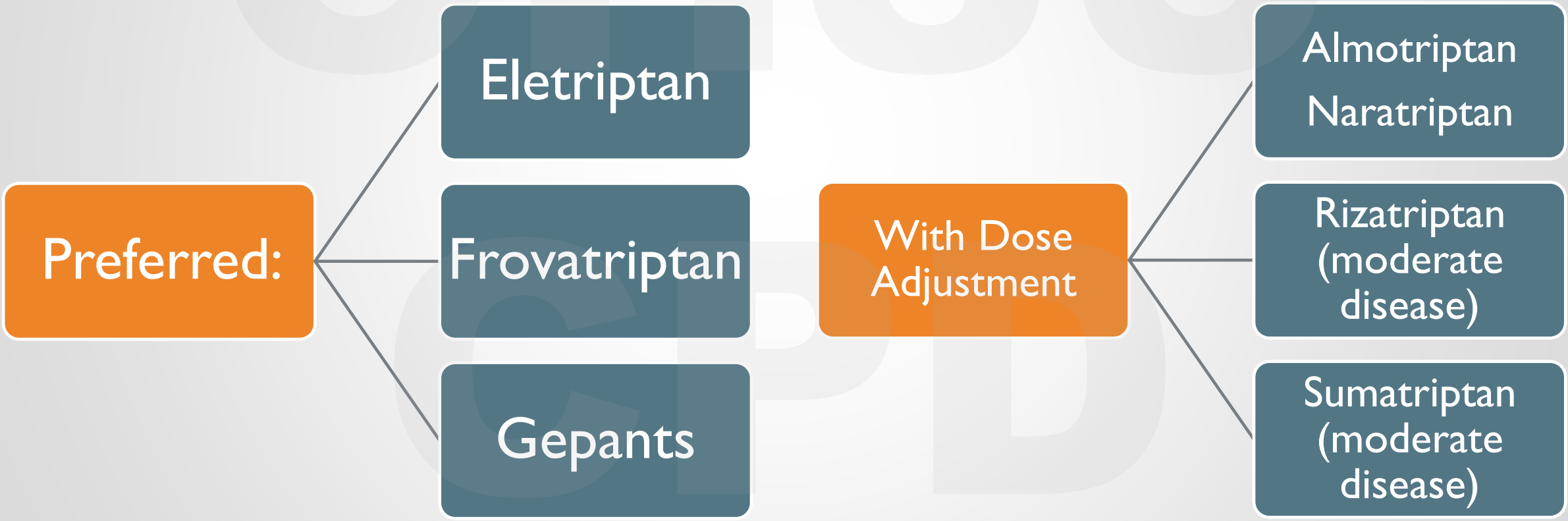
| | Renal impairment | Liver impairment | Cardiovascular disease |
|---|---|---|---|
| Nerve blocks | No recommendations available | No recommendations available | No recommendations available |
| Simple analgesics | | | |
| Acetaminophen | CrCl>50 mL/min: 4-hour intervals<br>CrCl 10-50 mL/min: 6-hour intervals<br>CrCl <10mL/min: 8-hour interval | Mild/moderate: max 2–3 g in 24 h<br>Severe: contraindicated | No dose adjustments |
| NSAIDs | Mild/moderate: avoid; if required, use at lower doses<br>Severe (CrCl <30 mL/min): contraindicated | Mild/moderate: avoid; if required, use at lower doses<br>Severe: contraindicated | Caution in CVD/CVRF (exception: anti-platelets)<br>Contraindicated: severe HF and cerebrovascular bleeding<br>Highest risk: Celecoxib, diclofenac, ibuprofen |
| Ergotamine | | | |
| Dihydroergotamine | Mild/moderate: No dose recommendations available<br>Severe: contraindicated | Mild/moderate: No dose recommendations available<br>Severe: contraindicated | Contraindicated |
| Anti-Emetics | | | |
| Metoclopramide | Mild: no dose adjustment<br>Moderate/severe: max dose 30 mg in 24 h<br>End-stage/dialysis: max dose 20 mg in 24 h | Mild: no dose adjustment<br>Moderate/severe: max dose 30 mg in 24 h | Caution |
| Prochlorperazine | Mild/moderate: caution (no specific data available)<br>Severe: contraindicated | Mild/moderate: caution (no specific data available)<br>Severe: contraindicated | Caution |
| Triptans | | | |
| Almotriptan | Mild/moderate: No dose adjustment<br>Severe: avoid/caution (max dose 12.5 mg in 24 h) | Mild/moderate: caution; 6 mg initial dose (max 12.5 mg in 24 h)<br>Severe: contraindicated | Contraindicated |
| Eletriptan | Mild/moderate: No dose adjustment<br>Severe: avoid/caution (max dose 20 mg in 24 h) | Mild/moderate: no dose adjustment<br>Severe: contraindicated | Contraindicated |
| Frovatriptan | Mild/moderate: No dose adjustment<br>Severe: No dose adjustment | Mild/moderate: no dose adjustments<br>Severe: contraindicated | Contraindicated |
| Naratriptan | CrCl >15mL/min: initial dose 1 mg; max dose 2.5 mg in 24 h<br>End stage: contraindicated | Mild/moderate: initial dose 1 mg; max dose 2.5 mg in 24 h<br>Severe: contraindicated | Contraindicated |
| Rizatriptan | Mild/moderate: No dose adjustment<br>Severe: avoid/caution (5 mg initial dose; max 10 mg in 24 h) | Mild: No recommendations available<br>Moderate: caution; if required, 5 mg initial dose (max 10 mg in 24 h)<br>Severe: contraindicated | Contraindicated |
| Sumatriptan | Mild/moderate: contraindicated<br>Severe: contraindicated | Mild/moderate: oral/ intranasal contraindicated; no dose adjustment for SC (6 mg)<br>Severe: Contraindicated | Contraindicated |
| Zolmitriptan | Mild/moderate: No dose adjustment<br>Severe: No dose adjustment | Mild: no recommendations available<br>Moderate/severe: caution; doses <2.5 mg (initial 1.25 mg) with BP monitoring | Contraindicated |
| Selective serotonin receptor agonist | | | |
| Lasmiditan | Mild/moderate: No dose adjustment<br>Severe: No dose adjustment | Mild/moderate: no dose adjustment<br>Severe: Not studied, recommended to avoid | No dose adjustment available |
| Gepants | | | |
| Rimegepant | Mild/moderate: no dose adjustment<br>Severe: no dose adjustment<br>End-stage/dialysis: avoid use | Mild/moderate: no dose adjustment<br>Severe: avoid use | No dose recommendations available |



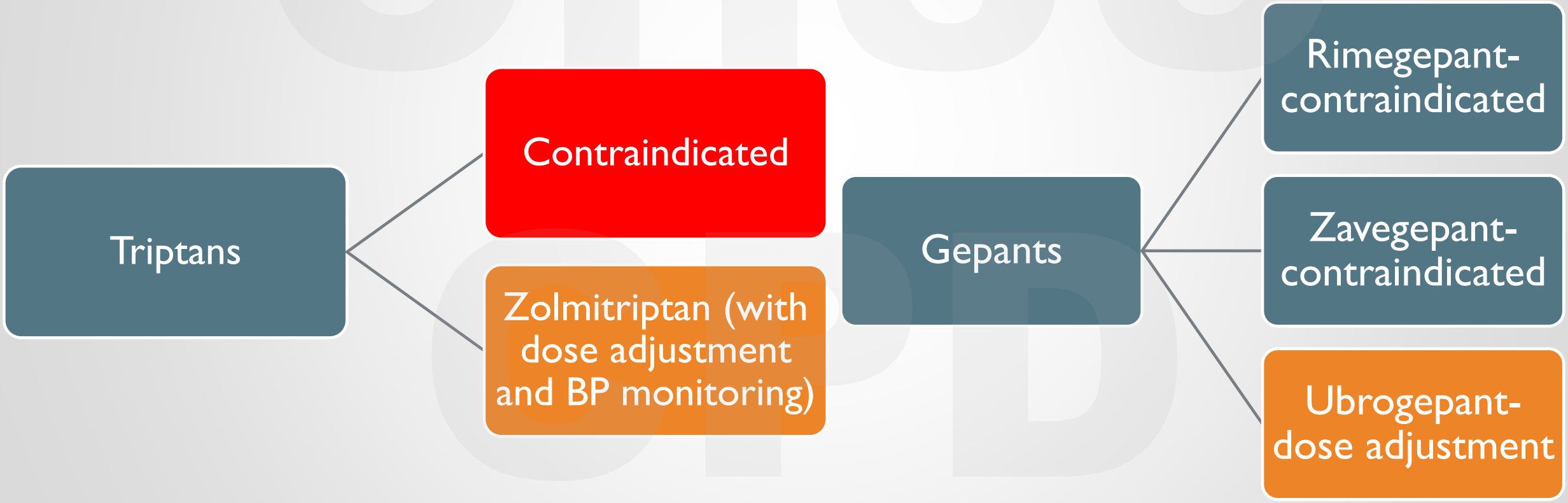
**Table 2** Preventive migraine treatment dose recommendations in renal, hepatic, and cardiovascular disease

