# Treat the Patient, Not the Level: A Focus on Psychotropic Medication Associated Lab Abnormalities


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# Objectives

- Recall the significance of hyperammonemia, elevated TSH, hyperprolactinemia and clozapine levels in patients taking psychotropic medications
- Recognize mechanisms of psychotropic medications that may result in these lab abnormalities
- Identify clinically significant lab abnormalities associated with psychotropic medications and appropriate treatments

# Abbreviations

- VPA: valproic acid
- GABA: gamma-aminobutyric acid
- PHT: phenytoin
- PHB: phenobarbital
- CBZ: carbamazepine
- NSAIDs: non-steroidal anti-inflammatory drugs
- ACE-I: angiotensin converting enzyme inhibitor
- CKD: chronic kidney disease
- PCOS: polycystic ovary syndrome
- TDM: therapeutic drug monitoring
- PPD: pack per day

# Valproic Acid Induced Hyperammonemia

# Valproic Acid

## Mechanism

- Inhibits voltage-sensitive sodium channels
- Increase GABA
- Regulates downstream signal transduction cascades

## Side Effects

- Hepatotoxicity, thrombocytopenia, and hyperammonemia

## Serum Level

- Goal: 50 – 100mcg/L (125mcg/L in bipolar)

## Lab Monitoring

- Steady State: ~3 days
- Baseline liver enzymes, platelets, and albumin

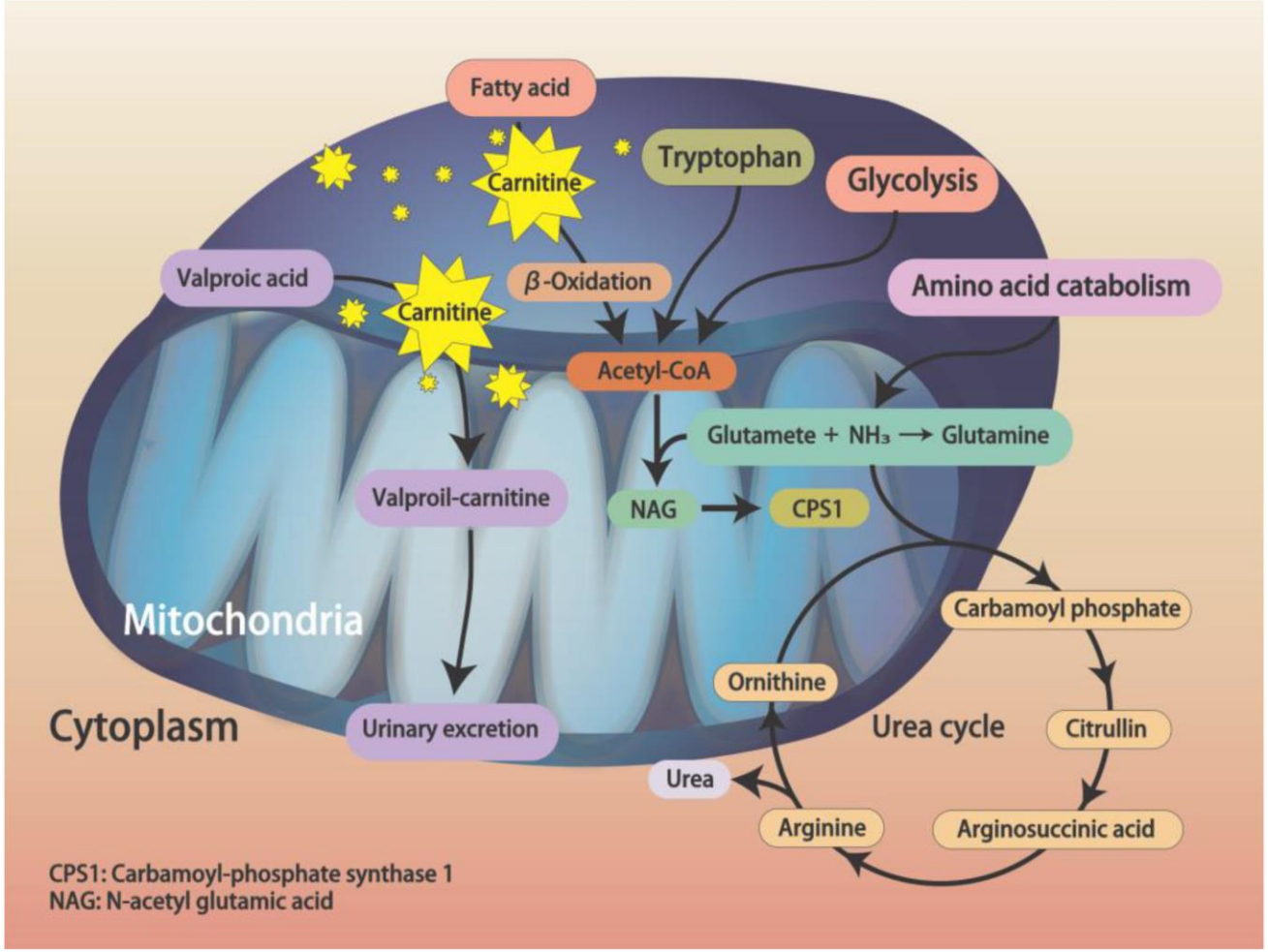
## Interactions

- Anticoagulants
- Phenytoin, phenobarbital
- Carbamazepine
- Lamotrigine
- Carbapenems

Valproic Acid. Package Insert.

# Background

- Ammonia is produced by metabolism of amino acids and other nitrogen containing products
  - Converted by the liver into urea to be excreted
- Carnitine is responsible for the transport and oxidation of fatty acids in the mitochondria




*Brain Sci.* 2020, 10, 187


Biochemistry, Ammonia. StatPearls
*Brain Sci.* 2020, 10, 187
*Clin Toxicol (Phila)*. 2009;47(2):101-111.

# Valproic Acid Induced Hyperammonemia

## Prevalence

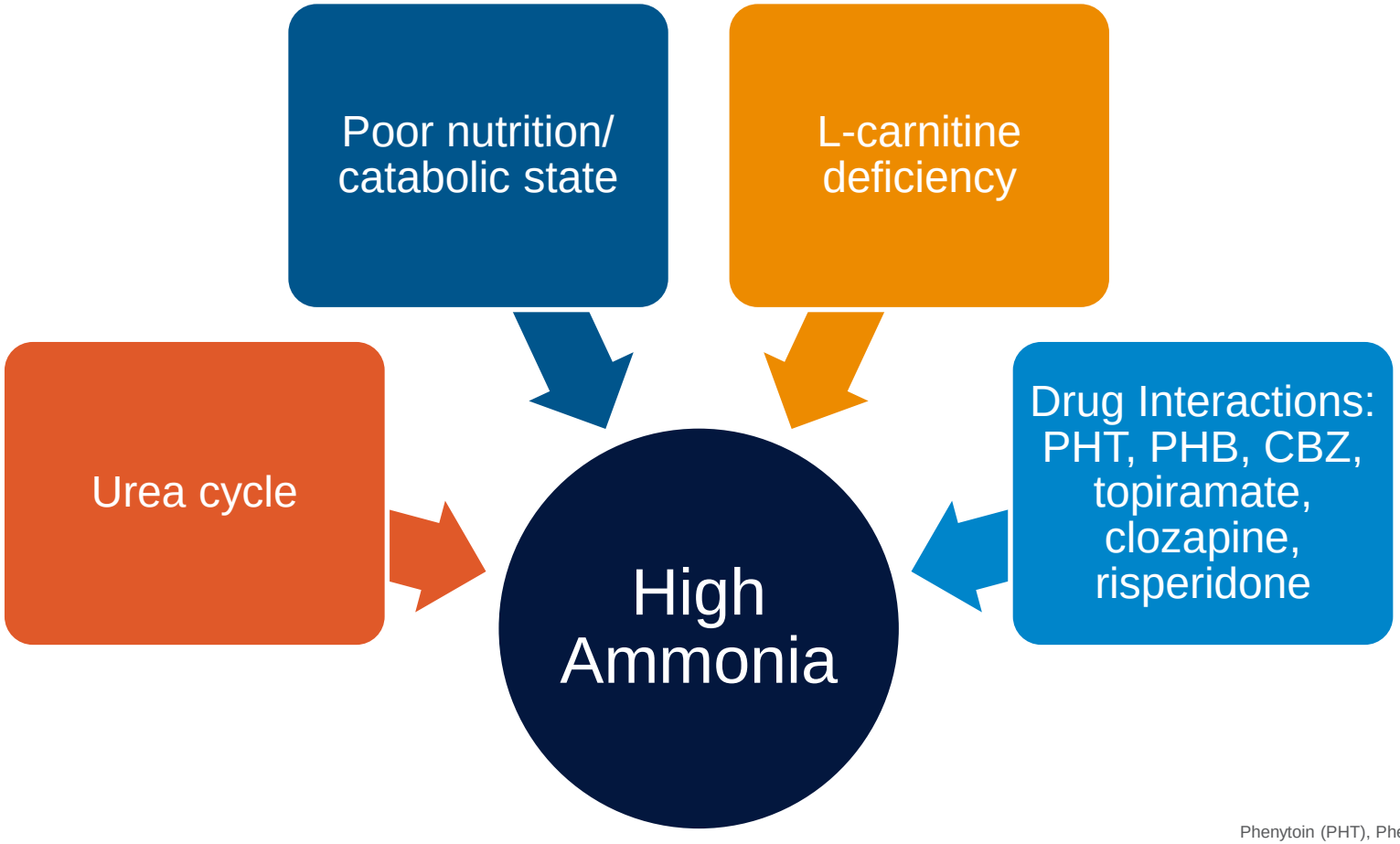
- VPA hepatic encephalopathy is rare
- 16-52% of high ammonia levels is asymptomatic

