The thyroid is a butterfly-shaped endocrine gland located at the front of the neck below the Adam’s apple. It is composed of the isthmus, found in the middle of the thyroid gland, and one wing-shaped lobe on both the left and right side. The tissue is mostly comprised of thyroid follicles. A sticky fluid called colloid within the follicles produces thyroid hormones. The thyroid gland secretes these thyroid hormones which regulate metabolism and influence the metabolic rate in a couple of ways. Thyroid hormones increase the amount of oxygen the cells use in the body and stimulate tissue to produce proteins. Thyroid hormones also regulate vital body functions such as heart rate, breathing, temperature, weight, fertility, digestion, and much more.

There are two major Thyroid hormones, triiodothyronine (T3), which is a thyroid hormone with three iodines, and thyroxine (T4), a thyroid hormone with four iodines. These are created when the colloid produced intermediaries of a tyrosine attached to either one or two iodines are linked by covalent bonds. Once the thyroid hormones are created, they are stored in the colloid until the thyroid stimulating hormone (TSH) stimulates the colloid. Once this occurs, the colloid releases T3 and T4 into the bloodstream. As mentioned previously, these hormones have a number of effects on the body. On a basic level, T3 and T4 assist in nutrient breakdown and increase the use of oxygen in order to produce adenosine triphosphate (ATP). The body temperature is increased from this ATP production due to the inefficiency of the process. Proper levels of thyroid hormones are critical for good health in adults as well as development in children.

The most common test for thyroid issues is a blood test to check the levels of T3, T4, and TSH. Typically, TSH will be the first hormone level checked as TSH tells the thyroid how much T3 and T4 to make. A high level of TSH can point to hypothyroidism while a low level of TSH can point to hyperthyroidism. If your thyroid isn’t making the necessary T3 and T4, the pituitary gland will continue to make and release TSH into the blood. Therefore, high levels of TSH point to hypothyroidism, an underactive thyroid, and low levels point to hyperthyroidism, an overactive thyroid. You can also test for thyroid issues by testing the levels of T3 and T4 in the body. For both T3 and T4, high levels can point to hyperthyroidism and low levels can point to hypothyroidism. More specifically, because bound T4 is kept in reserves and can be affected by binding protein levels, free T4 is used as a better indication of hypo- or hyperthyroidism. Ultrasounds can also be used to check for thyroid nodules as well as to diagnose thyroid cancer.