| | Renal impairment | Liver impairment | Cardiovascular disease |
|---|---|---|---|
| TCAs | | | |
| Amitriptyline | No dose adjustment required | Caution; reduced dosing and close monitoring in mild, moderate, and severe† | Avoid use; if required, start at low dose with baseline/periodic ECGs† |
| Nortriptyline | No dose adjustment required | Caution; reduced dosing and close monitoring in mild, moderate, and severe† | Avoid use; if required, start at low dose with baseline/periodic ECGs† |
| SNRIs | | | |
| Duloxetine | Mild/moderate: no dosing information available<br>Contraindicated in severe and end-stage renal disease (CrCl<30 mL/min) | Contraindicated | Avoid use (not studied) |
| Venlafaxine | Mild/moderate: reduce dose by 25-50%<br>Severe/hemodialysis: reduce by at least 50% | Mild/moderate: reduce total daily dose by 50%<br>Severe: reduce daily dose >50% (initial dose of 37.5 mg) | Avoid use (not studied) |
| Beta-Blockers | | | |
| Atenolol | Caution<br>CrCl 15-35 mL/min: max dose 50 mg in 24 h<br>CrCl<15 mL/min: max 25 mg in 24 h | Caution; no dose recommendation available | No dose adjustment required* |
| Metoprolol | Caution; no dose adjustment is generally needed | Caution; reduce initial and maintenance dose† | No dose adjustment required* |
| Nadolol | Caution; no dose recommendation available<br>CrCl > 50 mL/min dosing interval 24 h<br>CrCl 31-50 mL/min dosing interval 24–36 h<br>CrCl 10-30 mL/min dosing interval 24–48 h<br>Cr Cl <10 mL/min dosing interval 40–60 h | Caution; no dose recommendation available | No dose adjustment required* |
| Propranolol | Caution; (no specific recommendations, start low dose) | Caution; Mild/moderate: reduce dose†<br>Severe: reduce initial dose to 20 mg TID | No dose adjustment required* |
| Timolol | Caution; no dose recommendation available | Caution; no dose recommendation available | No dose adjustment required* |
| ACEi/ARB | | | |
| Candesartan | Mild: no dose adjustment<br>Moderate/Severe/Dialysis: lower initial dose (limited data available) † | Mild/moderate: No dose adjustment<br>Severe: caution; lower initial dose of 4 mg | No dose adjustment required |
| Lisinopril | Mild/moderate: No dose adjustment<br>CrCl 10-30 mL/min: half initial dose, up-titrate to max 40 mg in 24 h<br>CrCl<10 mL/min or dialysis: contraindicated | Caution; if required, baseline liver tests and close monitoring | No dose adjustment required |
| Calcium Channel Blocker | | | |
| Verapamil | Caution (no specific dose recommendations available); if required, monitor for abnormal PR prolongation and other signs of overdose | Mild/moderate: caution (no specific dose recommendations available)<br>Severe: contraindicated | No dose adjustment required** |
| Anti-Convulsant | | | |
| Topiramate | Caution; CrCl<70 ml/min, half initial dose recommended (no specific recommendations) | Caution (no specific recommendations) | No dose adjustment required |
| Valproic Acid | No dose adjustment required | Contraindicated | No dose adjustment required |

# MILD TO MODERATE LIVER DISEASE



# IN SEVERE LIVER DISEASE



# WHICH OF THESE STATEMENTS IS CORRECT IN PATIENTS WITH LIVER DISEASE?

A. Triptans should not be offered to patients with liver disease

B. Ergotamines are safe to use in patients with liver disease

C. Gepants such as Ubrogepant may be used in patients with liver disease

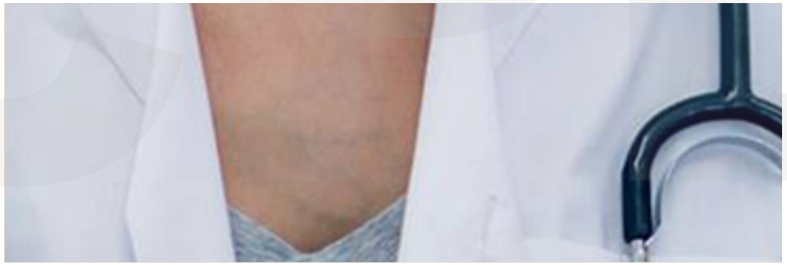
# CASE 1

49 yo F with migraine with aura, episodic migraine

- Dx with mild liver disease (Child Pugh Class A)
- Eletriptan was given
- What about her question about HRT?
- Transdermal estrogen-not contra-indicated with her diagnosis of liver disease
  - Considered the safer options
    - for women with non-alcoholic fatty liver disease
    - for women have undergone liver transplantation

Kim et al. Different effects of menopausal hormone therapy on non-alcoholic fatty liver disease based on the route of estrogen administration. Sci Rep 2023;13: 15461
Appelberg et al. Safety and efficacy of transdermal estradiol replacement therapy in postmenopausal liver transplanted women. Acta Obstetricia et Gynecologica Scandinavica 1998; 77: 660-664

# SHE HAS ONE MORE QUESTION



# CASE 1

She reports experiencing night sweats, difficulty sleeping for the last 5 years.

Her menstrual cycles are not as regular as they used to be.

She believes she is in perimenopause.

She also notes that she gained 30 lbs in the last few years.

- She would like to lose weight and has heard that GLP-1 agonist can also help with headaches.

# GLP-1 AGONIST FOR HEADACHES: IS IT REAL?

Krajnc et al. The Journal of Headache and Pain (2023) 24:89
https://doi.org/10.1186/s10194-023-01631-z

The Journal of Headache and Pain

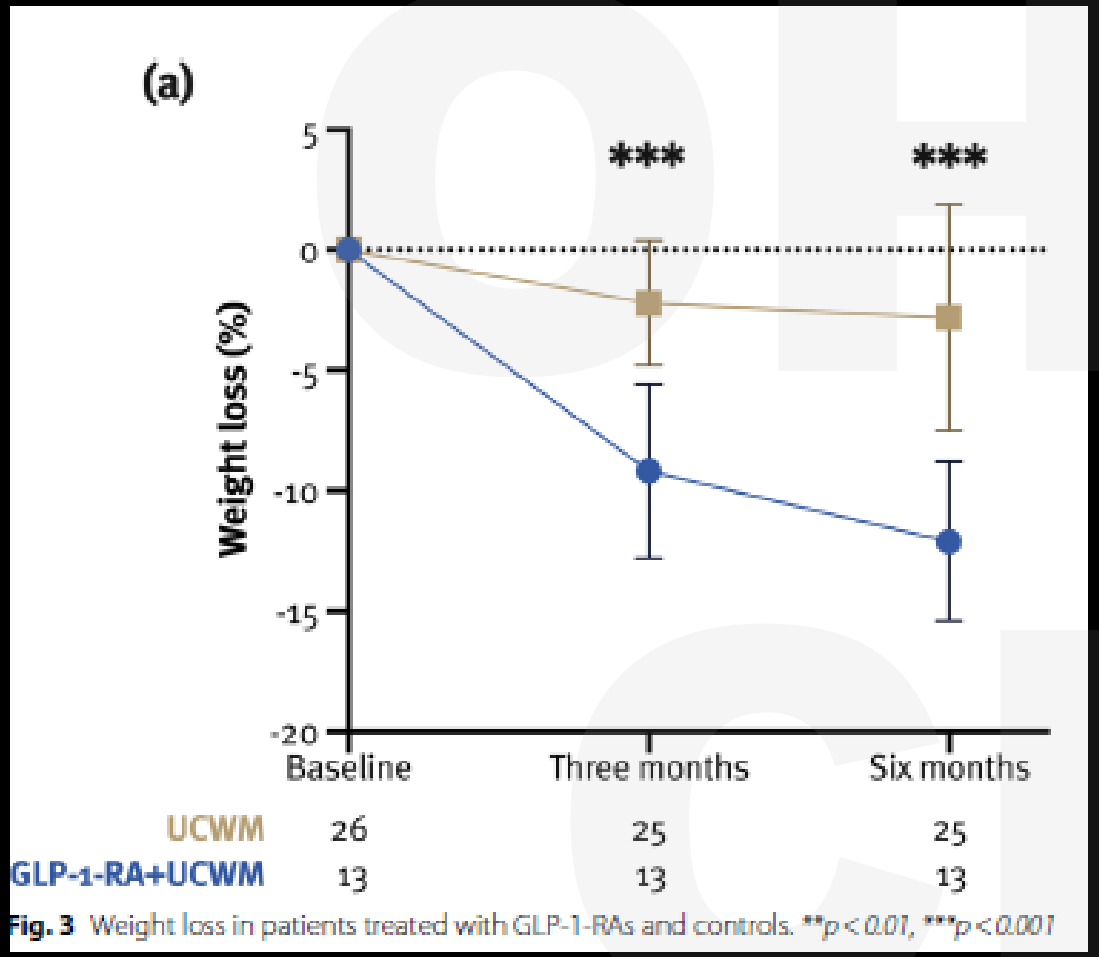
RESEARCH

Open Access

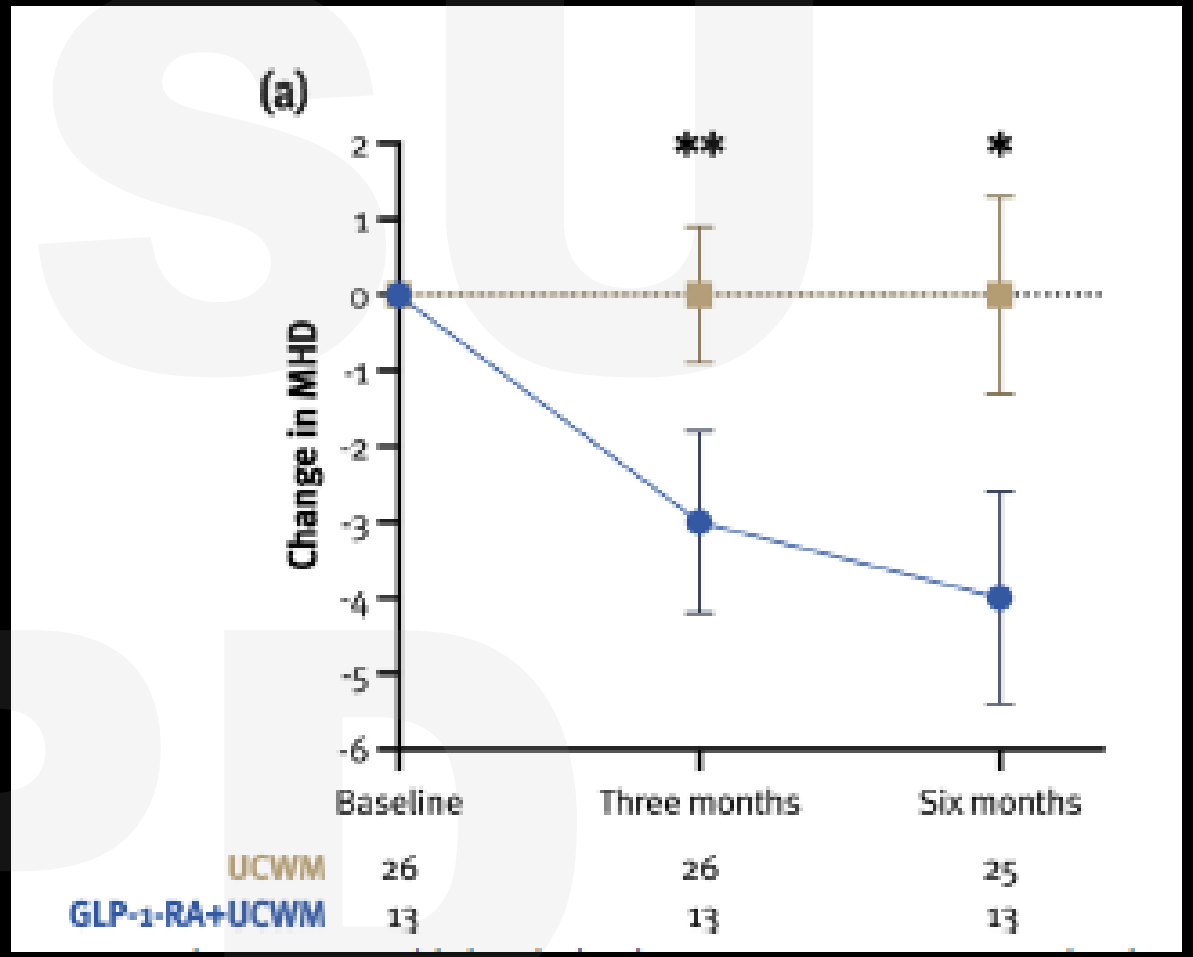
# Treatment with GLP-1 receptor agonists is associated with significant weight loss and favorable headache outcomes in idiopathic intracranial hypertension

