

**VA**



**U.S. Department of Veterans Affairs**

Veterans Health Administration  
*PBM Academic Detailing Service*

**A QUICK REFERENCE GUIDE (2017)**

# Headaches

Streamlining the Treatment of  
a Common Complaint

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# **VA PBM Academic Detailing Service**

## **Real Provider Resources**

## **Real Patient Results**

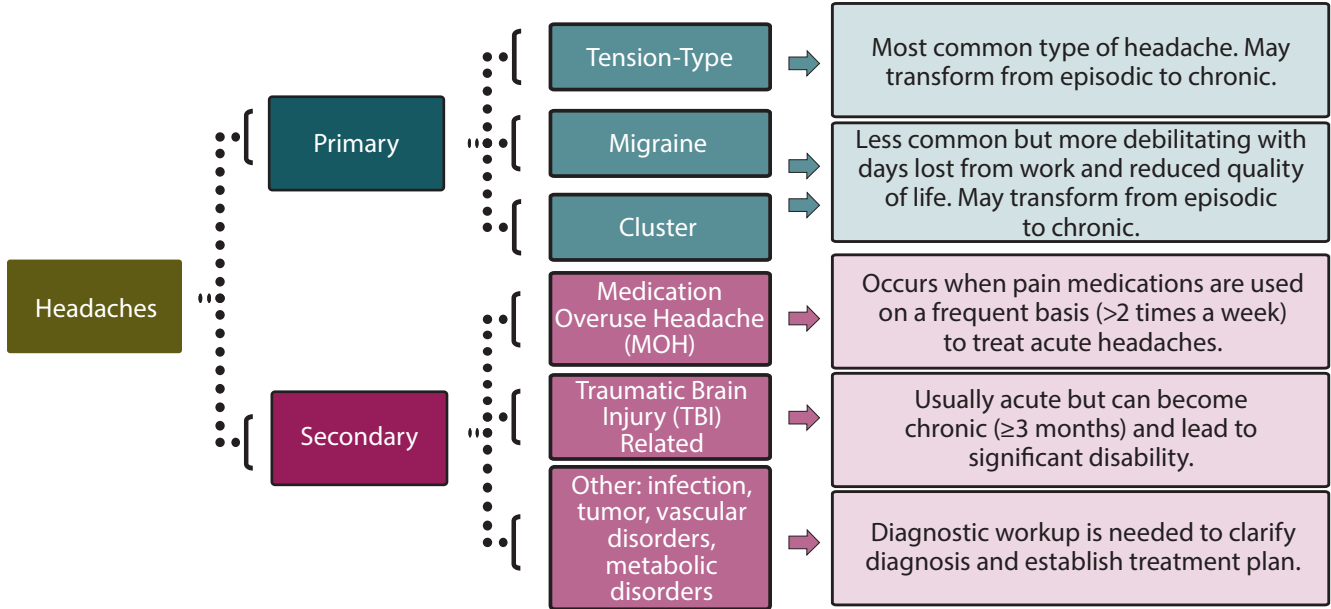
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# Type of Headaches<sup>1-4</sup>



## Acute Treatment for Tension-Type Headaches (TTH)<sup>5–10</sup>

First Line: Level A	Recommended Dose	Pregnancy Category*	Considerations
Acetaminophen	650–1000 mg every 4–6 hours PRN	B	May be less effective than aspirin and NSAIDs.
Aspirin	650–1000 mg every 4–6 hours PRN	C/D**	Caution in patients with history or high risk of GI ulcer and in patients with renal impairment.
NSAIDs: Ibuprofen  Naproxen  Ketorolac Injection	400–800 mg every 6–8 hours PRN 250–550 mg twice daily PRN 30–60 mg as a single dose IM	B/D**	Caution in patients with history or high risk of GI ulcer and in patients with renal impairment.

\*Pregnancy categories are defined on page 28–29. \*\*Pregnancy category D in third trimester. \*\*\*Muscle relaxants = methocarbamol, cyclobenzaprine, baclofen, tizanidine, carisoprodol. **NF = Not currently on VA National Formulary**; GI = gastrointestinal; IM = intramuscular; MOH = medication overuse headache; NSAIDs = Nonsteroidal anti-inflammatory drugs; OUD = opioid use disorder; PRN = as needed.