## Mechanism

- Disruption of the urea cycle
- Hepatic & renal process
- Affects renal uptake of glutamine
- L-carnitine deficiency

*Clin Toxicol (Phila)*. 2009;47(2):101-111.
*The Journal of the American Board of Family Medicine*. 2007;20(5):499-502.

# Risk Factors




Phenytoin (PHT), Phenobarbital (PHB). Carbamazepine (CBZ)

# Stages

- Stage 0: Minimal changes in concentration and memory
- Stage 1: Changes in sleep, lack of awareness and shortened attention span
- Stage 2: Lethargy, apathy, personality changes and slurred speech
- Stage 3: Drowsiness, marked confusion and disorientation
- Stage 4: Loss of consciousness and coma

Hyperammonemia. StatPearls

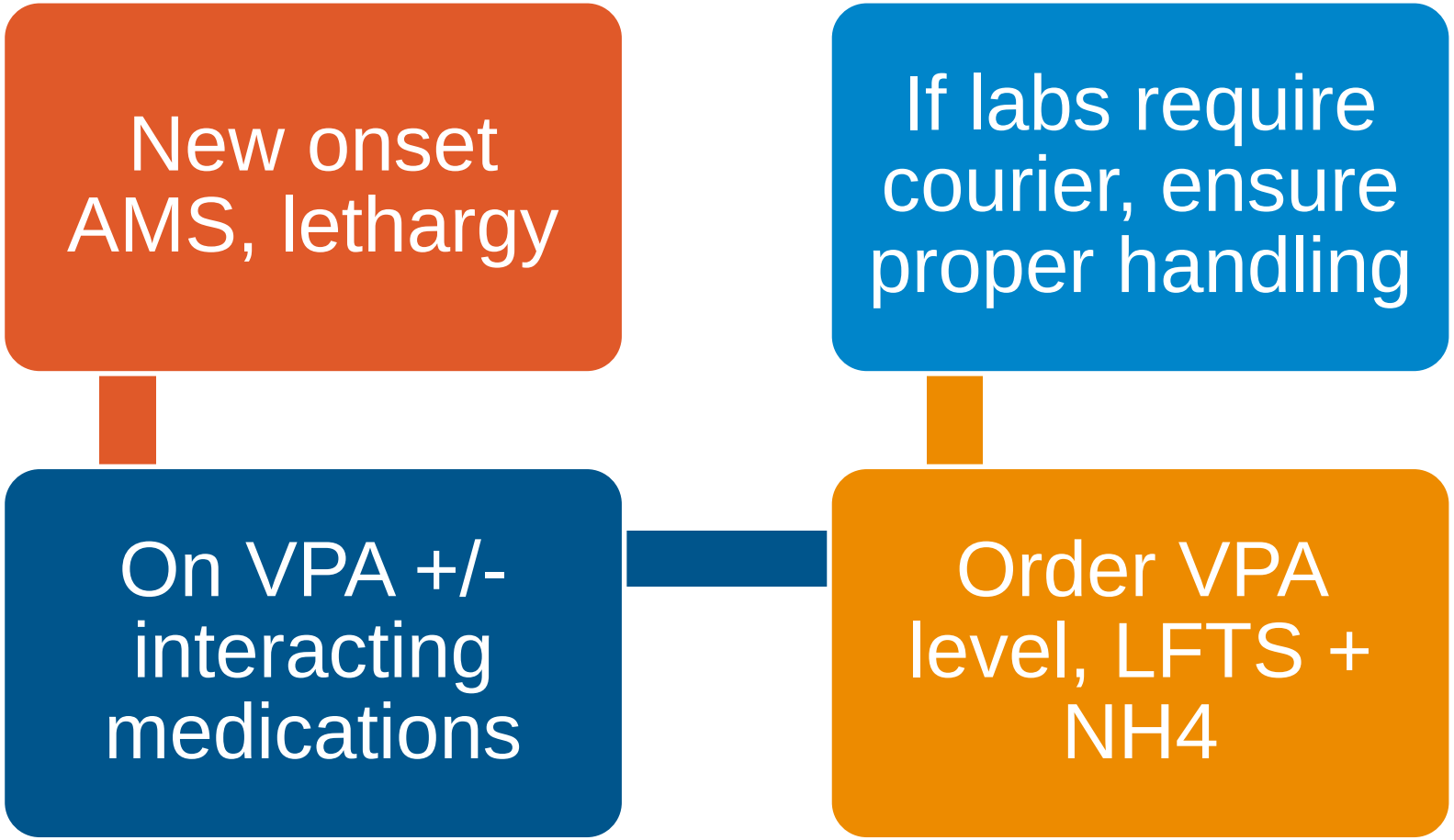
# Monitoring

| Age | Normal Ammonia Level |
|---|---|
| Children (> 1 month old) | < 50 micromol/L |
| Adults | < 30 micromol/L |

- Cut-off levels vary based on individual site
- Currently no screening requirements for patient's presenting with asymptomatic hyperammonemia

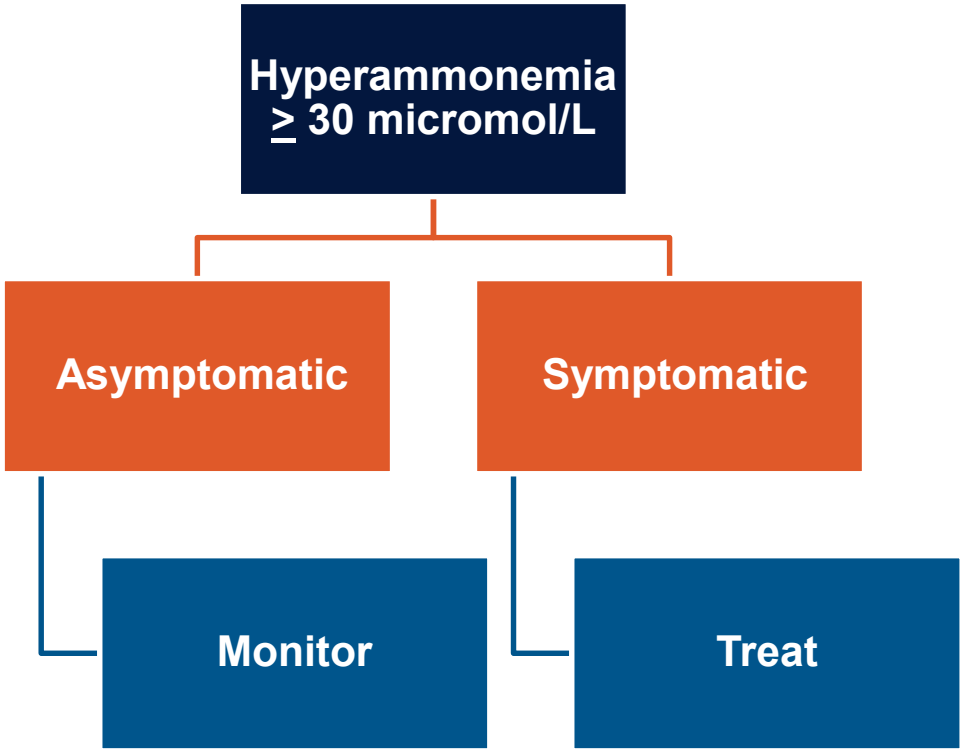
*Ment Health Clin*. 2018 Mar; 8(2):73-7.
Perspect Psychiatr Care. 2013;49(4):221-225

# Proper Interpretation of ammonia




Perspect Psychiatr Care. 2013;49(4):221-225

# Management




*Ment Health Clin*. 2018 Mar; 8(2):73-7.