It is important to understand that dietary iodine is required for the synthesis of T3 and T4. A lack of iodine in the diet can lead not only to severe thyroid disorders but to numerous other health issues as well. Iodine deficiency is common in the undeveloped world, but quite rare in the United States and other developed nations with access to iodized salt. Iodine deficiency can lead to an increased thyroid gland size called a goiter. A goiter is an enlargement of the thyroid.
**New Drugs of 2019**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic</th>
<th>Indication</th>
<th>Dosage &amp; Administration</th>
<th>Side Effects</th>
<th>Important Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accrufer®</td>
<td>Ferric maltol</td>
<td>Iron deficiency anemia</td>
<td>30mg capsule given twice daily on an empty stomach</td>
<td>GI upset</td>
<td>Less GI upset that other iron salt products; The body only absorbs as much iron as it needs from the product</td>
</tr>
<tr>
<td>AirDuo®</td>
<td>Fluticasone propionate + salmeterol</td>
<td>Maintenance treatment of asthma</td>
<td>1 inhalation twice daily; rinse mouth after use to avoid thrush</td>
<td>Naso-pharyngitis, thrush, cough, back pain and HA</td>
<td>NOT intended for rescue inhaler use; Contains built-in sensors that detect use and measure inspiratory flow rates- data from use is sent to a mobile phone</td>
</tr>
<tr>
<td>Duaklir®</td>
<td>Aclidinium bromide + formoterol fumarate</td>
<td>COPD maintenance tx</td>
<td>1 inhalation 400mcg/12mcg twice daily</td>
<td>Upper respiratory tract infection; HA</td>
<td>Fixed dose combination; risk of paradoxical bronchospasm</td>
</tr>
<tr>
<td>Evenity®</td>
<td>Rosmosozumab</td>
<td>Postmenopausal osteoporosis</td>
<td>210mg sub-cutaneously given once monthly x 1 year in MD office; then switch to anti-resorptive medication</td>
<td>Arthralgia, HA</td>
<td>Increases bone growth; reserve for high risk patients; carries black box warning for CV risk; Avoid use in women with MI or stroke in the last year; may cause atypical fractures or jaw osteonecrosis; Take calcium and Vit D; Cost $22,000/year</td>
</tr>
<tr>
<td>Gloperba®</td>
<td>Colchicine oral solution 0.6mg/5ml</td>
<td>Prevention of gout flares in adults</td>
<td>0.6mg (5ml) once or twice daily ; max dose is 1.2mg/day</td>
<td>N/V/D and abdominal pain</td>
<td>First liquid formulation Avoid use with liver and renal impairment</td>
</tr>
<tr>
<td>G-voke®</td>
<td>Glucagon</td>
<td>Severe hypoglycemia</td>
<td>Ready to use SQ injection; patients 12 and older recommended dose is 1mg to lower abdomen, outer thigh or outer upper arm</td>
<td>Nausea, vomiting, injection site edema and HA</td>
<td>First glucagon product available ready to use; follow directions for use on the foil packet</td>
</tr>
<tr>
<td>Ibsrela®</td>
<td>Tenapanor</td>
<td>Irritable bowel syndrome - constipation dominant</td>
<td>50mg twice daily</td>
<td>Diarrhea</td>
<td>Contraindicated in patients with known or suspected bowel obstruction; acts locally in the GI tract with minimal absorption</td>
</tr>
<tr>
<td>Inbria®</td>
<td>Levodopa</td>
<td>Parkinson’s disease “off” episodes as needed</td>
<td>Dry powder inhaler that must be loaded prior to each dose and each dose should be repeated; Max dose per OFF period is 84mg and max daily dose is 420mg</td>
<td>Sedation, cough, nausea, upper respiratory tract infection and discolored sputum</td>
<td>Capsules are for inhalation use ONLY – do not swallow; Fast acting and lasts about an hour; Avoid use in COPD, asthma, or other lung conditions due to risk of bronchospasm, Cost about $30 per dose</td>
</tr>
<tr>
<td>Qternmet XR®</td>
<td>Dapaglifozin + saxagliptan + metformin</td>
<td>DM type 2 already on metformin</td>
<td>Dose is individualized; take with food whole; do not crush, cut or chew</td>
<td>Same as individual component</td>
<td>Swallow tablets whole in the morning with food</td>
</tr>
<tr>
<td>Drug</td>
<td>Generic</td>
<td>Indication</td>
<td>Dosage &amp; Administration</td>
<td>Side Effects</td>
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<tr>
<td>Recarbrio®</td>
<td>Imipenem + cilastatin + relebactam</td>
<td>Antibiotic used to treat complicated UTIs, including pyelonephritis and complicated intra-abdominal infections when there are limited or no alternative txs</td>
<td>1.25 g (imipenem 500mg, cilastatin 500mg, relebactam 250mg) IV over 30 minutes every 6 hours if CrCL is &gt;90ml/min. Reduce dose with renal impairment</td>
<td>Nausea, diarrhea, HA, fever and increased liver enzymes</td>
<td>Avoid use if CrCl &lt;15ml/min unless dialyzed within 48 hours</td>
</tr>
<tr>
<td>Rocklatan®</td>
<td>Netarsudil 0.02% + latanoprost 0.005%</td>
<td>Reduce intraocular pressure with open angle glaucoma</td>
<td>Ophthalmic drops given once daily</td>
<td>Conjunctival hyperemia, pain at instillation site, corneal verticillata and conjunctival hemorrhage</td>
<td>Potential for brown pigmentation of iris and eyelid skin darkening as well as eyelash changes; may be permanent</td>
</tr>
<tr>
<td>Rybelsus®</td>
<td>Semaglutide</td>
<td>DM type 2</td>
<td>Starting dose is 3mg qd x 30d then increase to 7mg qd</td>
<td>N/V/D, GI pain, decreased appetite, constipation</td>
<td>First GLP-1 agent in a pill form; Avoid use if hx of thyroid cancer or pancreatitis</td>
</tr>
<tr>
<td>Sunosi®</td>
<td>Solriamfetol</td>
<td>Improve wakefulness in adults with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea</td>
<td>Narcolepsy: 75mg or 150mg once daily; OSA: 37.5mg, 75mg or 150mg</td>
<td>HA, nausea, decreased appetite, anxiety</td>
<td>Exact mechanism of action unknown Patients with OSA should still utilize CPAP treatment</td>
</tr>
<tr>
<td>Tosymra®</td>
<td>Sumatriptan nasal spray</td>
<td>Acute tx of migraines in adults</td>
<td>10mg as a single spray in 1 nostril; may repeat dose after at least 1 hour. MAX 30mg/24 hours; may be given at least 1 hour following a dose of another sumatriptan product</td>
<td>Tingling, dizziness, feeling warm or hot, feeling of burning, feeling of heaviness or pressure; flushing; abnormal taste and throat irritation</td>
<td>Rapid onset of action Can cause elevated BP and even heart attack 1st dose should be given in a medically supervised setting in patients with CV risk factors</td>
</tr>
<tr>
<td>Wixela Inhub®</td>
<td>Fluticasone propionate + salmeterol</td>
<td>Tx of asthma in patients &gt;4 and maintenance tx of COPD</td>
<td>Dry powder inhaler; use BID; available in 3 strengths: 100/50, 250/50, 500/50</td>
<td>Thrush</td>
<td>First generic version of Advair Diskus®; Only dose approved for COPD is 250/50; Inhaler should be discarded 1 month after opening ; rinse mouth after use; Contains risk of paradoxical bronchospasm; not indicated for acute bronchospasm</td>
</tr>
<tr>
<td>Xenleta®</td>
<td>Lefamulin</td>
<td>Antibiotic for community acquired pneumonia</td>
<td>Oral dose is 600mg every 12 hours for 5-7 days; IV dose is 150mg IV q12 (over 60 minute infusion) for 5-7 days; Hepatic impairment</td>
<td>Infusion: Administration site reactions; hepatic enzyme elevation, insomnia and HA Tablets: N/V/D</td>
<td>IV formulation once mixed is stable for 24 hours at room temp and 48 hours if refrigerated Tablets should be taken 1 hour before a meal or at least 2 hours after a meal and should not be crushed or chewed Warning: Risk of C Diff and QT prolongation</td>
</tr>
</tbody>
</table>
Overview of the Thyroid ..................................continued from page 1