Second Line: Level B	Recommended Dose	Pregnancy Category*	Considerations
Acetaminophen/ Caffeine <sup>NF</sup>	500 mg/65 mg: 1–2 tablets every 6 hours PRN	C	More effective for TTH than first line agents but higher risk of MOH from caffeine withdrawal; recommend using no more than 12 days each month to reduce the risk of MOH.
Aspirin/Caffeine <sup>NF</sup>	400 mg/32 mg: or 500 mg/32 mg: 1–2 tablets every 6 hours PRN	D	
Acetaminophen/ Aspirin/Caffeine <sup>NF</sup>	250 mg/250 mg/65 mg: 2 tablets every 4–6 hours PRN	D	
<b>Recommend Against</b>			<b>Considerations</b>
Opioids Tramadol Muscle Relaxants*** Butalbital Products			Avoid due to risk of MOH, OUD, and possible overdose with repetitive doses.
Triptans			Triptans are not effective for TTH.

\*Pregnancy categories are defined on page 28–29. \*\*Pregnancy category D in third trimester. \*\*\*Muscle relaxants = methocarbamol, cyclobenzaprine, baclofen, tizanidine, carisoprodol. **NF = Not currently on VA National Formulary**; GI = gastrointestinal; IM = intramuscular; MOH = medication overuse headache; NSAIDs = Nonsteroidal anti-inflammatory drugs; OUD = opioid use disorder; PRN = as needed.

## Preventive Treatment for Tension-Type Headaches (TTH)<sup>5-10</sup>

First Line: Level A	Starting Dose	Recommended Dose	Pregnancy Category*	Considerations
<b>Antidepressants.**</b>				Amitriptyline is the only tricyclic antidepressant with Level A evidence. Amitriptyline and imipramine have higher rates of anticholinergic side effects compared to nortriptyline and desipramine. Also beneficial for neuropathic pain. Doses below 10 mg may be necessary in some patients; a liquid formulation of nortriptyline (10 mg/5 ml) is available.
<b>Amitriptyline</b>	10–25 mg at bedtime	25–100 mg at bedtime	D	
<b>Nortriptyline</b>	10–25 mg at bedtime	25–100 mg at bedtime	D	
<b>Imipramine</b>	10–25 mg at bedtime	25–100 mg at bedtime	D	
<b>Desipramine</b>	10–25 mg at bedtime	25–100 mg at bedtime	C	

\*Pregnancy categories are defined on page 28–29. \*\*Antidepressants should be used with caution in patients at risk for suicide. \*\*\*Muscle relaxants = methocarbamol, cyclobenzaprine, baclofen, tizanidine, carisoprodol. ER = extended release; MOH = medication overuse headache; OUD = opioid use disorder.

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Second Line: Level B	Starting Dose	Recommended Dose	Pregnancy Category*	Considerations
<b>Antidepressants:**</b>				
<b>Mirtazapine</b>	7.5–15 mg at bedtime	30 mg at bedtime	C	Beneficial for patients with depression and tension-type headaches.
<b>Venlafaxine</b>	37.5 mg ER daily	150 mg ER daily	C	
Third Line: Level C	Starting Dose	Recommended Dose	Pregnancy Category*	Consideration
<b>Antidepressants:**</b>				
<b>Clomipramine</b>	25 mg daily	25–150 mg daily: may divide dose	C	Tricyclic antidepressant with similar anticholinergic effects to amitriptyline, but also may cause bone marrow suppression, hepatitis/ jaundice, hyponatremia.

\*Pregnancy categories are defined on page 28–29. \*\*Antidepressants should be used with caution in patients at risk for suicide. \*\*\*Muscle relaxants = methocarbamol, cyclobenzaprine, baclofen, tizanidine, carisoprodol. ER = extended release; MOH = medication overuse headache; OUD = opioid use disorder.

continued from page 4 (Preventive Treatment for Tension-Type Headaches (TTH))

Recommend Against				Considerations
<b>Opioids</b> <b>Tramadol</b> <b>Muscle Relaxants***</b> <b>Butalbital Products</b>				Avoid due to risk of MOH, OUD, and possible overdose with repetitive doses.
<b>Triptans</b>				Triptans not effective for TTH.

\*Pregnancy categories are defined on page 28–29. \*\*Antidepressants should be used with caution in patients at risk for suicide. \*\*\*Muscle relaxants = methocarbamol, cyclobenzaprine, baclofen, tizanidine, carisoprodol. ER = extended release; MOH = medication overuse headache; OUD = opioid use disorder.