# Treatment

| Lactulose | Levocarnitine | Dose Reduction of VPA | Discontinuation of VPA |
|---|---|---|---|
| • Binds to ammonia and increases excretion<br>• 20 – 30 g PO 2-4 times daily<br>• Side Effects: diarrhea, abdominal cramping, bloating, flatulence | • Supplements carnitine in the body<br>• 330 mg PO TID<br>• Side Effects: nausea, stomach discomfort | • Clinician preference on how much to decrease | • Recommended but not always possible |

*Ment Health Clin*. 2018 Mar; 8(2):73-7.
*Nutrients*. 2018;10(2):140.

# Treatment

## Rifaximin is not recommended for treatment of VPA induced hyperammonemia

- Works by inhibiting RNA synthesis in ammonia producing bacteria

## Some evidence for levocarnitine prophylaxis

- More research needs to be done to determine place in therapy

## Lactulose vs. Levocarnitine

- Levocarnitine recommended more often in literature
- Better tolerability
- Directly impacts VPA mechanism of action

Rifaximin. UpToDate
*Nutrients*. 2018;10(2):140.

# Literature Review
# Hyperammonemia in Patients Receiving Valproic Acid in the Hospital Setting

| Study Type | Inclusion Group | Outcomes |
|---|---|---|
| Retrospective review<br><br>Evaluated incidence of VPA-induced hyperammonemia in an adult inpatient population | Adults who received at least one dose of VPA | Incidence of hyperammonemia<br><br>Symptoms of hyperammonemia, diagnosis of VPA induced hyperammonemia, and treatment of VPA induced hyperammonemia |

*Ment Health Clin*. 2021;11(4):243-7.

# Literature Review
# Hyperammonemia in Patients Receiving Valproic Acid in the Hospital Setting

| Outcomes of VPA Therapy | |
|---|---|
| **Diagnosis** | **N (%)** |
| Hyperammonemia | 33 (20.4) |
| Symptomatic hyperammonemia | 26 (16.0) |
| VPA induced hyperammonemia | 13 (8.0) |
| Symptomatic VPA induced hyperammonemia | 12 (7.4) |

**While 20.4% of patients who received VPA developed hyperammonemia, only 8.0% of cases were determined to be VPA-induced and 7.4% were VPA-induced *and* symptomatic.**

*Ment Health Clin*. 2021;11(4):243-7.

# Literature Review
# Valproic Acid–induced Hyperammonemia: Incidence, Clinical Significance & Treatment Management

| Study Type | Inclusion Group | Outcomes |
|---|---|---|
| Retrospective review<br><br>Evaluated prevalence of VPA-induced hyperammonemia in an adult inpatient psychiatric unit | Adults who received at least one dose of VPA and had at least one ammonia level drawn during admission | Prevalence of hyperammonemia<br><br>Treatment prevalence and success |

*Ment Health Clin.* 2018;8(2):73-77.

# Literature Review
# Valproic Acid–induced Hyperammonemia: Incidence, Clinical Significance, and Treatment Management

| Outcomes of VPA Therapy | | |
|---|---|---|
| **Regimen** | **Prevalence, N (%)** | **Successful treatment, N (%)** |
| Discontinuation of VPA | 32 (28.3) | 18 (56.3) |
| Levocarnitine | 38 (33.6) | 19 (50.0) |
| Lactulose and levocarnitine | 19 (16.8) | 9 (47.4) |
| Lactulose | 55 (48.7) | 23 (41.8) |
| Dose Reduction | 25 (22.1) | 10 (40.0) |
| No treatment | 24 (21.2) | 7 (29.2) |

**Lactulose treatment was the most common, however, discontinuation of VPA was the most successful treatment for hyperammonemia.**

Ment Health Clin. 2018;8(2):73-77.

# Assessment Question #1

A 32-year-old female presents for a routine check-up and lab work after initiating valproic acid a few months prior. Her blood work shows an ammonia level of 42 micromol/L. She denies any confusion, fatigue, or behavioral changes. **What is the clinical significance of her ammonia level?**

a. The patient is at high risk for hyperammonemic encephalopathy
b. The patient may have supratherapeutic VPA levels
c. The patient likely has a deficiency in L-carnitine and should receive supplementation
d. Not clinically significant

# Assessment Question #1: Correct Response

A 32-year-old female presents for a routine check-up and lab work after initiating valproic acid a few months prior. Her blood work shows an ammonia level of 42 micromol/L. She denies any confusion, fatigue, or behavioral changes. **What is the clinical significance of her ammonia level?**

a. The patient is at high risk for hyperammonemic encephalopathy
b. The patient may have supratherapeutic VPA levels
c. The patient likely has a deficiency in L-carnitine and should receive supplementation
**d. Not clinically significant**

# Assessment Question #2

Which of the following treatment options is appropriate in patient being treated with VPA who presents with altered mental status and an ammonia level of 60 micromol/L?

a. Lactulose
b. Levocarnitine
c. Discontinuation of valproic acid
d. Reduction in valproic acid dose
e. All of the above

# Assessment Question #2: Correct Response

Which of the following treatment options is appropriate in patient being treated with VPA who presents with altered mental status and an ammonia level of 60 micromol/L?

a. Lactulose
b. Levocarnitine
c. Discontinuation of valproic acid
d. Reduction in valproic acid dose
e. **All of the above**

# Lithium-induced Thyroid Dysfunction

# Lithium

## Mechanism

- Alters sodium transport in nerve and muscle cells, resulting in intraneuronal metabolism of catecholamines
- Enhances uptake of tryptophan
- Increased synthesis of serotonin

## Therapeutic monitoring

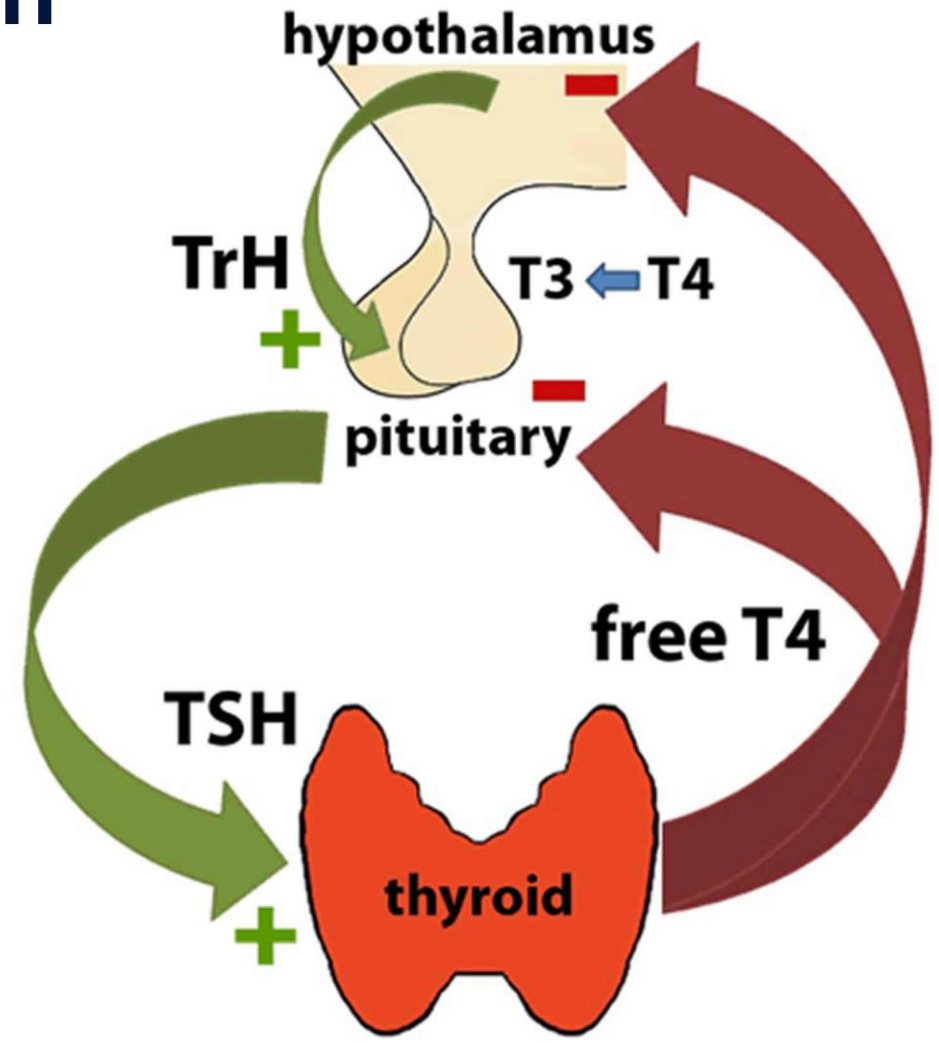
- Goal: 0.6 – 1.2 mEq/L
  - Steady state: ~ 5 days
- Monitor renal function & electrolytes with levels
- Baseline thyroid function