gland, although the thyroid gland may be functioning effectively with the presence of goiter. This is caused by the increased level of TSH in the body’s attempt to produce T3 and T4. A goiter may not require treatment, but the most common treatments are medications based on their effect on the thyroid (to be discussed later). Radioactive iodine treatment may be used in some cases. Radioactive iodine is administered orally and kills thyroid cells within the thyroid gland, effectively shrinking the gland. This treatment has life-long effects on the production of thyroid hormones.

The most common cause of hypothyroidism in the United States is not a lack of dietary iodine but rather an inflammation of the thyroid gland. Hypothyroidism symptoms can include fatigue, constipation, depression, weight gain, cold extremities, fertility issues, and a reduced heart rate. A common cause of hypothyroidism is Hashimoto’s disease, which affects 1 in 20 people. The disease is much more common in women, affecting about 8 times as many women as men. Hashimoto’s disease is an autoimmune disorder that causes your immune system to attack your thyroid. This results in damage to the thyroid and the inability to create enough thyroid hormones. Hashimoto’s thyroiditis is the most common cause of goiter in developed nations with access to iodized salt. A person can be genetically predisposed to a higher likelihood of developing Hashimoto’s disease, and is much more likely to develop the disease if they have other autoimmune disorders. The most common treatment for hypothyroidism is levothyroxine, a synthetic T4 replacement taken orally with rare and minimal side effects.

Hyperthyroidism is a condition in which the thyroid produces more thyroid hormones than needed in the body. Hyperthyroidism symptoms include fatigue, irritability, insomnia, rapid heartbeat, mood swings, and frequent bowel movements. Hyperthyroidism is less common than hypothyroidism, affecting approximately 1 in 100 people. There are several causes of hyperthyroidism including Graves’ disease, thyroiditis, and thyroid nodules. The most common cause of hyperthyroidism is Graves’ disease, an autoimmune disorder that causes the thyroid to produce too many thyroid hormones. Overactive thyroid nodules can also cause excess production of thyroid hormones. Overactive thyroid nodules are more often present in the elderly. Another cause of hyperthyroidism is thyroiditis, an inflammation of the thyroid that leads to thyroid hormones leaking out of the thyroid gland. This temporary hyperthyroidism can last up to 90 days followed by hypothyroidism for an extended period of time, from one year to a lifetime. There are several types of thyroiditis. Subacute thyroiditis occurs when a thyroid is inflamed and typically enlarged. Silent thyroiditis also involves an enlarged thyroid but is painless as opposed to subacute thyroiditis. Postpartum thyroiditis can develop in females after giving birth.