## Acute Treatment for Migraine Headache<sup>7-16</sup>

Mild First Line: Level A	Recommended Dose	Pregnancy Category*	Considerations
Acetaminophen	1000 mg every 6 hours PRN	B	Also consider for patients with mild-moderate migraines who cannot tolerate NSAIDs.
Mild to Moderate First Line: Level A	Recommended Dose	Pregnancy Category*	Considerations
Aspirin	325–650 mg every 4 hours PRN	C/D**	Addition of antiemetic to aspirin improves nausea/vomiting. Addition of caffeine may help with migraine pain but increases the risk of MOH.

\*Pregnancy categories are defined on page 28–29. \*\*Pregnancy Category D in third trimester. \*\*\*natriptan, frovatriptan, almotriptan can also be considered but are NF. **NF = Not currently on VA National Formulary**; HA = headache; IM = intramuscular; IV = intravenous; MOH = medication overuse headache; ODT = orally disintegrating tablet; OUD = opioid use disorder; SC = subcutaneous; SNRI = serotonin norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors.

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Mild to Moderate First Line: Level A	Recommended Dose	Pregnancy Category*	Considerations
<b>NSAIDs:</b>  <b>Ibuprofen</b>  <b>Naproxen</b>  <b>Ketorolac Injection</b>	400–800 mg every 6–8 hours PRN  250–550 mg twice daily PRN  30–60 mg as a single dose IM	B/D**	Limit use to no more than 10 days per month to prevent MOH.  May help during withdrawal of offending agent in MOH.

\*Pregnancy categories are defined on page 28–29. \*\*Pregnancy Category D in third trimester. \*\*\*naratriptan, frovatriptan, almotriptan can also be considered but are NF. **NF = Not currently on VA National Formulary**; HA = headache; IM = intramuscular; IV = intravenous; MOH = medication overuse headache; ODT = orally disintegrating tablet; OUD = opioid use disorder; SC = subcutaneous; SNRI = serotonin norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors.

Moderate to Severe First Line: Level A	Recommended Dose	Pregnancy Category*	Considerations
<b>Triptans:*** Sumatriptan</b>	Oral: 25–100 mg; may repeat after 2 hours. SC: 6 mg/0.5 ml; may repeat after 1 hour. Nasal: 5–20 mg/spray; may repeat after 2 hours.	C	Nasal and subcutaneous routes have a faster onset and are useful in patients with vomiting.  Limit of 9 tablets/month recommended to reduce risk of MOH.
<b>Rizatriptan</b>	Oral: 5–10 mg; ODT: 5–10 mg; may repeat after 2 hours.	C	Addition of NSAID may improve efficacy.  Contraindicated in patients with coronary artery disease and stroke.
<b>Zolmitriptan</b>	Oral: 1.25–5 mg, ODT: 2.5–5 mg; may repeat after 2 hours. Nasal: 5 mg/spray; may repeat after 2 hours.	C	Caution of possible serotonin syndrome when used with other serotonergic agents like SSRI, SNRI, bupropion, or tramadol.
<b>Eletriptan</b>	Oral: 20–40 mg; may repeat after 2 hours.	C	

\*Pregnancy categories are defined on page 28–29. \*\*Pregnancy Category D in third trimester. \*\*\*natriptan, frovatriptan, almotriptan can also be considered but are NF. **NF = Not currently on VA National Formulary**; HA = headache; IM = intramuscular; IV = intravenous; MOH = medication overuse headache; ODT = orally disintegrating tablet; OUD = opioid use disorder; SC = subcutaneous; SNRI = serotonin norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors.

Moderate to Severe First Line: Level A	Recommended Dose	Pregnancy Category*	Considerations
<b>Ergots:</b>  <b>Intranasal Dihydroergotamine<sup>NF</sup></b> <b>4 mg DHE/ml</b>	One spray in each nostril at HA onset, repeat in 15 minutes. Do not exceed 6 sprays/24 hours or 8 sprays in 7 day period	X	Contraindicated in patients with coronary artery disease and stroke.  Consider if patient does not respond to or cannot use a triptan.  Must wait at least 24 hours after triptan dose to use ergotamine products.