## What can effect lithium levels in the blood?

- Dehydration (vomiting, diarrhea)
- Renal function
- Sodium restriction
- Medications → NSAIDS, ACE-I

# Thyroid Hormone Regulation

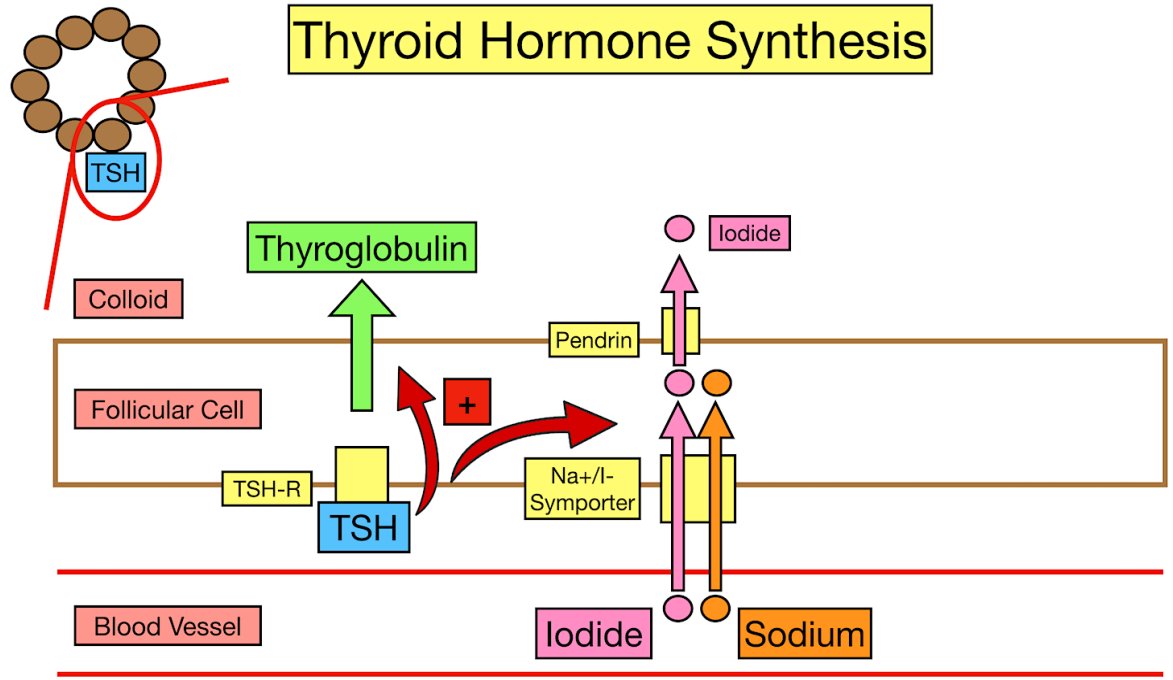
- Small, butterfly shaped gland located in the neck
- Physiology:
  - Hypothalamus
  - Pituitary
  - Thyroid
- Functions:
  - Makes and releases thyroxine (T4) and triiodothyronine (T3)




Professional CCM. Thyroid-Stimulating Hormone (TSH) levels. Cleveland Clinic

# Lithium Induced Thyroid Disorder

- Inhibits iodine uptake by blocking the Na-iodine transporter which prevents the formation of T3/T4
- Preventing the synthesis of T4/T3 causes the pituitary gland to increase TSH (negative feedback loop)




*International Journal of Bipolar Disorders*. 2016;4(1).
*J Physiol Pharmacol.* 2020;71(2):10.26402/jpp.2020.2.03.

# Lithium Induced Thyroid Disorder

## Goiter

- Swelling/enlargement of the thyroid gland
- Occurs in 40% of patients
- Can occur at any point during lithium treatment

## Hypothyroidism

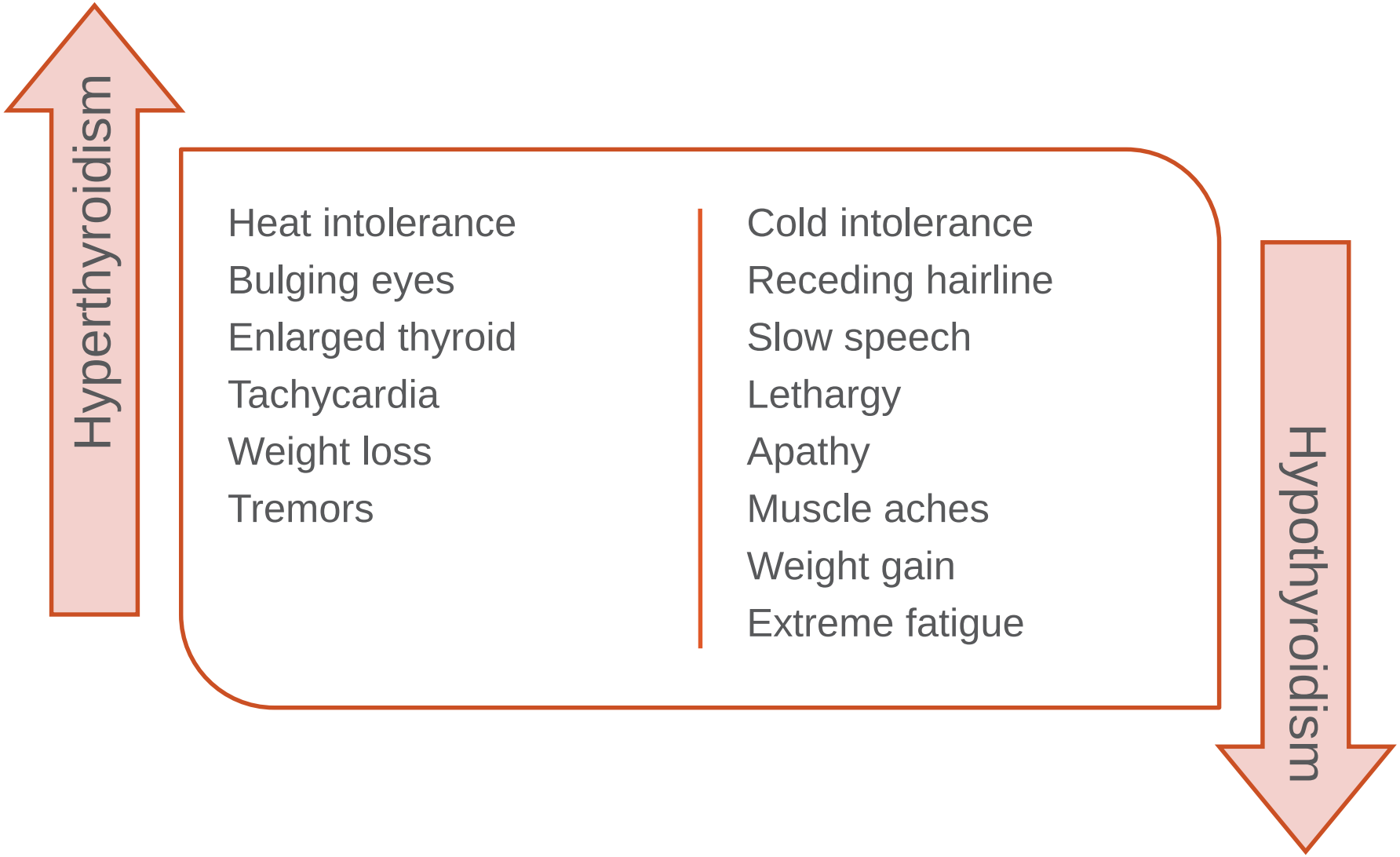
- Occurs in 20% of patients
- Onset of approximately 18 months

## Hyperthyroidism/Thyrotoxicosis

- Occurs in roughly 1.0 - 1.7% of patients
- Onset approximately 6 years
- Potentially fatal

*QJM: An International Journal of Medicine*, 2012;1,105:83–85

# Clinical Manifestations



# Thyroid Hormone Interpretation

| Free T4 | Free T3 | TSH | Significance |
|---|---|---|---|
| High | High | Low | Hyperthyroidism |
| Normal | High | Low | Early hyperthyroidism<br>T3- toxicosis |
| Normal | Normal | Low | Subclinical hyperthyroidism |
| Normal | Normal | Normal | Euthyroid |
| Normal/low | Normal/low | Normal/low | General ill health |
| Low | Normal | High | Subclinical hypothyroidism |
| Low | Normal/low | High | Hypothyroidism |

Thyroid disease | Sonic Bookings.