Nik Krajnc[1,2], Bianca Itariu[3], Stefan Macher[1,2], Wolfgang Marik[2,4], Jürgen Harreiter[3], Martin Michl[5], Klaus Novak[2,6], Christian Wöber[1,2], Berthold Pemp[5†] and Gabriel Bsteh[1,2*†]

# GLP -1 Agonist and Idiopathic intracranial hypertension




Weight loss




Change in monthly headache days

*** UCWM- Usual care and management

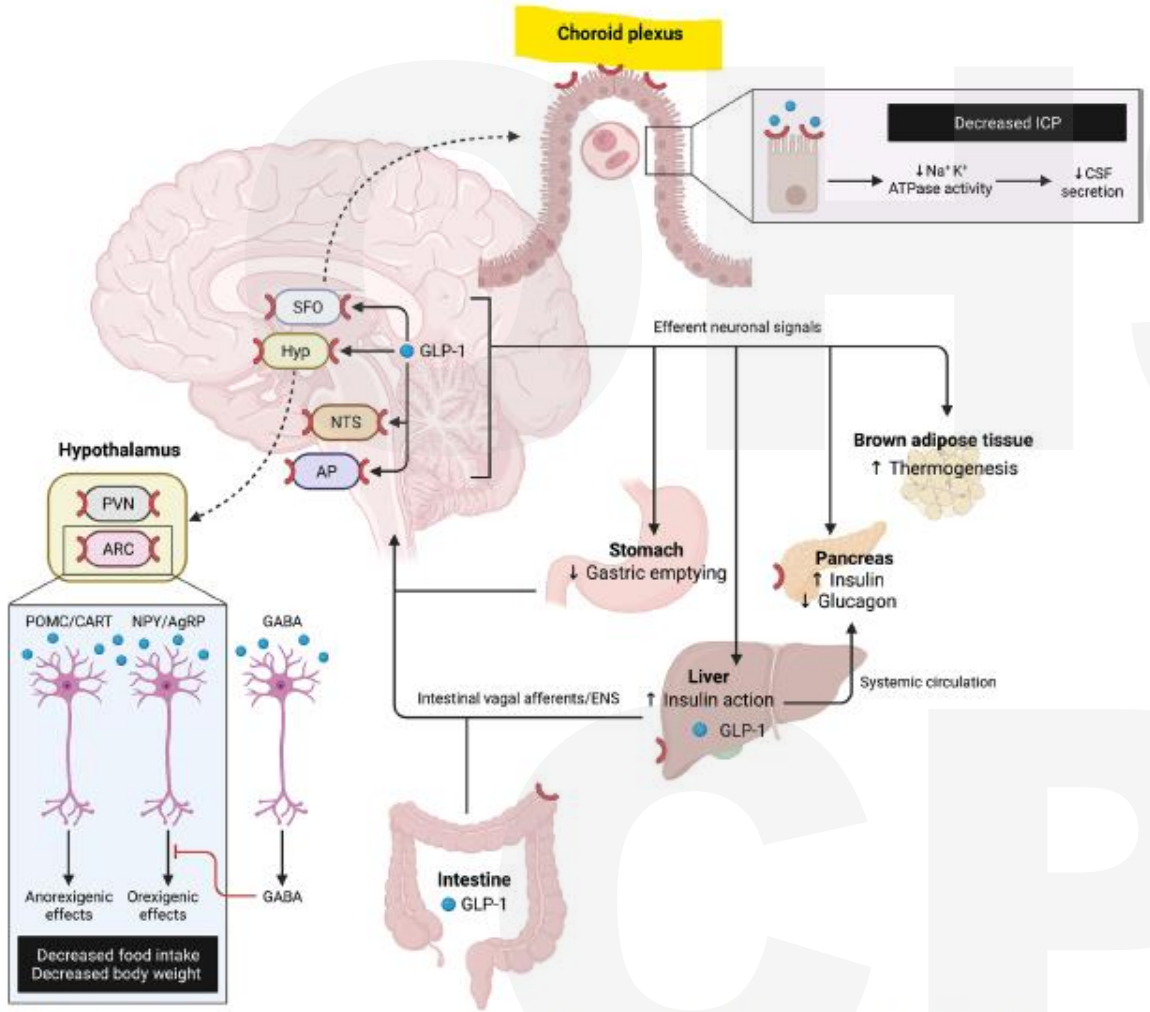



**Fig. 1** GLP-1 is secreted from enteroendocrine cells where it activates intestinal vagal afferents, located in the gut and portal circulation, further activating GLP-1-producing neurons in the nucleus tractus solitarii. These neurons project to several food-regulating areas, including the ventral tegmental area, the nucleus accumbens and the hypothalamus. There, GLP-1 directly activates POMC/CART neurons and indirectly inhibits, via GABAergic transmission, the NPY/AgRP neurons, which collectively results in signals reducing food intake. Efferent pathways, which originate in the brain stem, subsequently signal to peripheral organs to close the loop of feeding behavior and glucose metabolism regulation. GLP-1 receptors are also expressed on the choroid plexus epithelial cells, where the binding of GLP-1 reduces Na + K + ATPase activity, leading to decreased CSF secretion and consequently decreased ICP. Created with BioRender.com. AgRP: agouti-related peptide, AP: area postrema, CART: cocaine- and amphetamine-regulated transcript, CSF: cerebrospinal fluid, ENS: enteric nervous system, GLP-1: glucagon-like peptide-1, Hyp: hypothalamus, ICP: intracranial pressure, NPY: neuropeptide Y, NTS: nucleus tractus solitarii, POMC: proopiomelanocortin, SFO: subfornical organ

- Even after adjusting for weight loss between the groups, there was a trend toward better headache outcome with the GLP-1 agonist group.
- Might be due to the direct effect of GLP-1 agonist on intracranial pressure.

# GLP-1 FOR MIGRAINE PREVENTION

Received: 10 December 2024 | Accepted: 16 April 2025
DOI: 10.1111/head.14991

RESEARCH SUBMISSION

## Effectiveness and tolerability of liraglutide as add-on treatment in patients with obesity and high-frequency or chronic migraine: A prospective pilot study

Simone Braca MD | Cinzia Valeria Russo MD, PhD | Antonio Stornaiuolo MD | Gennaro Cretella MD | Angelo Miele MD | Caterina Giannini MD | Roberto De Simone MD

- This was a prospective study, evaluating the effectiveness of liraglutide as an add-on treatment of unresponsive migraine in patients with obesity.
- We consecutively enrolled patients with high-frequency or chronic migraine and a body mass index (BMI) of >30 kg/m2, and unresponsive to at least two preventive treatments.
- We excluded patients with papilledema, sixth nerve palsy, or pulsatile tinnitus, to rule out patients in which idiopathic intracranial hypertension could be clinically suspected.
- Liraglutide was administered 1.2 mg daily. The study was conducted from January to July 2024, with a 12-week follow-up period.
- The primary outcome of this study was the reduction of monthly days with headache after 12 weeks of treatment with liraglutide compared to baseline.
- 31 patients (26 females, 5 males) were enrolled, mean age: 44.9