\*Pregnancy categories are defined on page 28–29. \*\*Pregnancy Category D in third trimester. \*\*\*naratriptan, frovatriptan, almotriptan can also be considered but are NF. **NF = Not currently on VA National Formulary**; HA = headache; IM = intramuscular; IV = intravenous; MOH = medication overuse headache; ODT = orally disintegrating tablet; OUD = opioid use disorder; SC = subcutaneous; SNRI = serotonin norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors.

Second Line: Level B	Recommended Dose	Pregnancy Category*	Considerations
<b>Ergots:</b> <b>Dihydroergotamine mesylate (DHE) injection</b>	1 mg IV/IM/SC every hour PRN; not to exceed 2 mg IV or 3 mg IM/SC per 24 hour period; not to exceed 6 mg within one week	X	Contraindicated in patients with coronary artery disease and stroke.  Consider if patient does not respond to or cannot use a triptan. Must wait at least 24 hours after triptan dose to use ergotamine products.
<b>Recommend Against</b>			<b>Considerations</b>
<b>Opioids</b> <b>Tramadol</b> <b>Butalbital Products</b>			Avoid due to risk of MOH, OUD, and possible overdose with repetitive doses.

\*Pregnancy categories are defined on page 28–29. \*\*Pregnancy Category D in third trimester. \*\*\*naratriptan, frovatriptan, almotriptan can also be considered but are NF. **NF = Not currently on VA National Formulary**; HA = headache; IM = intramuscular; IV = intravenous; MOH = medication overuse headache; ODT = orally disintegrating tablet; OUD = opioid use disorder; SC = subcutaneous; SNRI = serotonin norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors.

## Adjunctive Medications for Nausea/Vomiting

Medication	Recommended Dose	Pregnancy Category*	Considerations
Prochlorperazine	5–10 mg oral every 4–6 hours as needed	C	May cause drowsiness, may cause sun-sensitivity (use sunscreen), report any visual disturbances, report any problems with extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome.
Promethazine	25 mg tablet or suppository every 4–6 hours as needed	C	
Chlorpromazine	10–25 mg oral every 4–6 hours as needed	C	
<b>Recommend Against:</b> Metoclopramide Tablet and Injection			FDA black box warning for possible permanent dyskinesia, especially in patients with frequent sustained use.

\*Pregnancy categories are defined on page 28–29.

## Preventive Treatment for Migraine Headaches<sup>7-10,14-18</sup>

First Line: Level A	Starting Dose	Recommended Dose	Pregnancy Category*	Considerations
<b>Beta Blockers:</b>				
<b>Metoprolol</b>	12.5–25 mg twice daily	100 mg twice daily	C	Consider in patients with coexisting hypertension or coronary artery disease (CAD).
<b>Propranolol</b>	80 mg SA daily	160–240 mg SA daily	C	Avoid beta blockers in presence of significant bronchospastic lung disease, bradycardia, hypoglycemia associated with diabetes therapies, or concurrent administration of allergy injections. Do not discontinue abruptly; taper slowly to prevent rebound hypertension and tachycardia.
<b>Timolol<sup>NF</sup></b>	10 mg twice daily	10–15 mg twice daily	C	Magnesium is first line migraine prevention during pregnancy. Propranolol is used for patients unable to use magnesium.

\*Pregnancy categories are defined on page 28–29. \*\*Pregnancy category X for migraine prevention and category D for epilepsy. \*\*\*Use antidepressants with caution in patients with risk for suicide. \*\*\*\*Pregnancy category D in third trimester. †See VA PBM Criteria for Use for Botulinum Toxin at [www.cmopnational.va.gov/cmop/PBM/default.aspx](http://www.cmopnational.va.gov/cmop/PBM/default.aspx). **NF = Not currently on VA National Formulary**; ER = extended release; MOH = medication overuse headache; OUD = opioid use disorder; SA = sustained release; SC = subcutaneous injection.

First Line: Level A	Starting Dose	Recommended Dose	Pregnancy Category*	Considerations
<b>Antiepileptic Drugs:</b>  <b>Topiramate</b>	25 mg at bedtime	50–100 mg to 100–200 mg at bedtime or separate dosing twice daily	D	May help for weight loss, consider in patients who have had weight gain with other seizure or antidepressant medications. Doses > 200 mg/day can reduce ethinyl estradiol serum concentrations in patients taking oral contraceptives; consider alternative method of birth control.
<b>Divalproex Sodium</b>	500 mg ER daily	1000 mg ER daily	X**	Consider in patients with mood disorders or seizure disorders. May cause weight gain. Black box warning for hepatotoxicity and pancreatitis. Need to monitor liver function tests.