# Monitoring

## Lithium Initiation

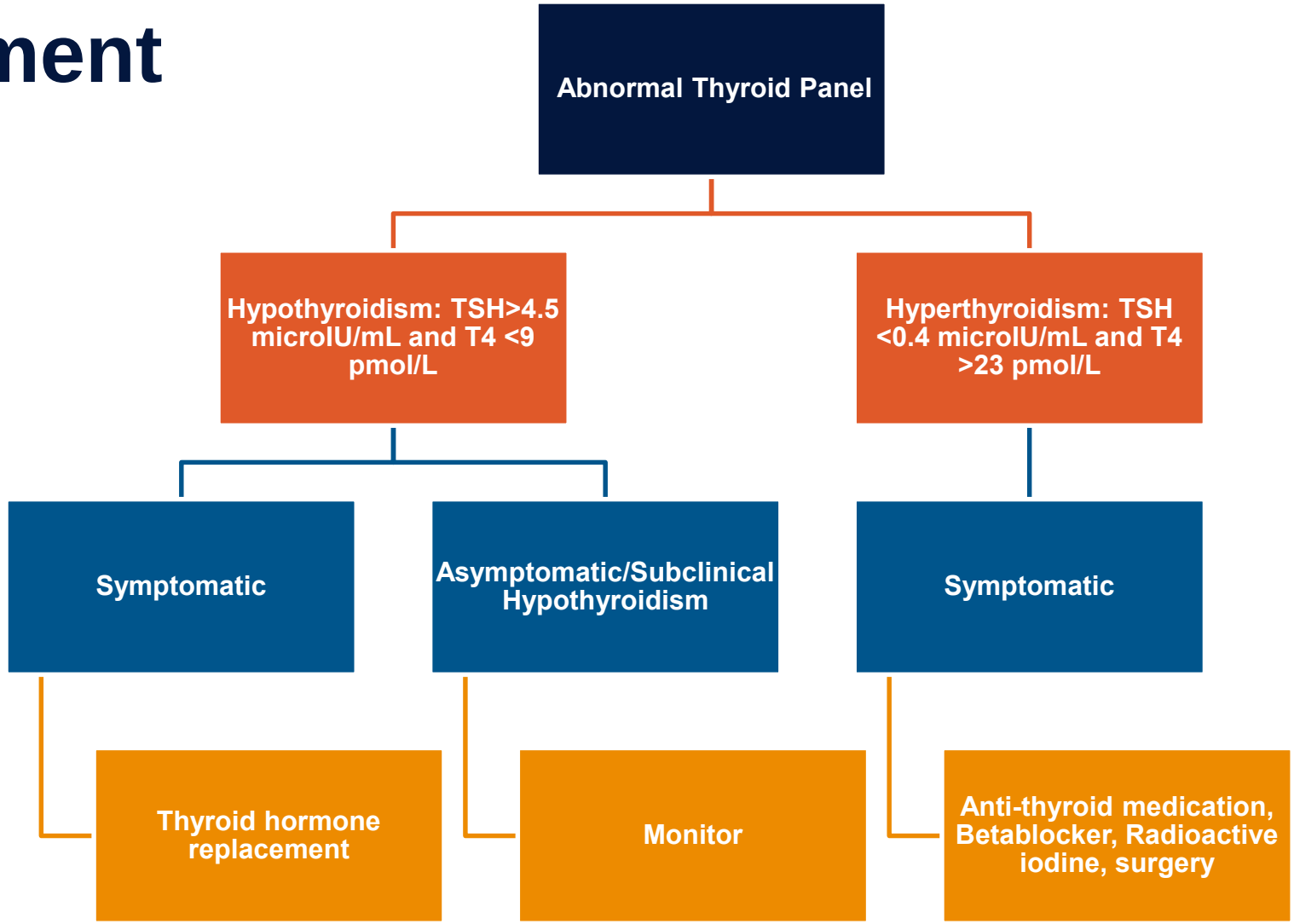
- Baseline thyroid function test
- Repeated at 1 year
- Yearly TSH labs thereafter
- Increased monitoring recommended if:
  - Female > 50 years old
  - Family history of thyroid disease
  - Thyroid auto-antibodies positive

## Lithium Induced Thyroid Dysfunction

- Baseline thyroid function test
- Repeat thyroid panel every 4-6 months
- Antibodies test and ultrasound scan every 2-3 years

*Clin Pract Epidemiol Ment Health*. 2006;2:23
*Thyroid Res*. 2013;6(1):3.

# Management





Lithium and the Thyroid. UpToDate. 2024
Subclinical Hypothyroidism. In: *StatPearls*.

# Treatment

## Hypothyroidism

- Levothyroxine 50 – 200 mcg PO daily

## Hyperthyroidism

- Beta blockers (propranolol, atenolol)
- Thionamides (methimazole)
- Radioiodine ablation
- Surgery

## Myxedema Coma

- Levothyroxine IV PLUS Liothyronine IV
  - Levothyroxine
    - Initial dose: 200 – 400mcg
    - Maintenance dose: 50 – 100mcg daily
  - Liothyronine
    - Initial dose: 5 – 20mcg
    - Maintenance dose: 2.5 - 10mcg every 8 hours

Lithium and the Thyroid. UpToDate. 2024
*Am Fam Physician. 2016;93(5):363-370.*
*Am Fam Physician.* 2000;62(11):2485-2490.

# Literature Review
# Long-term Lithium Therapy & Thyroid Disorders in Bipolar Disorder

| Study Type | Inclusion Group | Outcomes |
|---|---|---|
| Historical cohort study<br><br>Evaluated patients enrolled in the Bipolar Biobank at Mayo Clinic | Adults with bipolar disorder with lithium prescribed for a minimum of 1 year | Development of incident thyroid disorders |

*Brain Sci*. 2023;13(1):133.

# Literature Review
# Long-term Lithium Therapy & Thyroid Disorders in Bipolar Disorder

| Thyroid Status of Patients with Abnormal Thyroid Functioning | | |
|---|---|---|
| | Baseline (before lithium) | Study end (excluding baseline) |
| Hypothyroid/Hashimoto's | 11 | 29 |
| Subclinical Hypothyroid | 2 | 5 |
| Hyperthyroid (Graves' Disease) | 2 | 0 |
| Subclinical Hyperthyroid | 0 | 1 |
| Benign Nodule/Goiter | 1 | 7 |
| Toxic Nodule/Goiter | 0 | 1 |
| Total | 16 | 43 |

**One-third of patients receiving lithium developed a thyroid disorder, with the majority developing hypothyroidism.**

*Brain Sci*. 2023;13(1):133.

# Assessment Question #3

A patient presents with a chief complaint of fatigue, weight gain, and cold intolerance. She has been on lithium for the last 9 months for her bipolar disorder and has been tolerating it well. Her TSH comes back at 5.0 microIU/mL. What is the best option to treat this patient's hypothyroidism?

