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QUOTE OF THE MONTH

By: Matthew Kahn, Graphics Editor

Medicine is a science of uncertainty and an art of probability.

William Osler
Flight tickets, check. Passports, check. Luggage, check.
Month supply of Metformin, uh oh.

Two months separate many from the beginning of summer and the slew of travel plans already being made. Pharmacists are often your overlooked travel specialists during the summer months. Stop by your local pharmacy before your next trip to make sure you are all set to tackle the summer sun while staying adherent to your medication regimen.

Community Pharmacy:

If you are traveling within the United States or United States Territories and your normal pharmacy has locations there, you can fill your prescription while traveling. Community pharmacies such as Walgreens and CVS allow their patients to fill most of their prescriptions at any location in the United States to make staying healthy easy and convenient. There are certain regulations about which medications can be filled outside of stores they were received; stop by your local pharmacy before leaving to see if transfers are allowed for your medication regimen.¹

Insurance:

Some insurance companies offer their patients “vacation overrides.” A vacation override allows a patient to receive a month’s worth of medication before they are due for their next refill to ensure they have enough medication to get them through the time they are away and traveling. Contact your pharmacy prior to travel to see if this is a benefit your prescription insurance offers.²

International Travel:

Ciao! Bonjour! Hola! Whether you are traveling to a bustling city center or a town off the beaten path, make sure you are prepared for different pharmacy laws and products abroad. It is suggested for all international travelers to obtain an official letter head note from your doctors describing all medications you are taking and a brief description of the condition(s) for which they are being used for. This is both for your safety should you be hospitalized or receive medical care and for your safety should your bags be searched at any time. Pharmacy laws vary from country to country; ensure that the medications you are taking here in the United States are not illegal in any country you are traveling too, including short lay-overs at airports. Some countries may allow any medication, but limit the quantity allowed which may not last you the entire trip. For example, Japan has a list of prohibited substances from entering their country including any products containing pseudoephedrine or ephedrine and in Sweden, narcotic drugs like Percocet, are only allowed across borders in quantities lasting a five-day supply.³ Often United States medication names hold different names abroad; familiarize yourself with the generic name of your medication as it may be more recognizable to a foreign pharmacy should you need to stop in one. Commonly prescribed Januvia® is available in Italy under its generic name, sitagliptin.⁴ Lastly, remember that prescription insurance is a United States benefit. Many countries abroad do not take prescription insurance so you will be paying out of pocket.⁵

By: Katharine Russo, PharmD Candidate c/o 2021
Summer of adherence
Airplanes:

When traveling via airplane, always ensure that medications are taken in carry on or personal bags. You never know if the airline will lose your baggage and you do not want to be without your medication. According to the Transportation Security Administration (TSA), medication in capsule or tablet form can be brought in unlimited quantity onto a flight with proper screening, identification, and documentation. If it is a liquid medication over the standard 3.4 ounce limit, do not worry. Airlines allow liquid medication in excess of 3.4 ounces on the plane as long it is in reasonable quantity for the duration of the complete travel to your destination. Liquid medications will be subject to screening so be sure to tell the TSA officer if you are in possession of prescription liquid medication.6

Sources:

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Digital sensors in drugs and how they will impact pharmacotherapy

By: Jonathan Mercado, PharmD Candidate c/o 2019

In November of 2017, the FDA approved the first drug to contain digital sensors.1 Abilify MyCite® (aripiprazole) is indicated for schizophrenia and is manufactured by Japanese company, Otsuka Pharmaceutical.2 While patients may be hesitant to use a medication that digitally tracks whether or not they’ve taken it, the goal of the technology is to increase adherence to drug therapy and help healthcare providers identify potential issues that make adherence difficult for patients.

To better understand the significance of Abilify MyCite®, a review of the contemporary standards of schizophrenia treatment is necessary. Typically schizophrenia is managed using a single antipsychotic medication. Antipsychotics are divided into two general classes - first-generation antipsychotics (FGAs) and second generation antipsychotics (SGAs). Both classes work primarily by blocking dopamine receptors in the brain which is essential because excessive dopaminergic activity in the brain causes schizophrenia as well as hallucinations, disorganized speech and other symptoms patients experience. SGAs are unique and preferred because they also target a variety of other receptors in the brain rather than solely dopamine receptors, which reduces the risk of extrapyramidal symptoms (EPS). EPS are characterized as movement disorders that occur when the dopaminergic blockade invades the nigrostriatal pathway of the brain and leads to symptoms such as tremors, dystonia, and akathisia. They can eventually become irreversible if left untreated, a condition known as tardive dyskinesia. Typically one agent is chosen depending on patient-specific factors and the niches of each antipsychotic. If it fails, the medication is switched because some patients respond better to other drugs in the same class. Most antipsychotics are taken orally once or twice a day which can be difficult for schizophrenic patients to remember. If a patient is responding well to an oral agent, they can be given the long-acting injectable (LAI) version of the drug. LAs are available for select antipsychotics and last several weeks which significantly improves medication adherence.3 Aripiprazole is one of the safest SGAs and is available as an LAI, making it a great candidate for this new sensor containing dosage form which has the propensity to be more convenient for certain patients long-term.