\*Pregnancy categories are defined on page 28–29. \*\*Pregnancy category X for migraine prevention and category D for epilepsy. \*\*\*Use antidepressants with caution in patients with risk for suicide. \*\*\*\*Pregnancy category D in third trimester. †See VA PBM Criteria for Use for Botulinum Toxin at [www.cmopnational.va.gov/cmop/PBM/default.aspx](http://www.cmopnational.va.gov/cmop/PBM/default.aspx). **NF = Not currently on VA National Formulary**; ER = extended release; MOH = medication overuse headache; OUD = opioid use disorder; SA = sustained release; SC = subcutaneous injection.



First Line: Level A	Starting Dose	Recommended Dose	Pregnancy Category*	Considerations
<b>Valproic Acid Capsule</b>	250 mg twice daily	500–750 mg twice daily	X**	Similar side effects to divalproex. Syrup (250 mg/5 ml) available for patients unable to take capsules. Syrup on VA National Formulary, for patients who cannot take capsules.
Second Line: Level B	Starting Dose	Recommended Dose	Pregnancy Category*	Considerations
<b>Antidepressants:*** Amitriptyline</b>	10–25 mg at bedtime	25–100 mg at bedtime	C	Significant anticholinergic side effects, could consider nortriptyline or desipramine which have lower rates of anticholinergic side effects. For dosing of nortriptyline, desipramine, and imipramine see Preventive Treatment for Tension-Type Headaches (TTH) page 4.

\*Pregnancy categories are defined on page 28–29. \*\*Pregnancy category X for migraine prevention and category D for epilepsy. \*\*\*Use antidepressants with caution in patients with risk for suicide. \*\*\*\*Pregnancy category D in third trimester. \*See VA PBM Criteria for Use for Botulium Toxin at [vaww.cmopnational.va.gov/cmop/PBM/default.aspx](http://vaww.cmopnational.va.gov/cmop/PBM/default.aspx). **NF = Not currently on VA National Formulary**; ER = extended release; MOH = medication overuse headache; OUD = opioid use disorder; SA = sustained release; SC = subcutaneous injection.

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Second Line: Level B	Starting Dose	Recommended Dose	Pregnancy Category*	Considerations
Venlafaxine	37.5 mg ER daily	75–225 mg ER daily	C	Can also help with depressive symptoms and neuropathic pain; higher doses may increase blood pressure.
<b>Beta Blockers:</b>				See Beta Blockers section on page 13.
Atenolol	25–50 mg daily	50–100 mg daily	D	
Nadolol <sup>NF</sup>	20–40 mg daily	80–160 mg daily	C	

\*Pregnancy categories are defined on page 28–29. \*\*Pregnancy category X for migraine prevention and category D for epilepsy. \*\*\*Use antidepressants with caution in patients with risk for suicide. \*\*\*\*Pregnancy category D in third trimester. †See VA PBM Criteria for Use for Botulium Toxin at [vaww.cmopnational.va.gov/cmop/PBM/default.aspx](http://vaww.cmopnational.va.gov/cmop/PBM/default.aspx). **NF = Not currently on VA National Formulary**; ER = extended release; MOH = medication overuse headache; OUD = opioid use disorder; SA = sustained release; SC = subcutaneous injection.

Third Line: Level C	Starting Dose	Recommended Dose	Pregnancy Category*	Considerations
<b>Antihypertensives:</b>				
<b>Lisinopril</b>	5–10 mg daily	10–20 mg daily	C/D****	Can also help with hypertension and heart failure treatment.
<b>Clonidine</b>	0.05 mg twice daily	0.1 mg twice daily	C	Can also help with hypertension treatment. Do not discontinue abruptly; taper slowly to prevent rebound hypertension and agitation.
<b>Guanfacine</b>	0.5 mg at bedtime	0.5–1 mg daily	B	Can also help with hypertension and attention deficit disorder treatment (prior authorization might be necessary).
<b>Candesartan<sup>NF</sup></b>	8 mg daily	16 mg daily	C/D****	Can also help with hypertension and heart failure treatment.