a. Stop lithium immediately
b. Start levothyroxine
c. No changes

# Assessment Question #3: Correct Response

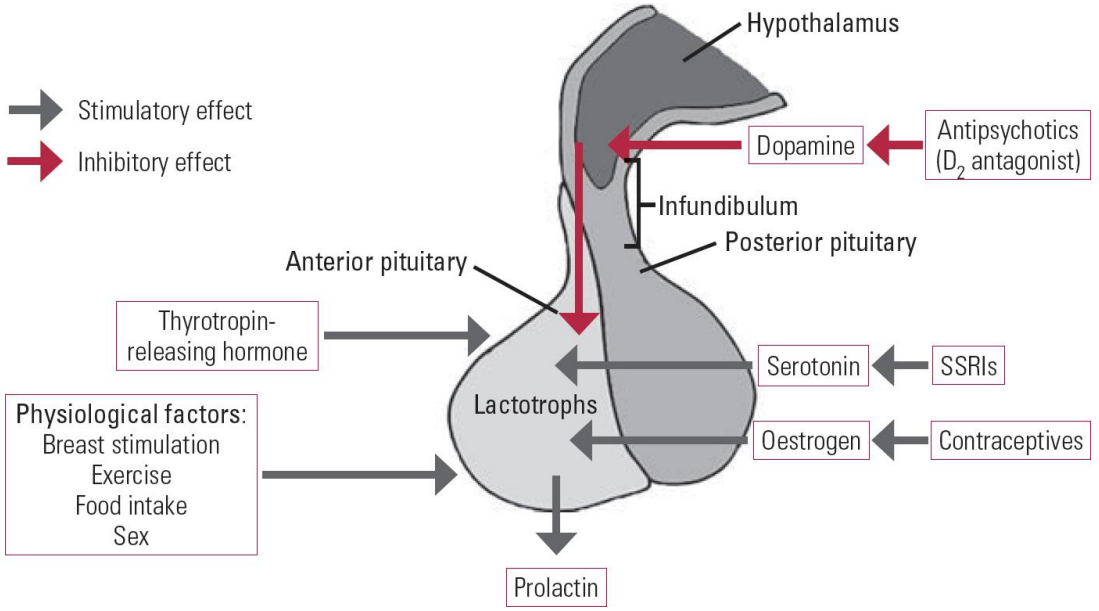
A patient presents with a chief complaint of fatigue, weight gain, and cold intolerance. She has been on lithium for the last 9 months for her bipolar disorder and has been tolerating it well. Her TSH comes back at 5.0 microIU/mL. What is the best option to treat this patient's hypothyroidism?

a. Stop lithium immediately
**b. Start levothyroxine**
c. No changes

# Antipsychotic Induced Hyperprolactinemia

# Prolactin

- Prolactin plays role in breast development and lactation in women
- Inducers of prolactin synthesis and secretion:
  - Estrogen
  - Thyrotropin-releasing hormone
  - Epidermal growth factor
  - **Dopamine receptor antagonists**




*BJPsych Advances*. 2017;23(4):278-286

*J of Clin Endocrinology & Metabolism. 2011;96(2):273-288*

# Prolactin Levels

| Population | Prolactin (µg/L) |
|---|---|
| Male | <20 |
| Non-pregnant female | <25 |
| Pregnant or lactating female | 200-600 |
| Female child/adolescent | 5-20 |

*N Engl J Med.* 2003;349:2035-2041
*BJPsych Advances*. 2017;23(4):278-286
*Acta Biomed*. 2019;90(1):149-157.

# Hyperprolactinemia

- Commonly associated with high potency first generation antipsychotics and some second-generation antipsychotics
  - Typically dose dependent
- Other causes: pregnancy/lactation, physical exercise, stress, food intake, hypothyroidism, CKD, PCOS, cirrhosis, epileptic seizure

*BJPsych Advances*. 2017;23(4):278-286

# Clinical Manifestations of Hyperprolactinemia

| Female | Male | Long-term Effects |
| --- | --- | --- |
| • Oligomenorrhea<br>• Amenorrhea<br>• Loss of libido<br>• Infertility<br>• Gynecomastia<br>• Galactorrhea | • Decreased libido<br>• Impotence<br>• Infertility<br>• Gynecomastia | • Osteoporosis<br>• Breast cancer |

*BJPsych Advances*. 2017;23(4):278-286

# Mechanisms that Influence Prolactin

## Increase Secretion

- Dopamine
- Serotonin
- Thyrotropin-releasing hormone (TRH)
- Oestrogen

## Decrease Secretion

- Gamma-aminobutyric acid (GABA)

*BJPsych Advances*. 2017;23(4):278-286

# Antipsychotic Induced Hyperprolactinemia Pathway

- Consequence of dopamine blockade in tuberoinfundibular pathway
- More common in first generation antipsychotics
- Second generation antipsychotics have lower D2-receptor affinity and stronger 5HT2A receptor blockage > milder prolactin elevations
  - Exceptions: **risperidone**, **paliperidone**
- Onset: prolactin levels increase within a few hours of initiating antipsychotic medication, reach a peak within 1–2 months and then gradually decrease

*BJPsych Advances*. 2017;23(4):278-286

# Medication Profiles

| Antipsychotic | Hyperprolactinemia Risk |
|---|---|
| Paliperidone | +++ |
| Risperidone | +++ |
| Typical antipsychotics | +++ |
| Lurasidone | ++ |
| Olanzapine | ++ (higher risk with increased doses) |
| Ziprasidone | ++ |
| Iloperidone | + |
| Asenapine | + |
| Aripiprazole | - |
| Brexpiprazole | - |
| Cariprazine | - |
| Clozapine | - |
| Quetiapine | - |
| Lumateperone | - |

*BJPsych Advances*. 2017;23(4):278-286
*DiPiro's Pharmacotherapy*. 2023.
*Int J Clin Pract*. 2015;69(11):1211-1220.

**+++: High Risk**
**++: Moderate Risk**
**+: Low Risk**
**-: Minimal or no risk**





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# Monitoring

- **Most guidelines do *not* recommend routine monitoring of prolactin levels in asymptomatic patients**
  - American Psychiatric Association (APA), Texas Medication Algorithm Project (TMAP), World Federation of Societies of Biological Psychiatry (WFSBP), Veterans Affairs/Department of Defense
- **Some guidelines recommend getting a baseline prolactin level**
  - National Institute for Health and Care Excellence (NICE), British Association for Psychopharmacology (BAP), Royal Australian and New Zealand College of Psychiatrists (RANZCP), Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD)

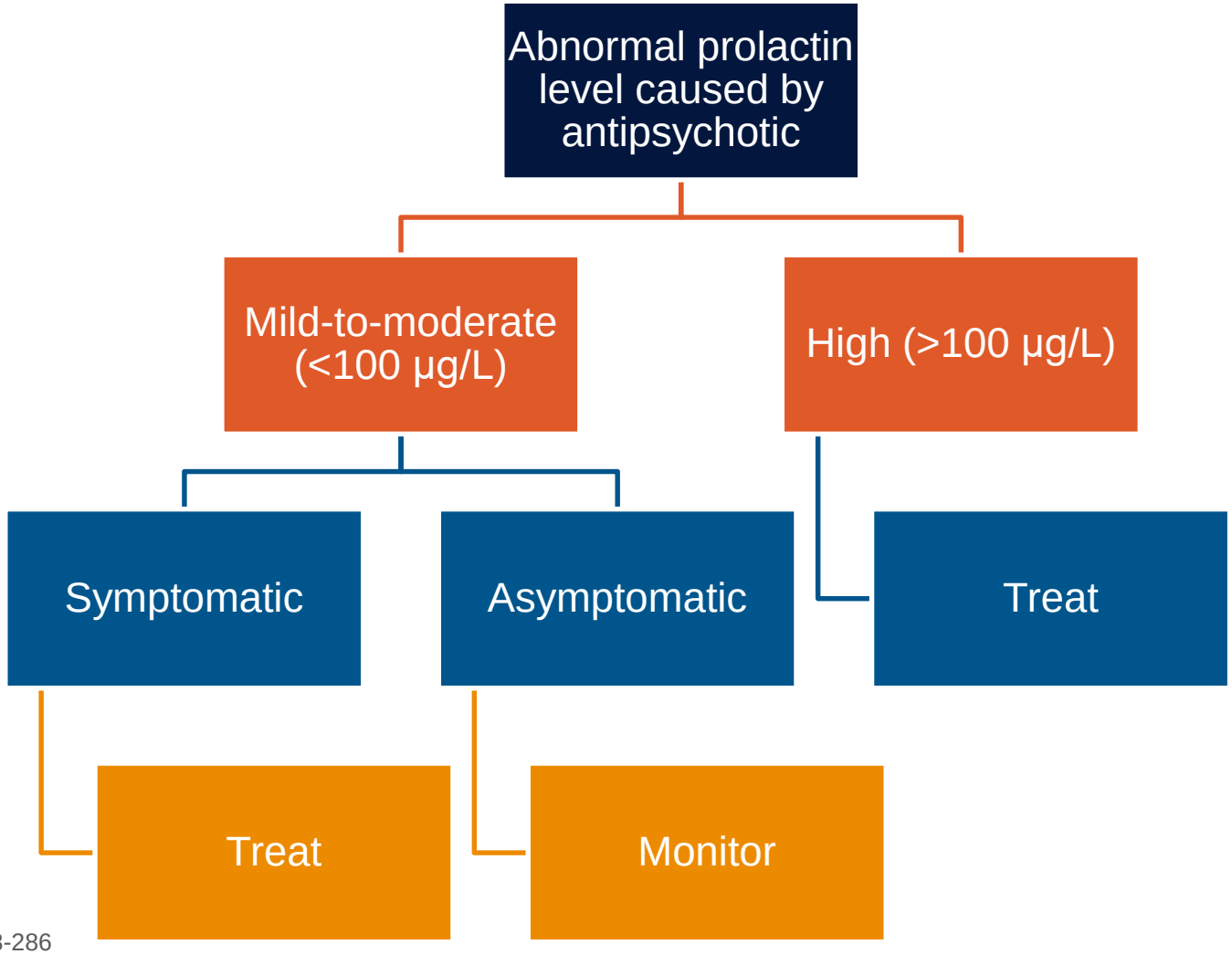
*BJPsych Advances*. 2017;23(4):278-286

# Diagnosis of Antipsychotic Induced Hyperprolactinemia

- Diagnosis of exclusion
- **If a patient is symptomatic and on an antipsychotic, it should *not* be assumed that the antipsychotic is the cause of the elevated prolactin**