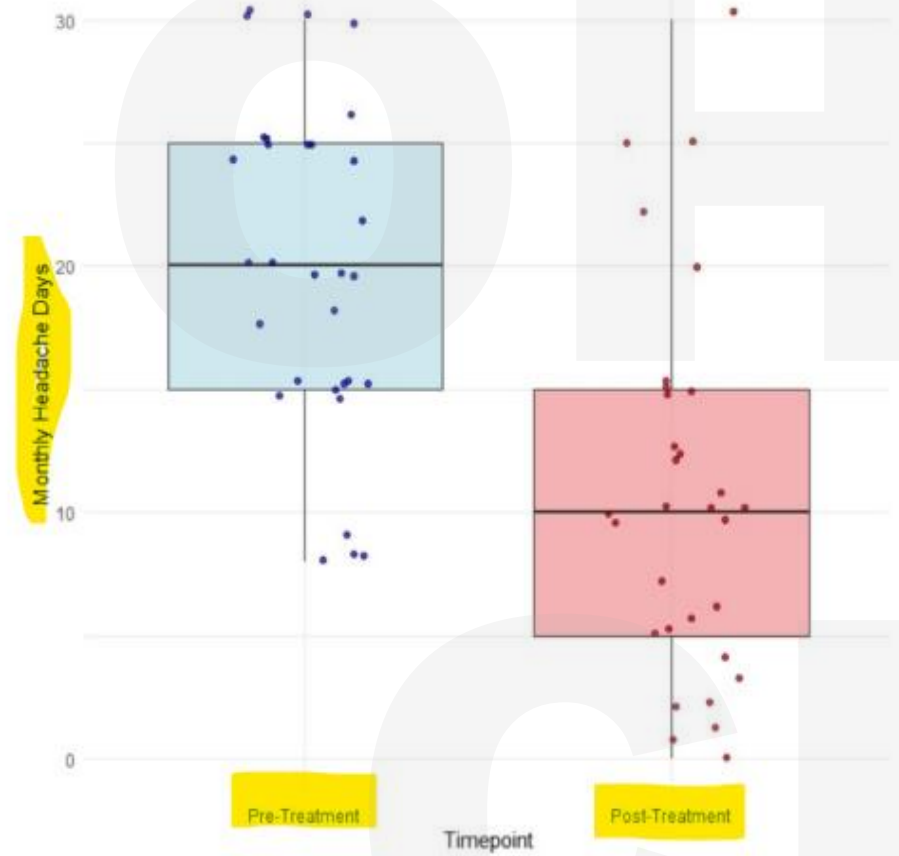



FIGURE 1 Mean monthly headache days. [Colour figure can be viewed at wileyonlinelibrary.com]

- The mean (SD) monthly days with headache decreased from 19.8 (6.7) to 10.7 (7.7) days post-treatment.

# BENEFIT INDEPENDENT FROM WEIGHT LOSS

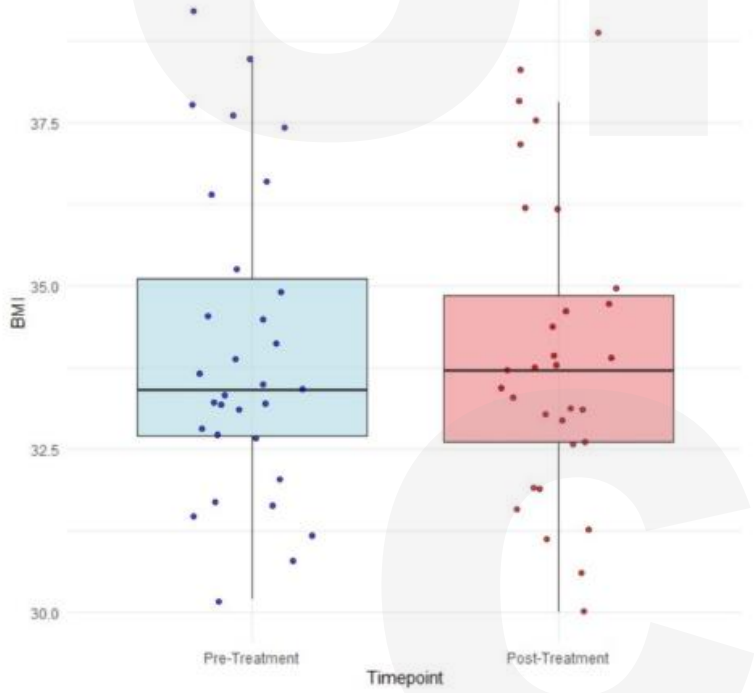



FIGURE 3 Mean body mass index (BMI). [Colour figure can be viewed at wileyonlinelibrary.com]

- BMI decreased slightly from a mean (SD) of 34.0 (2.3) to 33.9 (2.3) kg/m2, and this change was not significant
- Simple linear regression analysis showed that BMI reduction did not significantly predict headache frequency reduction.
- Conclusion: there might be ICP dysfunction component in the pathophysiology of migraine.

# CASE 1: GLP-1 AGONIST?

She reports experiencing night sweats, difficulty sleeping for the last 5 years.

Her menstrual cycles are not as regular as they used to be.

She believes she is in perimenopause.

She also notes that she gained 30 lbs in the last few years.

- We told her there was some initial small studies that were encouraging, however at the moment, GPL-1 agonists are not used in migraine management.

# CASE 1

49 yo F with migraine with aura, episodic migraine

- We see her 4 months later in clinic.
- She is feeling better, her PCP has started her on estrogen patch (she already had an IUD).
- Her sleep and joint pain have improved.
- She finds Eletriptan effective and tolerates it well.

# WHEN TO OFFER PREVENTATIVE TREATMENT

TABLE 4 Criteria for identifying patients for preventive treatment[8]

| Prevention should be … | Headache days/ month | Degree of disability required[a] |
|---|---|---|
| Offered | 6 or more | None |
| | 4 or more | Some |
| | 3 or more | Severe |
| Considered | 4 or 5 | None |
| | 3 | Some |
| | 2 | Severe |

[a]As can be measured by the Migraine Disability Assessment Scale, Migraine Physical Function Impact Diary, or Headache Impact Test.

Ailani J et al. The American Headache Society consensus statement: update on integrating new migraine treatments into clinical practice. Headache 2021;61(7):1021–1039

## Migraine Disability Assessment Questionnaire

On how many days in the last 3 months did you miss work or school because your headaches?

How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.)

On how many days in the last 3 months did you not do household work because of your headaches?

How many days in the last three months was your productivity in household work reduced by half of more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.)

On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?

## MIDAS (Migraine Disability Assessment) Scoring

| MIDAS Grade | Definition | MIDAS Score |
|---|---|---|
| I | Little or no disability | 0 to 5 |
| II | Mild disability | 6 to 10 |
| III | Moderate disability | 11 to 20 |
| IV | Severe disability | 21+ |

# PREVENTATIVE MIGRAINE TREATMENT

TABLE 6 Medications with evidence of efficacy in migraine prevention[a,20,85]

| Established efficacy[b] | | Probably effective[c] | |
|---|---|---|---|
| Oral | Parenteral | Oral | Parenteral |
| Candesartan | Eptinezumab | Amitriptyline | OnabotulinumtoxinA + CGRP mAb[d,e] |
| Divalproex sodium | Erenumab | Atenolol | |
| Frovatriptan[f] | Fremanezumab | Lisinopril | |
| Metoprolol | Galcanezumab | Memantine | |
| Propranolol | OnabotulinumtoxinA[d] | Nadolol | |
| Timolol | | Venlafaxine | |
| Topiramate | | | |
| Valproate sodium | | | |

Abbreviations: CGRP, calcitonin gene-related peptide; mAb, monoclonal antibody.

[a]The decision to prescribe preventive therapy in women who are pregnant or of childbearing potential should be based on the needs of individual patients and available safety data.

[b]Two or more Class I trials based on American Academy of Neurology evidence classification.[84]

[c]One Class I or 2 Class II trials based on American Academy of Neurology evidence classification.[84]

[d]Prevention of chronic migraine.[86]

[e]One Class IV trial based on American Academy of Neurology evidence classification.[84]

[f]Short-term prevention of menstrual-related migraine; evaluated and rejected by the FDA for this indication.

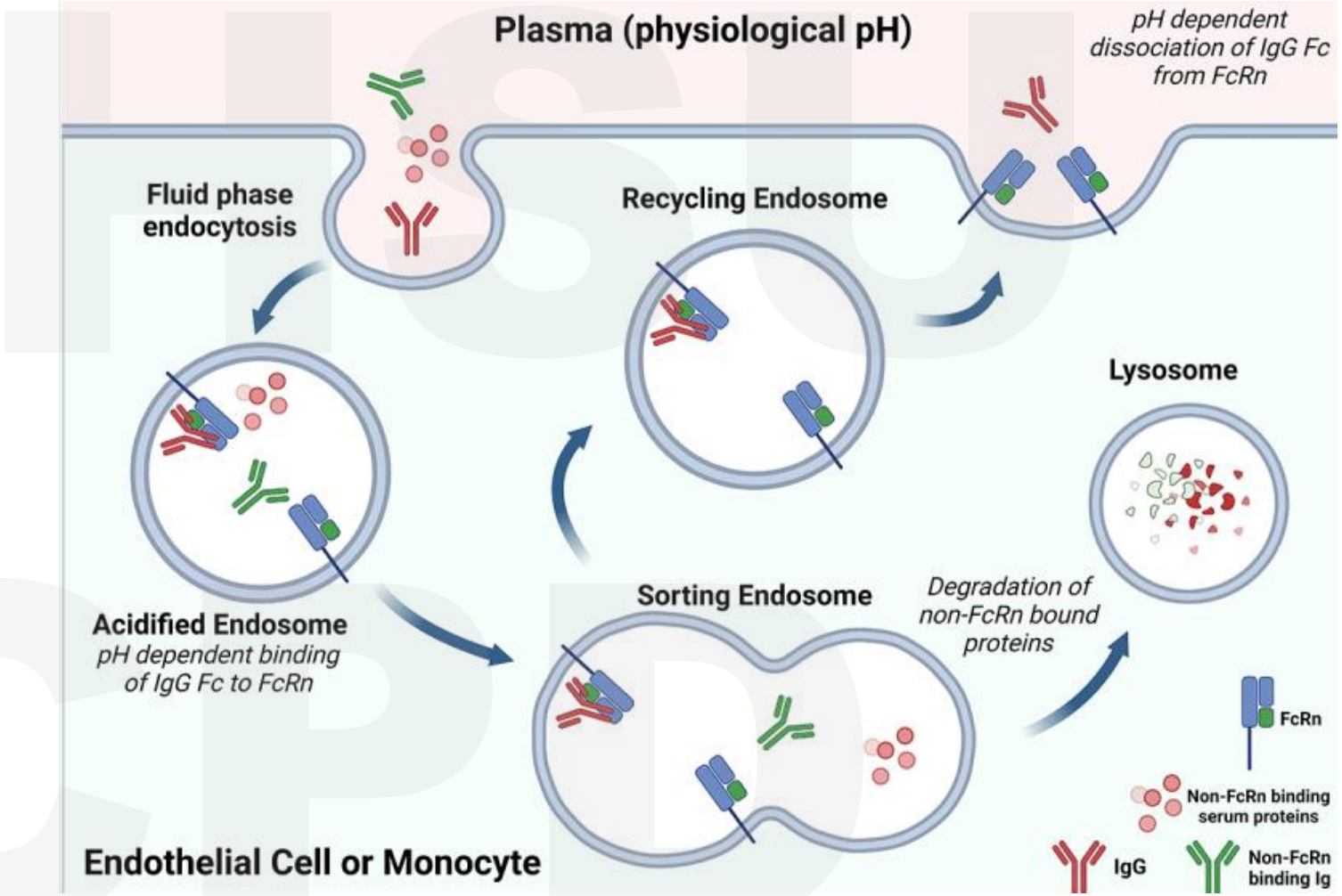
Ailani J et al. The American Headache Society consensus statement: update on integrating new migraine treatments into clinical practice. Headache 2021;61(7):1021–1039

# PREVENTATIVE MIGRAINE TREATMENT IN LIVER DISEASE

# CGRP MONOCLONAL ANTIBODIES

# CGRP MONOCLONAL ANTIBODIES

- They are eliminated mainly by proteolytic degradation via the reticuloendothelial system rather than hepatic metabolism
- They are degraded via general enzymatic proteolysis, are broken down into small peptides and amino acids




Brennan FR et al. Impact of antibody Fc engineering on translational pharmacology, and safety: insights from industry case studies. MAbs. 2025 Dec;17(1):2505092.