\*Pregnancy categories are defined on page 28–29. \*\*Pregnancy category X for migraine prevention and category D for epilepsy. \*\*\*Use antidepressants with caution in patients with risk for suicide. \*\*\*\*Pregnancy category D in third trimester. \*See VA PBM Criteria for Use for Botulinum Toxin at [vaww.cmopnational.va.gov/cmop/PBM/default.aspx](http://vaww.cmopnational.va.gov/cmop/PBM/default.aspx). **NF = Not currently on VA National Formulary**; ER = extended release; MOH = medication overuse headache; OUD = opioid use disorder; SA = sustained release; SC = subcutaneous injection.

Third Line: Level C	Starting Dose	Recommended Dose	Pregnancy Category*	Considerations
<b>Antihistamine: Cypheptadine</b>	2 mg twice daily	4–8 mg twice daily	B	First generation antihistamine with significant anticholinergic effects. Combining with propranolol may increase efficacy.
<b>Botulinum Toxin</b>	SC to head/ neck every 12 weeks	SC to head/neck every 12 weeks	C	Consider for patients with headaches ≥15 days a month not responding to first and second line agents. Efficacy only shown for chronic migraines. <sup>‡</sup>
<b>Recommend Against</b>				<b>Considerations</b>
<b>Opioids Tramadol Butalbital Products</b>				Avoid due to risk of MOH, OUD, and possible overdose with repetitive doses.

\*Pregnancy categories are defined on page 28–29. \*\*Pregnancy category X for migraine prevention and category D for epilepsy. \*\*\*Use antidepressants with caution in patients with risk for suicide. \*\*\*\*Pregnancy category D in third trimester. †See VA PBM Criteria for Use for Botulinum Toxin at [vaww.cmopnational.va.gov/cmop/PBM/default.aspx](http://vaww.cmopnational.va.gov/cmop/PBM/default.aspx). **NF = Not currently on VA National Formulary**; ER = extended release; MOH = medication overuse headache; OUD = opioid use disorder; SA = sustained release; SC = subcutaneous injection.

## Acute Treatment for Cluster Headaches<sup>7-10,19-27</sup>

First Line: Level A	Recommended Dose	Pregnancy Category*	Considerations
<b>Oxygen</b>	100% oxygen with flow of 6–12 L/minute for 15 minutes via face mask	N/A	Effective as monotherapy in about 60% of patients. Most effective in combination with triptan. Consider home oxygen therapy.
<b>Triptans:</b>			
<b>Sumatriptan</b>	SC: 6 mg/0.5 ml; may repeat in 1 hour Nasal: 5–20 mg/spray may repeat after 2 hours.	C	Injection is the preferred route since a fast onset is needed. Subcutaneous sumatriptan is effective in about 75% of patients.  Nasal spray is an alternative for patients unable or unwilling to use an injection.
<b>Zolmitriptan</b>	Nasal: 5 mg/spray; may repeat after 2 hours.	C	Triptans are contraindicated in patients with cardiovascular disease.

\*Pregnancy categories are defined on page 28–29. \*\*Level B evidence is for sumatriptan and zolmitriptan but can consider other triptans if those agents are not tolerated. Naratriptan, frovatriptan, almotriptan can also be considered but are not currently on formulary. SC = subcutaneous injection; ODT = orally disintegrating tablet; SSRI = selective serotonin reuptake inhibitors; SNRI = serotonin norepinephrine reuptake inhibitors; MOH = medication overuse headache; OUD = opioid use disorder.

Second Line: Level B	Recommended Dose	Pregnancy Category*	Considerations
<b>Triptans:</b> <b>Sumatriptan</b>  <b>Zolmitriptan</b>  <b>Rizatriptan**</b>  <b>Eletriptan**</b>	Oral: 25–100 mg; may repeat after 2 hours  Oral: 1.25–5 mg, ODT: 2.5–5 mg; may repeat after 2 hours.  Oral: 5–10 mg; ODT: 5–10 mg; may repeat after 2 hours.  Oral: 20–40 mg; may repeat after 2 hours.	C	Injectable and intranasal therapies are recommended first line before oral therapy since onset is slower with oral therapy.  Caution of possible serotonin syndrome when used with other serotonergic agents like SSRI, SNRI, bupropion, or tramadol.

\*Pregnancy categories are defined on page 28–29. \*\*Level B evidence is for sumatriptan and zolmitriptan but can consider other triptans if those agents are not tolerated. Naratriptan, frovatriptan, almotriptan can also be considered but are not currently on formulary. SC = subcutaneous injection; ODT = orally disintegrating tablet; SSRI = selective serotonin reuptake inhibitors; SNRI = serotonin norepinephrine reuptake inhibitors; MOH = medication overuse headache; OUD = opioid use disorder.