*J of Clin Endocrinology & Metabolism. 2011;96(2):273-288*

# Management




*BJPsych Advances*. 2017;23(4):278-286

# Treatment

**Switch** to an antipsychotic with a lower risk of hyperprolactinemia (aripiprazole, asenapine, clozapine, quetiapine, olanzapine)

**Decrease dose** of antipsychotic

**Adjunctive** aripiprazole

**Adjunctive** dopamine agonist (bromocriptine or cabergoline)

*BJPsych Advances*. 2017;23(4):278-286

# Treatment

- Brexpiprazole and cariprazine may have similar prolactin sparing properties to aripiprazole due to their partial D2 agonism
- Lack of data to support brexpiprazole and cariprazine as adjunct treatment for hyperprolactinemia at this time

*Savvy Psychopharmacology*. March 2018:42-46.

# Literature Review
# Pharmacological Treatment Strategies for Antipsychotic-induced Hyperprolactinemia: A Systematic Review & Network Meta-analysis

| Study Type | Inclusion Group | Outcomes |
|---|---|---|
| Meta-analysis<br><br>Placebo-controlled and head-to-head RCTs that compared different strategies were included | Adults with schizophrenia and experienced antipsychotic induced hyperprolactinemia | Change in prolactin levels |

*Transl Psychiatry*. 2022;12(1):267.

# Literature Review
# Pharmacological Treatment Strategies for Antipsychotic-induced Hyperprolactinemia: A Systematic Review & Network Meta-analysis

| Subgroup analyses of network meta-analysis (prolactin >50 ng/ml) | | |
|---|---|---|
| **Intervention** | **MD (CI)** | **Certainty of evidence** |
| Adjunctive aripiprazole (5 mg) | -64.26 (-87.00, -41.37) | **High** |
| Adjunctive aripiprazole (10 mg) | -55.97 (-90.10, -29.76) | **High** |
| Adjunctive aripiprazole (>10 mg) | -62.07 (-97.12, -39.72) | **High** |
| Adjunctive vitamin B6 | -91.84 (-165.31, -17.74) | Moderate |
| Adjunctive metformin | -76.20 (-191.38, 37.08) | Moderate |
| Adjunctive dopamine agonist | -49.56 (-119.15, 18.69) | Low |

**No effective strategy was found for patients with AP-induced hyperprolactinemia <50 ng/ml. Adjunctive aripiprazole had the best evidence for decreasing AP-induced hyperprolactinemia >50 ng/mL.**

*Transl Psychiatry*. 2022;12(1):267.

# Assessment Question #4

A 21 YO M with a history of schizophrenia presents to the outpatient psychiatric clinic complaining of breast enlargement. He was started on risperidone 2 weeks ago and is currently stabilized on risperidone 2 mg BID. The patient's prolactin level results at 63 ng/dL. There are no other potential causes of hyperprolactinemia identified.

**How would you manage his treatment regimen?** Select all that apply.

A. Decrease dose of risperidone to 1 mg BID
B. Switch risperidone to haloperidol 5 mg daily
C. Add adjunctive aripiprazole 5 mg daily
D. Switch risperidone to quetiapine 100 mg daily

# Assessment Question #4:  Correct Response

A 21 YO M with a history of schizophrenia presents to the outpatient psychiatric clinic complaining of breast enlargement. He was started on risperidone 2 weeks ago and is currently stabilized on risperidone 2 mg BID. The patient's prolactin level results at 63 ng/dL. There are no other potential causes of hyperprolactinemia identified.

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**C. Add adjunctive aripiprazole 5 mg daily**
**D. Switch risperidone to quetiapine 100 mg daily**

# Clozapine Levels

# Clozapine

- Second-generation antipsychotic approved for the use of treatment-resistant schizophrenia
- Substrate of CYP1A2 (major), CYP2C19 (minor), CYP2C9 (minor), CYP2D6 (minor), CYP3A4 (major)
- Must fail 2 adequate treatment trials with an antipsychotic before initiating
- BBWs: severe neutropenia, orthostatic hypotension/bradycardia/syncope, seizures, myocarditis/cardiomyopathy/mitral valve incompetence, increased mortality in elderly patients with dementia-related psychosis

*CNS Drugs.* 2022 Sep;36(9):1015.
Clozaril: Package Insert. Revised 2024.

# Clozapine Levels

- Clozapine levels are not routinely used to guide therapy
- Labs are typically the concentrations of clozapine and norclozapine
- Dose required to achieve therapeutic clozapine levels varies greatly
  - May be high variation even in stable patients
  - Some may require supratherapeutic levels
- TDM may be a useful tool for supporting dosing decisions because it provides direct feedback on blood concentrations without waiting for symptoms to respond or for side effects to develop

*CNS Drugs.* 2022 Sep;36(9):1015.

# Factors Influencing Clozapine Levels

## Increase Levels

- Female sex
- Estrogen
- Older age
- Asian or Native American ancestry
- Obesity
- Inflammation
- High levels of caffeine use
- Low CYP1A2 expression
- CYP1A2 inhibitors
- Valproic acid

## Decrease Levels

- CYP1A2 inducers
  - Smoking, phenobarbital, phenytoin, topiramate > 400 mg/day

*CNS Drugs.* 2022 Sep;36(9):1015.

# When to Obtain a Clozapine Level

- Trough level (at least 6 hours after last dose)
- Obtain level after 5 days of a consistent clozapine dose
- Obtaining a level may be recommended if:
  - Clozapine dose is ≥600 mg/day (every 3 months)
  - Change in smoking habits
  - Adherence concerns
  - Adverse effects

*CNS Drugs.* 2022 Sep;36(9):1015.
Clozaril: Package Insert. Revised 2024.