# ONABOTULINUMTOXINA INJECTION

ONABOTULINUMTOXINA

IS NOT DETECTABLE IN THE PERIPHERAL BLOOD FOLLOWING INTRAMUSCULAR INJECTION

HEPATIC IMPAIRMENT  IS NOT EXPECTED TO AFFECT ITS PHARMACOKINETICS.

# GEPANT: CGRP RECEPTOR ANTAGONIST

ATOGEPANT & RIMEGEPANT

METABOLIZED PRIMARILY THROUGH HEPATIC SYSTEM (VIA CYP 3A4)

NO DOSE ADJUSTMENT NEEDED IN MILD-MOD LIVER DISEASE

AVOID USE IN SEVERE HEPATIC DISEASE

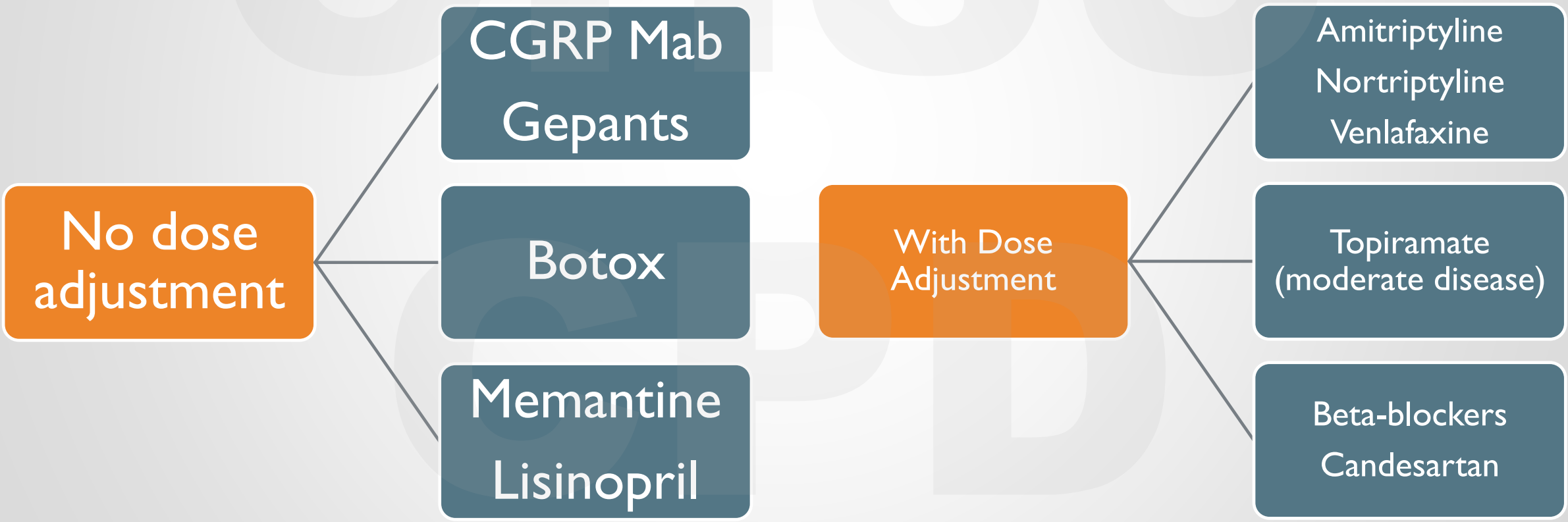
# LISINOPRIL

- NOT METABOLIZED THROUGH THE HEPATIC SYSTEM
- EXCRETED RENALLY UNCHANGED

# MEMANTINE

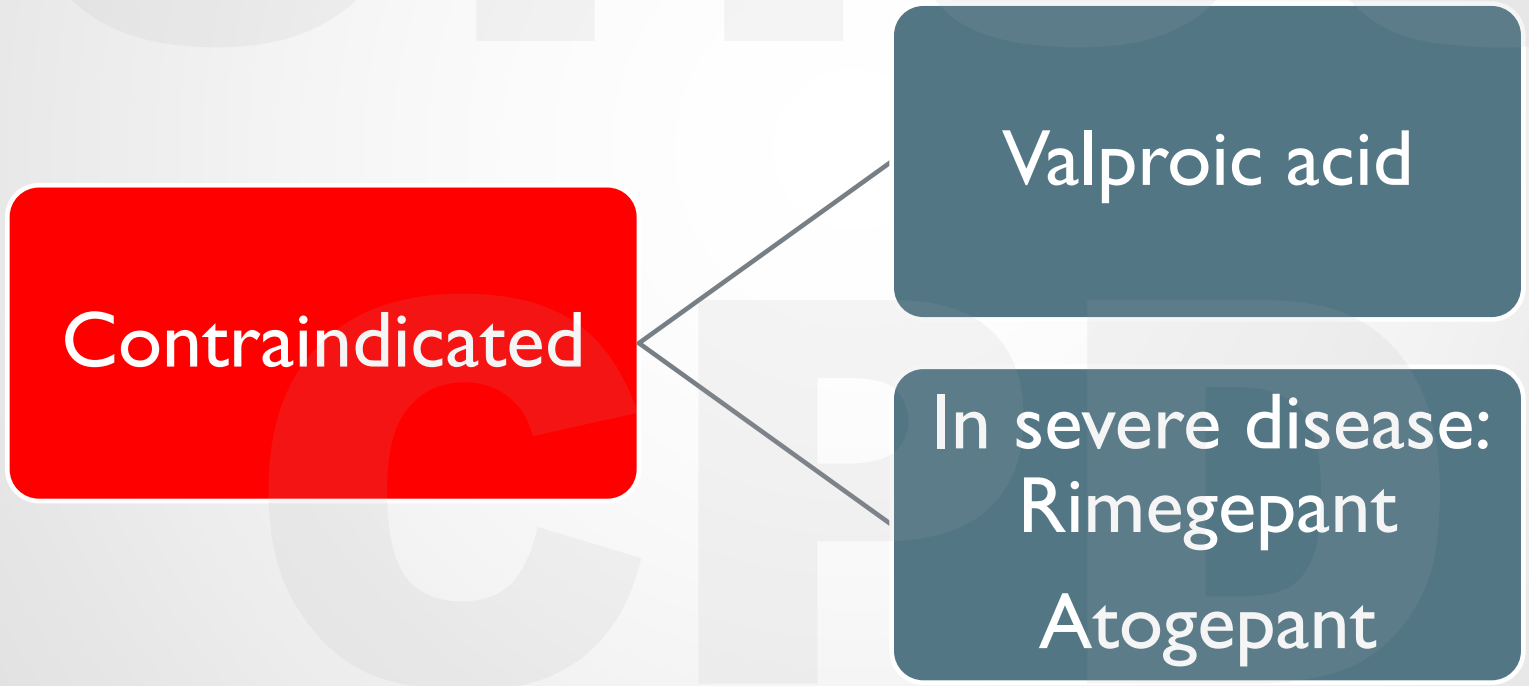
- METABOLIZED PARTIALLY THROUGH THE LIVER
- NO DOSE ADJUSTMENT NEEDED IN MILD-MOD LIVER DISEASE
- INDEPENDENT OF THE CYP ENZYME SYSTEM

# PREVENTATIVE MIGRAINE TREATMENT IN MILD TO MODERATE LIVER DISEASE




Hird, M.A., Sandoe, C.H. Migraine Management in Medically Complex Patients: a Narrative Review. Curr Neurol Neurosci Rep 2024; 24 :423–438

# PREVENTATIVE MIGRAINE TREATMENT IN LIVER DISEASE

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# CASE 2

50 yo woman with migraine without aura since age 23, hypothyroidism, ureteropelvic junction obstruction s/p nephrectomy at age 29 who reports more difficulty breaking her migraine headaches.

She experiences headaches between 4-6 days per month.

- She uses Sumatriptan or Aspirin to break her migraine headaches.

Because she has only one kidney, she wants to make sure the medication we try next is safe for her kidney.