There are three major treatments for hyperthyroidism, although the best treatment per patient will vary more than with hypothyroidism. The most commonly prescribed medication is methimazole as it has the least severe side-effects; however, in the majority of hyperthyroid cases radioactive iodine will be used. Radioactive iodine will permanently reduce the level of thyroid hormone and can commonly result in hypothyroidism. As hypothyroidism can be more easily treated than hyperthyroidism, this is often a desired result. The third major treatment for hyperthyroidism is surgical removal of a portion or all of the thyroid gland. Similarly to radioactive iodine treatment, the result of this treatment is hypothyroidism which is commonly treatable with thyroid hormone supplements.
THYROID GLAND INFOGRAPHIC

HOW ARE THYROID HORMONES PRODUCED

THYROID GLAND
THE THYROID GLAND IS A BUTTERFLY-SHAPED ORGAN LOCATED IN THE BASE OF YOUR NECK

THYROID GLAND TAKES IODINE, AND CONVERT IT INTO:
- thyroxine (T4)
- triiodothyronine (T3)

THE THYROID'S HORMONES REGULATE VITAL BODY FUNCTIONS, INCLUDING:

- Heart rate
- Body temperature
- Muscle strength
- Body weight
- Menstrual cycles
- Nervous systems
- Cholesterol levels
- Breathing

UP TO 60 PERCENT OF THOSE WITH THYROID DISEASE ARE UNAWARE OF THEIR CONDITION
Medications that Effect the Thyroid

Introduction
Awareness of potential interactions between medications and the effects they have on the thyroid is very crucial for clinicians to monitor in order to intervene and avoid unnecessary testing and treatment for patients. It is also important to know that there are medications that may even alter the results of thyroid laboratory tests that can mimic Graves’ disease, central hypothyroidism, and central hyperthyroidism. There are diverse mechanisms in the way medications can interact with the thyroid. Each step in the thyroid process including thyroid hormone control, synthesis, release, transport, and metabolism is susceptible to drug interactions. Medications can affect thyroid hormone release, thyroid autoimmunity, protein binding, absorption of thyroid hormone, as well as direct damage to the thyroid.

Pathophysiology
Thyrotropin, which is a protein produced by your body, controls all aspects of the thyroid hormone synthesis and release. Thyrotropin secretion is stimulated by thyrotropin-releasing hormone and inhibited by a negative feedback system. Iodide from your diet is transported then bound to tyrosine deposits in thyroglobulin molecules. These thyroglobulin’s are coupled together to form either thyroxine (T4) or triiodothyronine (T3) which are used to monitor levels to determine therapy options. One hundred percent of T4 is produced in the thyroid whereas 80% of T3 is derived in the peripheral tissues such as the liver and kidneys. More than 99% of circulating T4 and T3 is bound to serum protein including thyroxine-binding globulin, transthyretin, and albumin. Metabolism of thyroid hormone occurs in numerous tissues which include liver, kidney, thyroid, skin, and placenta. Additional pathways include glucuronidation and sulfation which excrete in bile, feces, or urine.

Drug that Affects Thyroid Hormone Release
Lithium is indicated for the treatment of manic episodes and the maintenance of bipolar disorder. It can be used off label for depression, bipolar depression, and cluster headaches. Lithium can decrease the thyroid hormone release in the body and can cause goiter, which is an enlargement of the thyroid gland. The reported prevalence of hypothyroidism among patients receiving lithium varies widely. Two risk factors for this interaction include female sex and an age greater than 40 years old. Lithium has also been linked to thyroiditis, but the causes are unknown. Approximately half of patients have positive tests for thyroid antibodies indicating thyroiditis.

Drugs that Enhance Thyroid Autoimmunity
Newer medications designed to promote immune system targeting of cancer cells also increase the risk of autoimmune disorders which may also lead to thyroid dysfunction as noted in the literature. Thyrotoxicosis typically develops within 4-8 weeks after the start of therapy but may occur within 2 weeks with combination therapy. Some cases may resolve within 3-10 weeks but there is also the chance for very moderate or severe cases that can not be resolved. PD-1 inhibitors and CTLA-4 inhibitors are the drug classes which are noted for thyroid dysfunction and these medications include:
- Ipilimumab (Yervoy®) – CTLA-4 inhibitor
- Tremelimumab – CTLA-4 inhibitor
- Pembrolizumab (Keytruda®) - PD-1 inhibitor