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Recommend Against			Considerations
Opioids Tramadol Butalbital Products			Avoid due to risk of MOH, OUD, and possible overdose with repetitive doses.

\*Pregnancy categories are defined on page 28–29. \*\*Level B evidence is for sumatriptan and zolmitriptan but can consider other triptans if those agents are not tolerated. Naratriptan, frovatriptan, almotriptan can also be considered but are not currently on formulary. SC = subcutaneous injection; ODT = orally disintegrating tablet; SSRI = selective serotonin reuptake inhibitors; SNRI = serotonin norepinephrine reuptake inhibitors; MOH = medication overuse headache; OUD = opioid use disorder.

## Preventive Treatment for Cluster Headache<sup>7-10,19-22,28-31</sup>

First Line: Level A	Starting Dose	Recommended Dose	Pregnancy Category*	Considerations
<b>Antihypertensive:</b> <b>Verapamil**</b>	120 mg ER daily	120–480 mg ER daily	C	Few drug interactions; well tolerated. Constipation with higher doses. Monitor for bradycardia and EKG changes.
Second Line: Level B	Starting Dose	Recommended Dose	Pregnancy Category*	Considerations
<b>Mood Stabilizer:</b> <b>Lithium***</b>	300 mg daily	600–900 mg daily in divided doses	D	Drug interactions; more side effects; need to monitor drug levels. Target serum levels 0.4–0.8 mEq/L.

\*Pregnancy categories are defined on page 28–29. \*\*Use single suboccipital injection of short and long-acting betamethasone as transitional therapy while starting verapamil. May consider doses >480 mg daily but should be referred to a headache specialist and have EKG monitoring.

\*\*\*Use for episodic and chronic cluster headache; all other preventatives were evaluated only for episodic cluster headache. **NF = Not currently on VA National Formulary**; ER = extended release; MOH = medication overuse headache; OUD = opioid use disorder.



Second Line: Level B	Starting Dose	Recommended Dose	Pregnancy Category*	Considerations
Antiepileptic: Topiramate***	25 mg daily	100–200 mg at bedtime or divided twice daily	D	May help for weight loss, consider in patients who have had weight gain with other seizure or antidepressant medications. Doses > 200 mg/day associated with reduction in ethinyl estradiol serum concentrations in patients taking oral contraceptives; alternative method of birth control should be considered.

\*Pregnancy categories are defined on page 28–29. \*\*Use single suboccipital injection of short and long-acting betamethasone as transitional therapy while starting verapamil. May consider doses >480 mg daily but should be referred to a headache specialist and have EKG monitoring. \*\*\*Use for episodic and chronic cluster headache; all other preventatives were evaluated only for episodic cluster headache. **NF = Not currently on VA National Formulary**; ER = extended release; MOH = medication overuse headache; OUD = opioid use disorder.

Third Line: Level C	Starting Dose	Recommended Dose	Pregnancy Category*	Considerations
<b>Antiepileptic:</b>  <b>Divalproex Sodium</b>  <b>Sodium Valproate***</b>	500 mg ER daily  250 mg twice daily	1000 mg ER daily  500–750 mg twice daily	X  X	Consider in patients with mood disorders or seizure disorders. Black box warning for hepatotoxicity and pancreatitis. Need to monitor liver function tests.  Similar side effects to divalproex. Syrup (250 mg/5 ml) available for patients unable to take capsules. Syrup also on VA National Formulary, restricted to patients who cannot take capsules.

\*Pregnancy categories are defined on page 28–29. \*\*Use single suboccipital injection of short and long-acting betamethasone as transitional therapy while starting verapamil. May consider doses >480 mg daily but should be referred to a headache specialist and have EKG monitoring.

\*\*\*Use for episodic and chronic cluster headache; all other preventatives were evaluated only for episodic cluster headache. **NF = Not currently on VA National Formulary**; ER = extended release; MOH = medication overuse headache; OUD = opioid use disorder.