ARS

# WHICH OF THIS STATEMENT IS CORRECT REGARDING ACUTE TREATMENT IN PATIENTS WITH KIDNEY DISEASE?

A. Sumatriptan is preferred triptan for patients with kidney disease
B. Zolmitriptan is safe for patients with kidney disease
C. Ubrogepant is preferred gepant for patients with kidney disease
D. Diclofenac sodium is preferred NSAID for patients with kidney disease

**Chronic kidney disease classification based upon glomerular filtration rate**

| GFR stages | GFR (mL/min/1.73 $m^2$) | Terms |
|---|---|---|
| G1 | ≥90 | Normal or high |
| G2 | 60 to 89 | Mildly decreased |
| G3a | 45 to 59 | Mildly to moderately decreased |
| G3b | 30 to 44 | Moderately to severely decreased |
| G4 | 15 to 29 | Severely decreased |
| G5 | <15 | Kidney failure (add D if treated by dialysis) |

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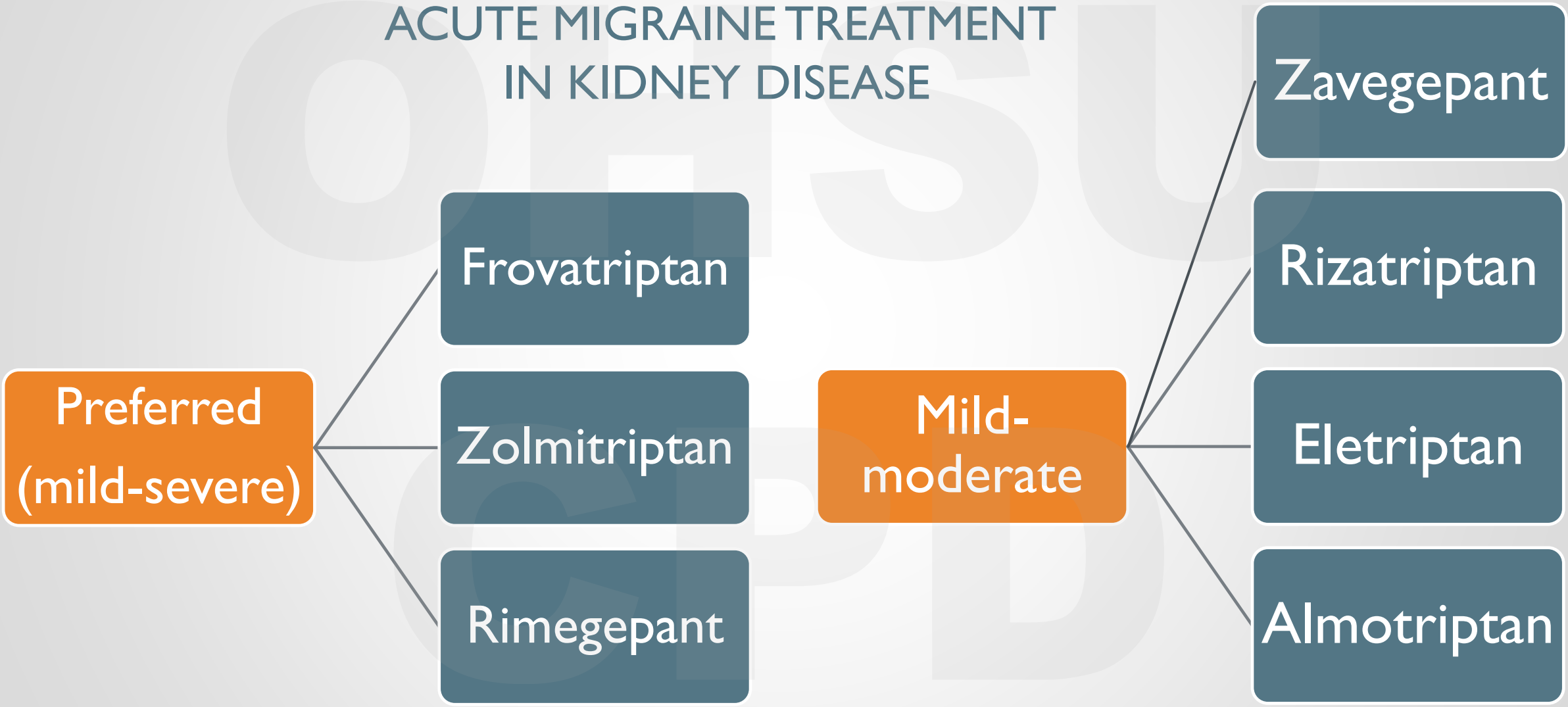
- Glomerular filtration rate (GFR) is generally considered to be the best marker of overall kidney function
- Declining GFR is the hallmark of progressive kidney disease

# ACUTE MIGRAINE TREATMENT IN KIDNEY DISEASE

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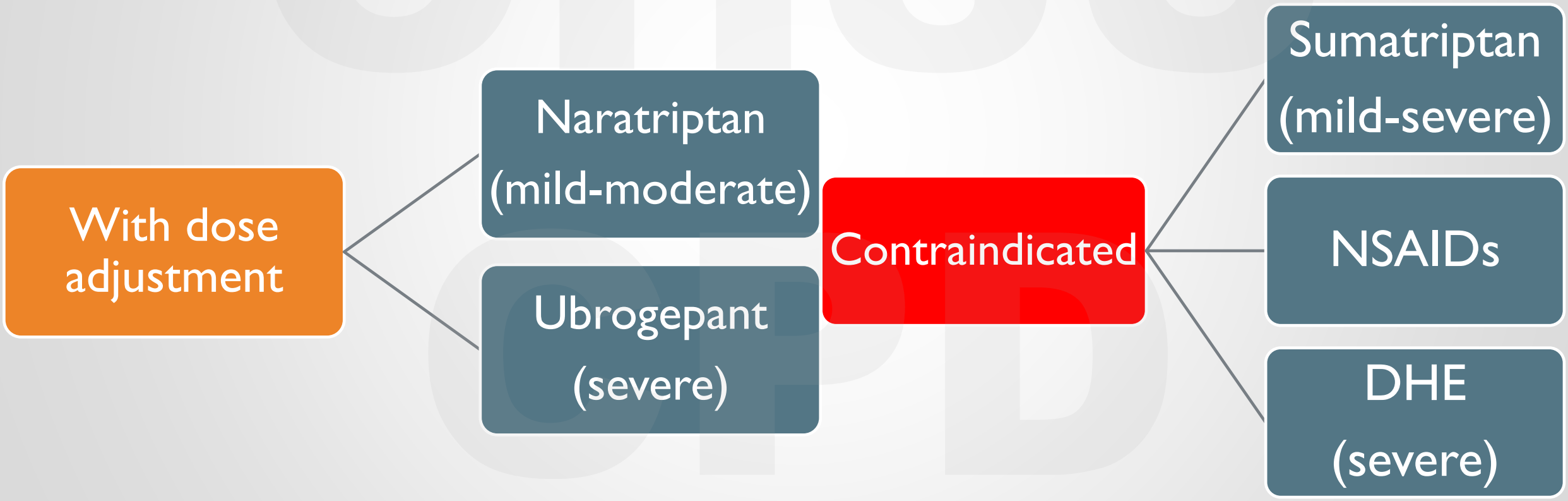


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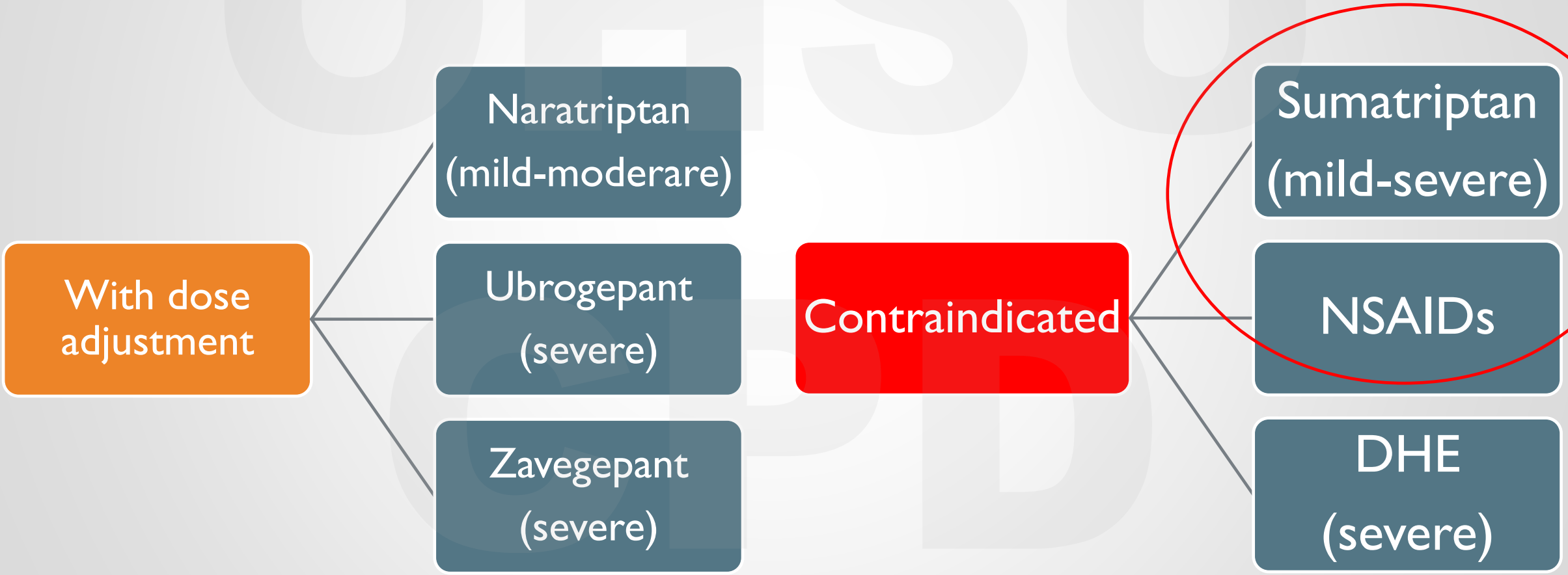