Drug causing Direct Thyroid Damage
Amiodarone causes destructive thyroiditis in about 5-10% of patients and it is believed to result from direct cytotoxic effects on the thyroid cells. Certain types of amiodarone induced thyroid damage can be treated with glucocorticoids. It is difficult to determine which type is responsive, so the urgent need for treatment in patients with cardiac status often prompts clinicians to provide anti-thyroid drugs and glucocorticoids initially. Patients may present with:
- Elevated heart rate
- Worsening arrhythmia
- Non-tender thyroid physical exam
Drugs Affecting Absorption of Thyroid Hormone

Thyroid medication is recommended to be taken on an empty stomach since approximately 60-80% of it will be absorbed within 2-4 hours of administration. When taken without regard to food, approximately 40-80% would be absorbed after the oral dose. One very common medication that a lot of patients take that can increase the levotiroxine requirement is the drug class of proton-pump inhibitors which include omeprazole, esomeprazole, and lansoprazole. There are also a few other medications that can interfere with gastrointestinal absorption of the thyroid hormone which include:

- Ferrous sulfate
- Calcium carbonate
- Aluminum hydroxide
- Sucralfate
- Raloxifene
- Bile acid sequestrants

Effect of Thyroid Dysfunction on Drug Metabolism

Pharmacokinetics and efficacy of medications can be affected by hyperthyroidism and hypothyroidism. Warfarin requires a lower dose during hyperthyroidism as result of accelerated turnover of vitamin K-dependent clotting factors. Statin therapy, which includes atorvastatin, rosuvastatin, pravastatin, etc, has been associated with an increased risk of myopathy in the presence of hypothyroidism. Hyperthyroidism can also accelerate the metabolism of a variety of medications along with hypothyroidism delaying the clearance of these medications which include:

- Propranolol
- Cardiac glycosides
- Glucocorticoids

Abnormal Lab Tests Summary

<table>
<thead>
<tr>
<th>Medication</th>
<th>Thyrotropin</th>
<th>Free T4</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Biotin</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Normal</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Normal</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Normal</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Heparin</td>
<td>Normal</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Normal</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Salsalate</td>
<td>Normal</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

As mentioned previously, medications can be associated with abnormal results in laboratory tests. It is very important to distinguish these effects to prevent unnecessary diagnostic and therapeutic interventions.

Drugs Affecting Absorption of Thyroid Hormone

There are several medications that increase thyroxine-binding globulin. These medications include:

- Oral estrogen
- Raloxifene
- Methadone
- Heroin
- Fluorouracil
- Mitotane

Conversely there are also medications that can reduce thyroxine-binding globulin which include:

- Androgens
- Glucocorticoids
- Niacin

Effect of Thyroid Dysfunction on Drug Metabolism

Pharmacokinetics and efficacy of medications can be affected by hyperthyroidism and hypothyroidism. Warfarin requires a lower dose during hyperthyroidism as result of accelerated turnover of vitamin K-dependent clotting factors. Statin therapy, which includes atorvastatin, rosuvastatin, pravastatin, etc, has been associated with an increased risk of myopathy in the presence of hypothyroidism. Hyperthyroidism can also accelerate the metabolism of a variety of medications along with hypothyroidism delaying the clearance of these medications which include:

- Propranolol
- Cardiac glycosides
- Glucocorticoids

Drugs Causing Abnormal Lab Tests

As mentioned previously, medications can be associated with
To all the Pharm Notes Family,

Instead of New Year’s Resolutions, why not spend a minute to learn from the year behind us…… (from Tsh Oxenreider, The Art of Simple).

1. What was the single best thing that happened this past year?
2. What was the single most challenging thing that happened?
3. What was an unexpected joy this past year?
4. What was an unexpected obstacle?
5. Pick three words to describe this past year.
6. Pick three words your partner or close friend would use to describe your year.
7. Pick three words your partner or close friend would use to describe their year.
8. What were the best books you read this year?
9. Who were your most valuable relationships with?
10. What was your biggest personal change from January to December of this past year?
11. In what way did you grow emotionally?
12. In what way did you grow spiritually?
13. In what way did you grow physically?
14. In what way did you grow in your relationships with others?
15. What was the most enjoyable part of your work?
16. What was the most challenging part of your work?
17. What was your single biggest time waster in your life this past year?
18. What was the best way you used your time this past year?
19. What was biggest thing you learned this past year?
20. Create a phrase or statement that describes this past year for you.

Happy New Year!

Cathy Fuquay
PharmNotes Editor