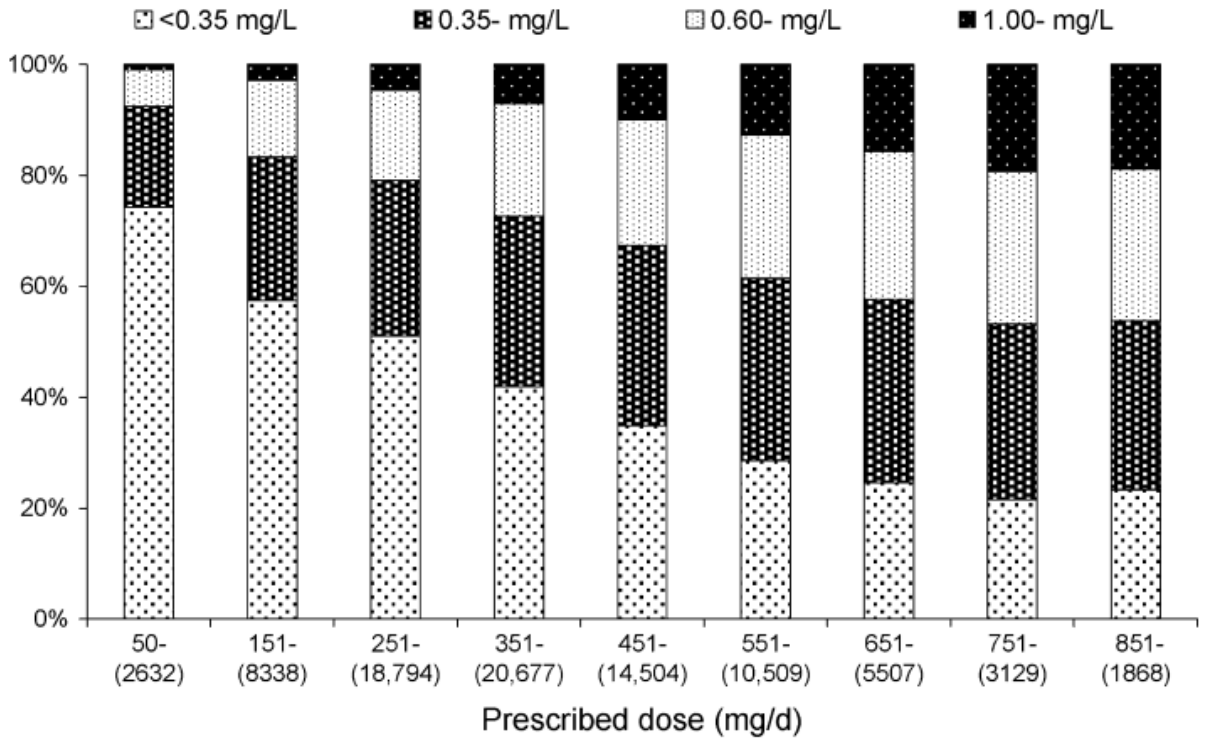
# Clozapine Level Interpretation

| Clozapine Trough | |
|---|---|
| **Level** | **Interpretation** |
| **200-370 ng/mL** | Beneficial range |
| **>600 ng/mL** | Greater risk for adverse effects |
| **>1300 ng/mL** | Substantial risk for seizures |

| Clozapine:Norclozapine | |
|---|---|
| **Ratio** | **Interpretation** |
| **>2:1** | Poor metabolism, presence of metabolic inhibitor, or early level |
| **<2:1** | Ultrarapid metabolizer, presence of metabolic inducer, or non-adherence within past 24 hours |

*Am J Psychiatry* 1996;153:1579- 84.
*CNS Drugs.* 2022 Sep;36(9):1015.
*Therapeutic Advances in Psychopharmacolo*gy. 2011;1(2):47-66.

# Literature Review
# Plasma Clozapine, Norclozapine & the Clozapine: Norclozapine Ratio in Relation to Prescribed Dose & Other Factors: Data From a Therapeutic Drug Monitoring Service, 1993–2007




*Ther Drug Monit*. 2010;32(4):438-447.

# Literature Review
# Plasma Clozapine, Norclozapine & the Clozapine: Norclozapine Ratio in Relation to Prescribed Dose & Other Factors: Data From a Therapeutic Drug Monitoring Service, 1993–2007

## Plasma clozapine level at a given dose increased by…

**48%** In non-smokers

**17%** In women

**5%** Every 10 kg above 80 kg

**4%** Every 5 years above 40 years old

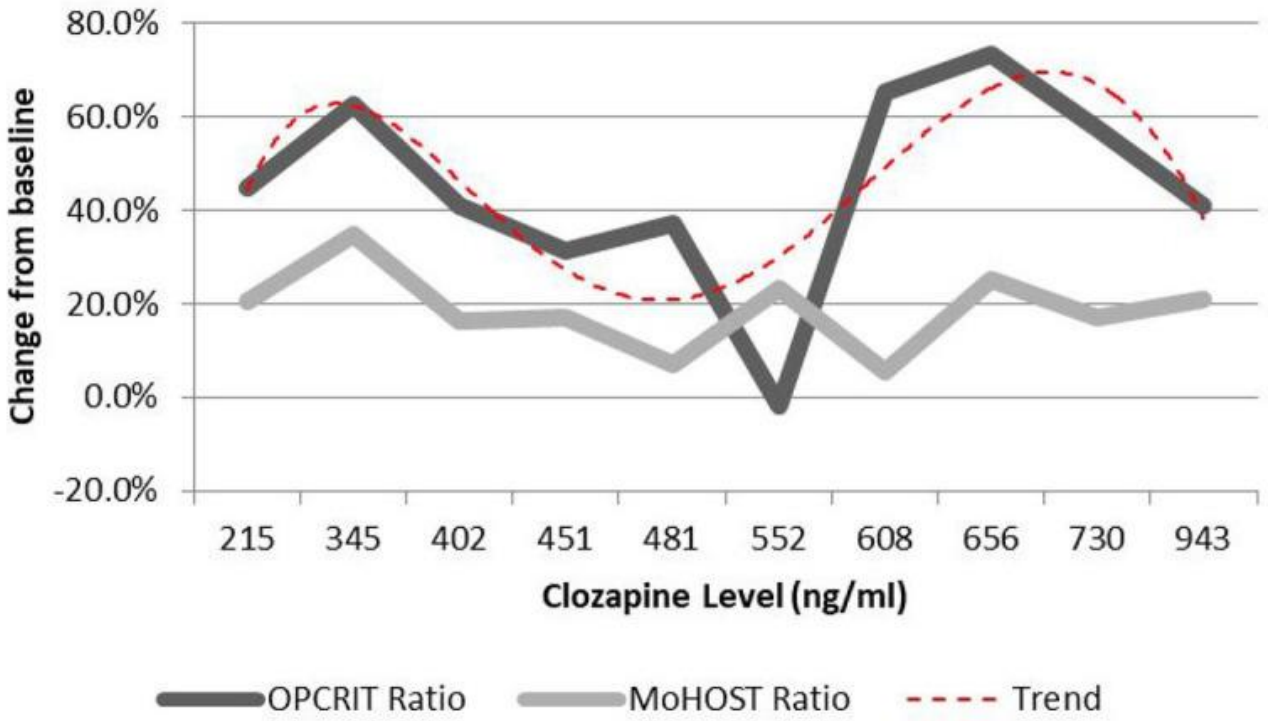
*Ther Drug Monit*. 2010;32(4):438-447.

# Literature Review
# Outcomes in Treatment-resistant Schizophrenia: Symptoms, Function & Clozapine Plasma Concentrations

| Study Type | Inclusion Group | Outcomes |
|---|---|---|
| Retrospective review | Patients with treatment-refractory psychosis admitted to a specialized tertiary-level service and treated with clozapine | • Clinical symptoms (OPCRIT score)<br>• Functional status (MoHOST score) |

*Ther Adv Psychopharmacol*. 2021;11:20451253211037179.

# Literature Review
# Outcomes in Treatment-resistant Schizophrenia: Symptoms, Function & Clozapine Plasma Concentrations




*Ther Adv Psychopharmacol*. 2021;11:20451253211037179

**There was not a significant correlation between clinical/functional status and clozapine concentrations. There were two peaks of optimal clinical improvement, noted at 350 ng/mL and 650 ng/mL.**

*Ther Adv Psychopharmacol*. 2021;11:20451253211037179.

# Assessment Question #5

A patient with schizophrenia was started on clozapine during their inpatient psychiatric hospitalization. The clozapine dose was titrated to 300 mg/day. The patient reported smoking 1 PPD prior to admission and was started on a nicotine patch (21 mg/day). Since discharge, the patient has stopped using the nicotine patch and has resumed smoking 1 PPD.

Their clozapine level prior to discharge was 375. A repeat level was obtained at a 1 month follow-up that showed a decrease in the clozapine level. **What is the mechanism of clozapine that may have caused the drug level to decrease?**

A. Substrate of CYP1A2
B. Substrate of CYP2D6
C. Substrate of CYP3A4

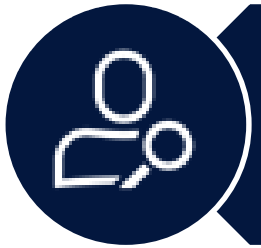
# Assessment Question #5: Correct Response

A patient with schizophrenia was started on clozapine during their inpatient psychiatric hospitalization. The clozapine dose was titrated to 300 mg/day. The patient reported smoking 1 PPD prior to admission and was started on a nicotine patch (21 mg/day). Since discharge, the patient has stopped using the nicotine patch and has resumed smoking 1 PPD.

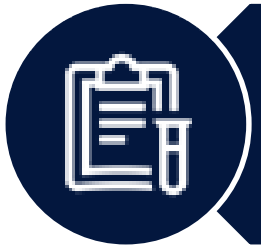
Their clozapine level prior to discharge was 375. A repeat level was obtained at a 1 month follow-up that showed a decrease in the clozapine level. **What is the mechanism of clozapine that may have caused the drug level to decrease?**

A. **Substrate of CYP1A2**
B. Substrate of CYP2D6
C. Substrate of CYP3A4

# Summary



When evaluating lab abnormalities associated with psychotropic medications, the patient should be evaluated first rather than the lab result



The patient’s symptoms, presentation and other potential causes of the lab abnormality should be considered

The discontinuation of the associated psychotropic medication is not always necessary and should be evaluated on a case by case basis

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# Thank you!

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