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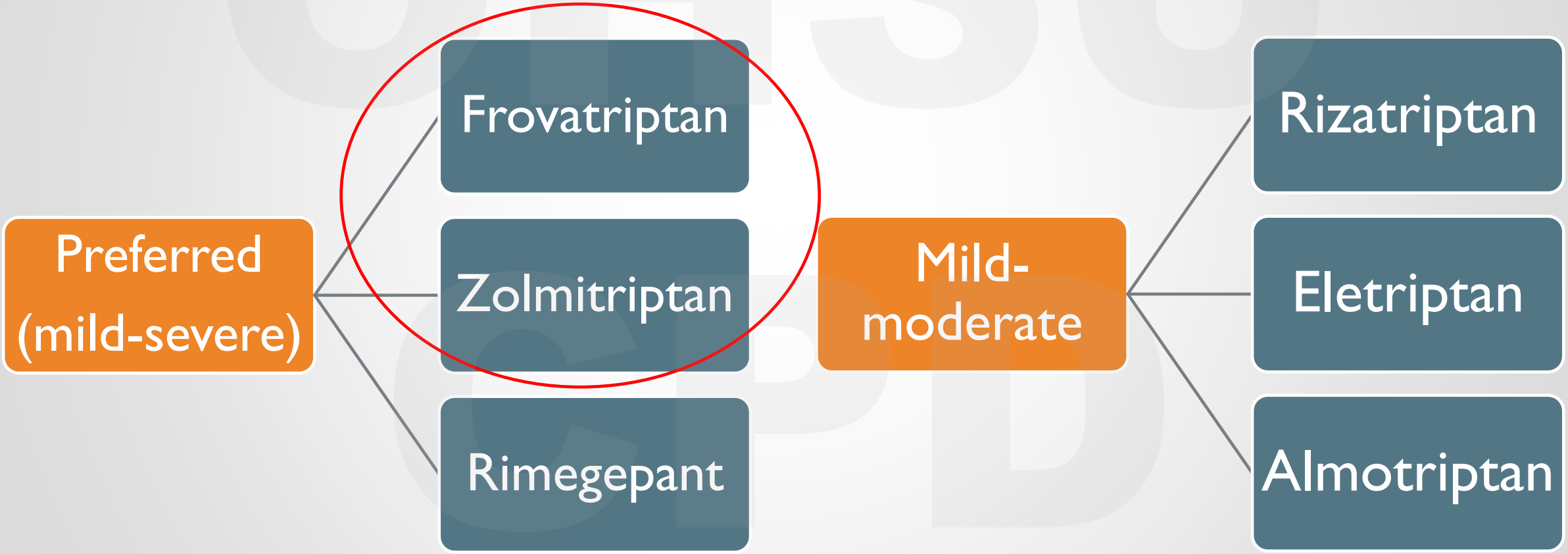


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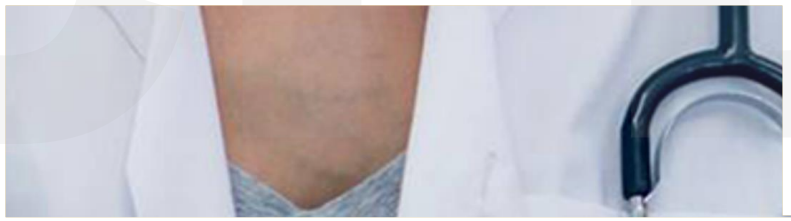
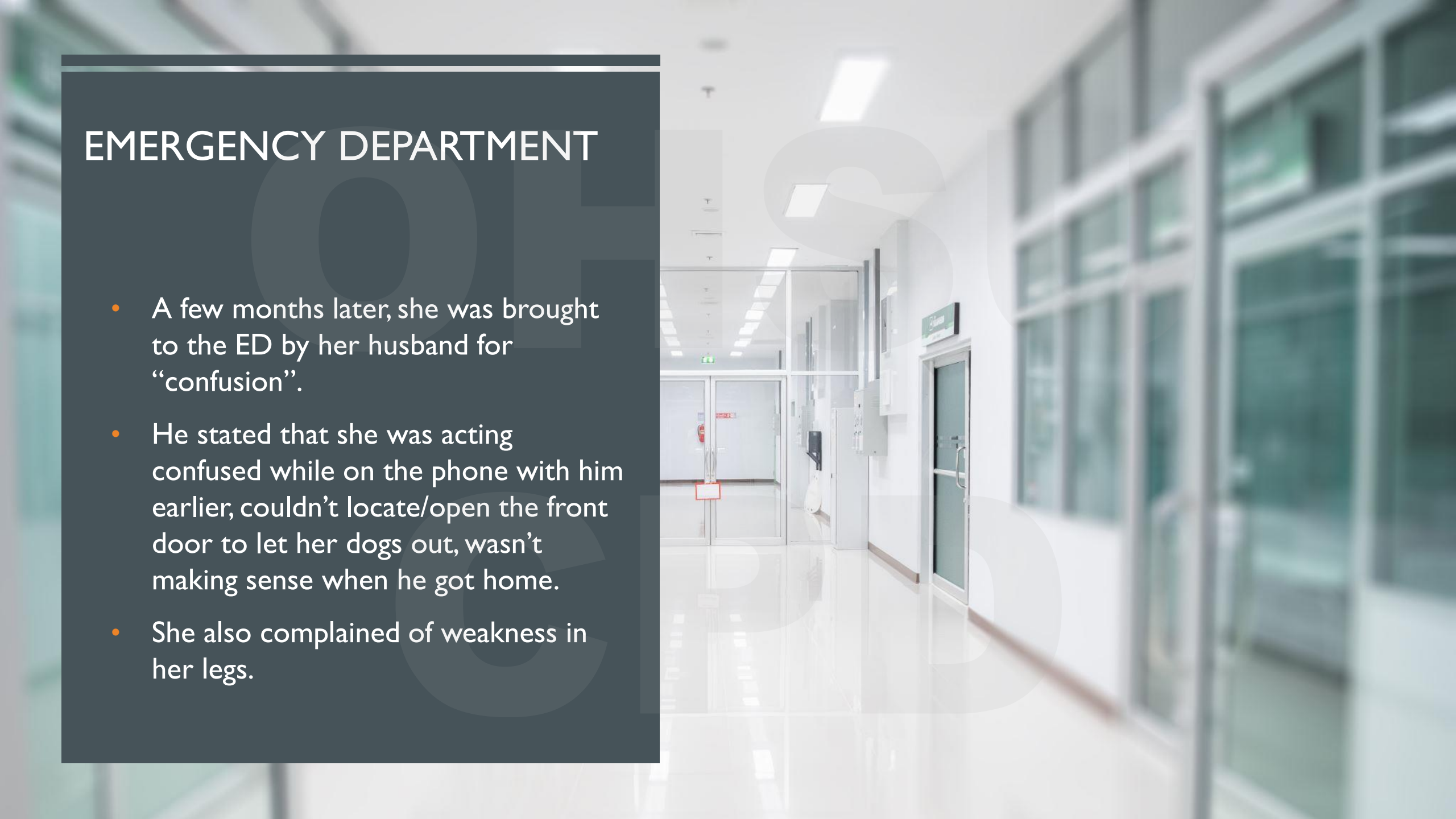
# ZOLMITRITPAN 5MG WAS GIVEN



# EMERGENCY DEPARTMENT

- A few months later, she was brought to the ED by her husband for "confusion".
- He stated that she was acting confused while on the phone with him earlier, couldn't locate/open the front door to let her dogs out, wasn't making sense when he got home.
- She also complained of weakness in her legs.



# EMERGENCY DEPARTMENT

BP 103/86 Pulse 94 Temp 36.5 °C (97.7 °F) Resp 28

Constitutional: She appears well-developed and well-nourished.

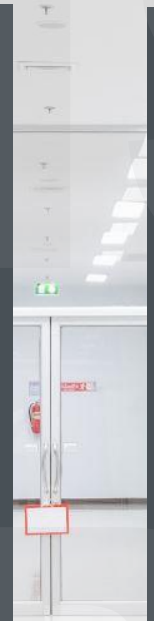
HENT:

Head: Normocephalic and atraumatic.

Eyes: Pupils are equal, round, and reactive to light.

Neck: Normal range of motion.

Cardiovascular: Normal rate and regular rhythm.



Pulmonary/Chest: Breath sounds normal.

Tachypnea with increased depth of ventilation. No increased work of breathing

Abdominal: Soft.

Musculoskeletal: Normal range of motion.

Neurological: She is alert. She has normal strength. Coordination abnormal.

Psychiatric: Her mood appears anxious. Her affect is labile. Her speech is tangential. Thought content is delusional. Cognition and memory are impaired. She expresses inappropriate judgment

# EMERGENCY DEPARTMENT

| | |
|---|---|
| **Sodium**<br>135 - 145 mmol/L | 135 |
| **Potassium**<br>3.5 - 5.2 mmol/L | 3.5 |
| **Chloride**<br>95 - 109 mmol/L | 107 |
| **CO2**<br>22 - 32 mmol/L | 14 ⌄ |
| **Anion Gap**<br>3 - 12 mmol/L | 14 ^ |
| **Glucose**<br>70 - 99 mg/dL | 129 ^ |
| **BUN**<br>6 - 20 mg/dL | 23 ^ |
| **Creatinine**<br>0.44 - 1.03 mg/dL | 1.25 ^ |
| **GFR Non-Black (CKD-EPI)**<br>>=60 mL/min/1.73m2 | 50 ⌄ |
| **GFR Black (CKD-EPI)**<br>>=60 mL/min/1.73m2 | 58 ⌄ |

| | |
|---|---|
| **Protein, Total**<br>6.2 - 8.4 g/dL | 7.4 |
| **Albumin**<br>3.5 - 5 g/dL | 4.2 |
| **Globulin**<br>2.2 - 3.5 g/dL | 3.2 |
| **Calcium**<br>8.6 - 10.2 mg/dL | 8.9 |
| **Bilirubin, Total**<br>0.1 - 1.2 mg/dL | 0.5 |
| **Alkaline Phosphatase**<br>30 - 110 U/L | 55 |
| **ALT**<br>15 - 54 U/L | 11 ⌄ |
| **AST**<br>15 - 41 U/L | 16 |
| **Calculated OSMO**<br>269 - 289 mOsm/kg | 275 |

# EMERGENCY DEPARTMENT

- CTA head & neck-neg
- CTA of chest to rule out pulmonary emboli-neg
- Utox-neg
- Send out additional labs- worry about medication toxicity/overdose

OVERDOSE OF WHICH ONE OF THESE MEDICATIONS WILL BE CONSISTENT WITH OUR PATIENT SYMPTOMS (CONFUSION, HYPERVENTILATION, ACUTE KIDNEY INJURY ?