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Third Line: Level C	Starting Dose	Recommended Dose	Pregnancy Category*	Considerations
<b>Antispasmodic:</b>  <b>Baclofen***</b>	5 mg two to three times daily	5–10 mg two to three times daily	C	May cause drowsiness. Caution for patient needing to drive, operate heavy machinery. Possible fall risk in elderly and patients with balance problems.
<b>Recommend Against</b>				<b>Considerations</b>
<b>Opioids</b> <b>Tramadol</b> <b>Butalbital Products</b>				Avoid due to risk of MOH, OUD, and possible overdose with repetitive doses.

\*Pregnancy categories are defined on page 28–29. \*\*Use single suboccipital injection of short and long-acting betamethasone as transitional therapy while starting verapamil. May consider doses >480 mg daily but should be referred to a headache specialist and have EKG monitoring.

\*\*\*Use for episodic and chronic cluster headache; all other preventatives were evaluated only for episodic cluster headache. **NF = Not currently on VA National Formulary**; ER = extended release; MOH = medication overuse headache; OUD = opioid use disorder.

## Dietary Supplements\* for Headache Treatment<sup>7,8,17,22,32-40</sup>

Second Line: Level B	Type of Headache	Recommended Dose	Pregnancy Category**	Considerations
<b>Magnesium (Hydroxide, Oxide)</b>	Migraine prophylaxis	400–1200mg daily; dosed once or twice a day	Likely safe***	Diarrhea is common with use of magnesium. Can be used for the prevention and treatment of migraine in pregnancy.
<b>Riboflavin (Vitamin B2)<sup>‡</sup></b>	Migraine prophylaxis	400 mg daily	Possibly safe****	Diarrhea and frequent urination can occur. May cause fluorescent yellow discoloration of urine.
<b>Petasites (Butterbur)<sup>‡</sup></b>	Migraine Prophylaxis	50–75 mg twice daily	Likely unsafe	May cause excessive belching. Important to use preparations having pyrrolizidine alkaloids (PA) removed, since these can be carcinogenic, hepatotoxic and cause bleeding problems. Supplements should be labeled PA-free. Petadolex <sup>®</sup> brand is PA-free.

\*Federal law does not require dietary supplements (nutraceuticals) to be proven safe or effective to FDA standards before being sold to consumers. \*\*FDA has not listed a pregnancy category for most nutraceuticals, pregnancy risk categories are from Natural Medicine Database. \*\*\*parenteral magnesium sulfate is pregnancy category D but oral magnesium sulfate and other salts have been classified as likely safe. \*\*\*\*likely safe at the recommended dietary allowance of 1.4 mg a day but possibly safe at higher doses. ‡Not available from VA Pharmacy.

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Third Line: Level C	Type of Headache	Recommended Dose	Pregnancy Category	Considerations
Melatonin	Cluster Prophylaxis	10 mg at bedtime	Possibly unsafe	Need to use for 4–8 weeks to determine efficacy.
Coenzyme Q10 <sup>±</sup>	Migraine Prophylaxis	100 mg three times daily	Possibly unsafe	Need to use for a minimum of three months to determine efficacy.

\*Federal law does not require dietary supplements (nutraceuticals) to be proven safe or effective to FDA standards before being sold to consumers. \*\*FDA has not listed a pregnancy category for most nutraceuticals, pregnancy risk categories are from Natural Medicine Database. \*\*\*parenteral magnesium sulfate is pregnancy category D but oral magnesium sulfate and other salts have been classified as likely safe. \*\*\*\*likely safe at the recommended dietary allowance of 1.4 mg a day but possibly safe at higher doses. <sup>±</sup>Not available from VA Pharmacy.

## US FDA Pregnancy Category Definitions\*

Category	Definition
<b>A</b>	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.
<b>B</b>	Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
<b>C</b>	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

\*New FDA ruling, the Pregnancy and Lactation Labeling Rule (PLLR) requires removal of pregnancy letter categories by June 2020. PLLR labeling not currently available for the drugs listed in this Quick Reference Guide.

continued from page 28 (US FDA Pregnancy Category Definitions\*)

Category	Definition
<b>D</b>	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
<b>X</b>	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

\*New FDA ruling, the Pregnancy and Lactation Labeling Rule (PLLR) requires removal of pregnancy letter categories by June 2020. PLLR labeling not currently available for the drugs listed in this Quick Reference Guide.

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# U.S. Department of Veterans Affairs

This reference guide was created to be used as a tool for VA providers and is available to use from the Academic Detailing SharePoint. These are general recommendations only; specific clinical decisions should be made by the treating provider based on an individual patient's clinical condition.

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