A. Zolmitriptan
B. Sumatriptan
C. Acetaminophen
D. Aspirin

# EMERGENCY DEPARTMENT

## Acetaminophen

| Component | |
|---|---|
| Ref Range & Units | |
| **Acetaminophen (Tylenol)** | **29** |
| <=30 ug/mL | |

Comment: Acetaminophen toxicity guidelines 4 hr post dose: >150, 8 hr post dose: >75, 12 hour post dose: >40, unknown post dose: >50 ug/mL.

## Salicylate

| Component | |
|---|---|
| Ref Range & Units | |
| **Salicylate** | **95 !!** |
| <30 mg/dL | |

# EMERGENCY DEPARTMENT

**Assessing severity of salicylate toxicity**

| | Mild (or early) toxicity | Moderate (or middle) toxicity | Severe (or late) toxicity |
|---|---|---|---|
| **Symptoms** | ▪ Tinnitus<br>▪ Nausea | ▪ Vomiting | ▪ Confusion |
| **Signs** | ▪ Tachypnea<br>▪ Mild hyperpnea and/or tachycardia may start to develop | ▪ Mild hyperthermia<br>▪ Tachycardia<br>▪ Hyperpnea<br>▪ Diaphoresis | ▪ Hyperthermia<br>▪ Cerebral edema<br>▪ Pulmonary edema<br>▪ Hypotension |
| **Mental status** | ▪ Normal | ▪ Normal<br>▪ Mild disorientation may start to develop | ▪ Altered mentation<br>▪ Disorientation<br>▪ Agitation<br>▪ Coma<br>▪ Seizures |
| **Serum salicylate concentration*** | ▪ 30 to 50 mg/dL (2.2 to 3.6 mmol/L) | ▪ 50 to 90 mg/dL (3.6 to 7.2 mmol/L) | ▪ Acute toxicity: >90 mg/dL (>6.5 mmol/L)<br>▪ Chronic toxicity: >60 mg/dL (>4.3 mmol/L) |
| **Blood pH** | ▪ Normal or alkalotic (>7.45) | ▪ Alkalotic (>7.45)¶ | ▪ Acidotic (<7.3) |
| **Urine pH** | ▪ >5 | ▪ <5 | ▪ <5 |

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# CASE 2

- She had been experiencing head cold with concurrent headaches about a week prior to her ED presentation.
- Her Zolmitriptan was not effective for these headaches, so she started to take ASA around the clock (325 mg every 3-4 hours) ~2000 mg/day
- She was admitted to the ICU and had urgent hemodialysis (which brought her Salicylate level down from 95 to 8 mg/dl).
- She was discharged after 4 days.

Ingested Aspirin dose and level of toxicity

- <150 mg/kg: No symptoms or minimal symptoms
- 150 to 300 mg/kg: Mild to moderate toxicity
- 301 to 500 mg/kg: Severe toxicity
- >500 mg/kg: Potentially lethal

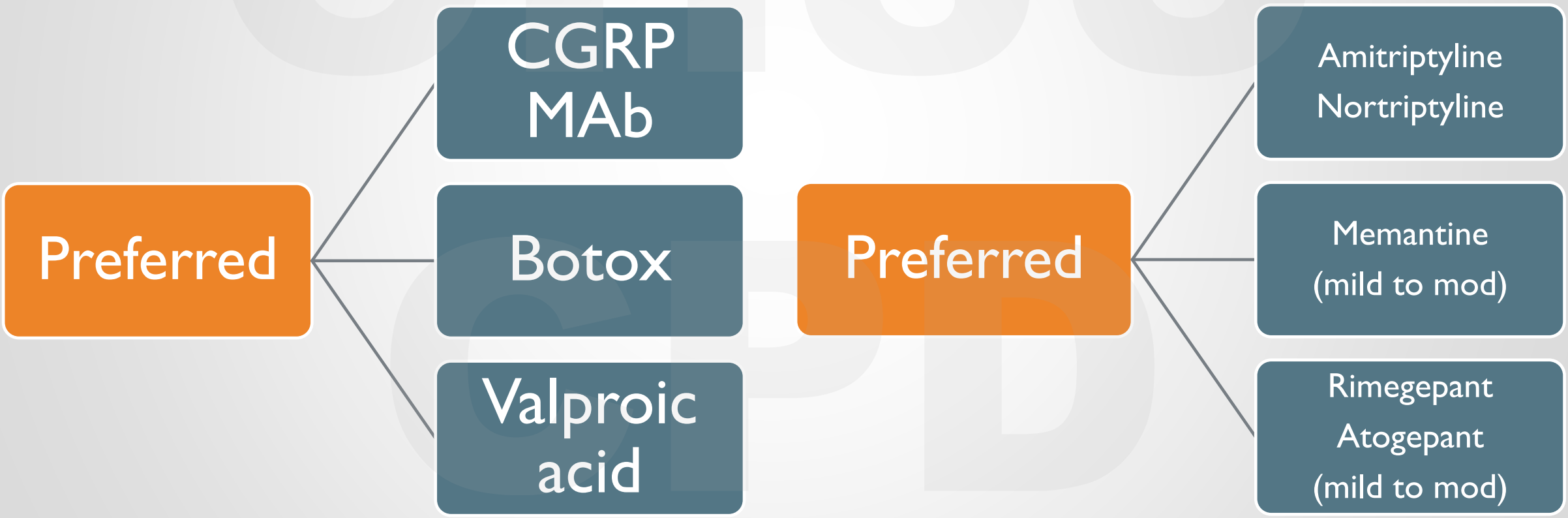
150 mg x 60 kg= 9,000 mg/day

*Uptodate.com*

## WHICH MIGRAINE PREVENTATIVE TREATMENT WOULD BE APPROPRIATE FOR PATIENTS WITH KIDNEY DISEASE?

A. Amitriptyline 30 mg at night
B. Rimegepant 75 mg ODT every other day
C. Memantine 10 mg twice per day
D. Valproic Acid 500 mg twice per day
E. All of the above

# PREVENTATIVE MIGRAINE TREATMENT IN KIDNEY DISEASE

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# SUMMARY

Patients with migraine with visual aura:

- Low dose estrogen may be offered in younger patients
- Hormone replacement therapy may be used in perimenopausal patients.

Migraine patients with liver disease:

- Eletriptan and Frovatriptan are preferred triptans, gepants are also safe to use
- CGRP MAb, Botox, Lisinopril and Memantine may be used as preventative agents

Migraine patients with kidney disease:

- Zolmitriptan, Frovatriptan and Rimegepant are preferred as they do not need dose adjustment
- TCA, Memantine, CGRP Mab, Botox and Valproic acid may be used safely as preventative agents
- Remind patients of danger of ASA/NSAIDs

# THANK YOU

# REFERENCES


1. Khatera Ibrahimia, Emile G.M. Couturierb, Antoinette MaassenVanDenBrinka. Migraine and perimenopause. Maturitas 2014;78 :277–280.
2. Spector JT Kahn SR Jones MR et al. Migraine headache and ischemic stroke risk: an updated meta-analysis. Am J Med 2010; 123: 612–624
3. MacClellan LR Giles W Cole J et al. Probable migraine with visual aura and risk of ischemic stroke: the stroke prevention in young women study. Stroke 2007; 38: 2438–2445.
4. Schürks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ. 2009;339:b3914.
5. Simona Sacco, Silvia Ricci, Diana Degan, Antonio Carolei. Migraine in women: the role of hormones and their impact on vascular diseases. Journal of Headache and Pain 2012;13:177–189.
6. Calhoun AH. Hormonal Contraceptives and Migraine With Aura-Is There Still a Risk? Headache. 2017 Feb;57(2):184-193.
7. Canonico M, Carcaillon L, Plu-Bureau G, Oger E, Singh-Manoux A, Tubert-Bitter P, Elbaz A, Scarabin PY. Postmenopausal Hormone Therapy and Risk of Stroke: Impact of the Route of Estrogen Administration and Type of Progestogen. Stroke. 2016 Jul;47(7):1734-41.
8. Ailani J, Burch RC, Robbins MS, Board of Directors of the American Headache Society. The American Headache Society consensus statement: update on integrating new migraine treatments into clinical practice. Headache 2021;61(7):1021–1039
9. Hird, M.A., Sandoe, C.H. Migraine Management in Medically Complex Patients: a Narrative Review. Curr Neurol Neurosci Rep 2024; 24 :423–438
10. Kim, S.E., Min, JS., Lee, S. et al. Different effects of menopausal hormone therapy on non-alcoholic fatty liver disease based on the route of estrogen administration. Sci Rep 2023;13: 15461
11. Appelberg, J., Isoniemi, H., Nilsson, C.G., Höckerstedt, K. and Ylöstalo, P. (1998), Safety and efficacy of transdermal estradiol replacement therapy in postmenopausal liver transplanted women. Acta Obstetricia et Gynecologica Scandinavica, 77: 660-664
12. Krajnc N, Itariu B, Macher S, Marik W, Harreiter J, Michl M, Novak K, Wöber C, Pemp B, Bsteh G. Treatment with GLP-1 receptor agonists is associated with significant weight loss and favorable headache outcomes in idiopathic intracranial hypertension. J Headache Pain. 2023 Jul 18;24(1):89
13. Braca S, Russo CV, Stornaiuolo A, Cretella G, Miele A, Giannini C, De Simone R. Effectiveness and tolerability of liraglutide as add-on treatment in patients with obesity and high-frequency or chronic migraine: A prospective pilot study. Headache. 2025 Nov-Dec;65(10):1831-1838.
14. Brennan FR, Polli JR, Sathish J, Ramones M, Wolf B, Schlothauer T, Peters SJ, Maier CC, Ji C, Wensel DL, Witcher D, Ryan PC, Manetz TS, Flora A, Soper B, Fogal B, Dzielak L, Wang X, Shastri PN, Price K, Doyle M, Sharda N, Struthers M, Brinkhaus M, Balbino B, Stefanich E, Honda M, Andersen JT, Mitchell-Ryan S, Humphreys DP. Impact of antibody Fc engineering on translational pharmacology, and safety: insights from industry case studies. MAbs. 2025 Dec;17(1):2505092.