Abilify MyCite® operates by having a miniature digital sensor comparable to the size of a spec of salt, in a capsule, which is inactive until it comes into contact with intestinal fluid. Upon contact, the sensor sends a message to a patch worn by the patient with information about the date and time the capsule was taken. The information sent to the patch is further forwarded to a phone application that can be accessed by healthcare providers, family and guardians.2 While this may seem like a brilliant step forward in pharmacotherapy, the most notable issue for patients is the lack of trust and invasion of privacy.

Trust between healthcare providers and patients is essential in providing effective treatment. Decades of practice have helped healthcare providers understand that only when they believe in their patients does a rapport founded in trust begin to form. That trust is what opens up meaningful conversations between clinicians and patients that can guide treatment in the right direction. It keeps patients open-minded regarding clinical recommendations and has been associated with positive health outcomes.4 Abilify MyCite® has a mechanism of monitoring that is counter-intuitive to the idea of trust, and can in many ways maim the patient-provider relationship that is often necessary for cooperation in therapy. However, the risk may be worth it considering statistics illustrating non-adherence, particularly in psychiatric patients.

It is estimated that thirty-three to sixty-nine percent of medication-related hospital visits are due to non-
adherence. While non-adherence is not a rare sight, it is significant issue in psychiatric patients. The mean rate of medication adherence among all psychiatric patients is estimated to be seventy-six percent, leaving roughly a quarter of patients that do not take their medications as prescribed, if at all. Among schizophrenic patients, the target population of Abilify MyCite®, only fifty to sixty percent are adherent to their medication. Many barriers to adherence exist for patients with any disease state, including but not limited to a dislike of the adverse effects of their medication, the cost of the medication, forgetfulness, and a lack of understanding about what the medication is or how it helps their condition. For psychiatric patients, the predominant reason for non-adherence is due to side effects which can range from drowsiness to metabolic issues such as weight gain.

Abilify MyCite® exhibits new technology, but its method of monitoring has existed for some time. Already we have medication bottles that register the time and date that they are opened, very similarly to how Abilify MyCite® intends to. In many cases these self-tracking bottles and awareness that they are being monitored have helped patients and provided them with motivation to keep up with their medication regimen. However, in practice, such bottles are rare because most patients do not find comfort in having a big brother-like system for something as personal as their medications. Considering the nature of the disease it tackles, Abilify MyCite® has a clear role in therapy but should never become the default, especially when initiating treatment with a new patient. The positive outcomes of a healthy patient-provider relationship are more likely to lead to better health outcomes and patient satisfaction than an impersonal mechanism used to track patients. For the minority of patients that are repeatedly non-adherent and open minded towards innovative therapies, this new medication is an excellent option that may motivate them to be adherent. Whether this technology will be implemented in medications which are indicated for other disease states remains to be seen, but its advancement in pharmacotherapy is surely a bold one despite its niche role.

SOURCES:
Pharmacists’ role in flu emergencies

By: Yao Jiang, PharmD Candidate c/o 2019

While each flu season comes and goes, the 2017-2018 flu season caught health care professionals by surprise. According to the Centers for Disease Control and Prevention (CDC), this season’s flu activity was the most widespread since the 2009 influenza pandemic caused by the influenza A (H1N1) virus, or the swine flu. The agency also reported that this year’s hospitalization and mortality rates reached and surpassed those during the severe 2014-2015 flu season. To put things in perspective, the flu vaccine is only thirty percent effective against the influenza A (H3N2) strain. The influenza A (H3N2) strain was the most predominant strain this year and is often associated with severe illness in pediatric and geriatric populations. To gauge the severity, there were 142 influenza-associated pediatric deaths and 731 pediatric hospitalizations during this past flu season.

On January 25, 2018, New York State Governor Andrew M. Cuomo signed executive order No. 176 declaring an influenza disaster emergency in New York. This executive order allowed pharmacists who are already licensed immunizers to also administer the influenza vaccine to children between ages 2 to 18. While this executive order seemed to expand the pharmacist’s scope of practice, it also introduced more training and liabilities in that it was only applicable to pharmacists who are certified in pediatric CPR. Pharmacists should be careful regarding which flu vaccines they choose to administer to their pediatric patients. Only three vaccines, Fluarix®, FluLaval®, and Fluzone® are indicated for those ≥6 months. There are other flu vaccines available, but the lower age limit is 3 years and older. Pharmacists should also be aware that they are not to administer vaccines with more than trace amounts of thiomersal, a mercury containing preservative, to children less than 3 years old. More than trace amounts of thiomersal is defined as more than 0.625 µg of mercury per 0.25 ml of vaccine. All influenza vaccines in prefilled syringes or single-dose vials comply with the thiomersal trace limit. However, multi-dose influenza vials do contain excess thiomersal. Pharmacists should keep in mind that the dosage of all flu vaccines are not uniform at 0.5 ml. Fluzone®, when given to patients aged 6 to 35 months, should be administered at 0.25 ml. If given to patients older than 3 years of age, it’s administered at 0.5 ml.

In an effort to support pediatric immunizations, New York State Commissioner of Health Howard A. Zucker also published non-standing orders for epinephrine and diphenhydramine to be administered to children during an anaphylactic reaction to the flu shot.

To further expand vaccination to children, the New York State Vaccines for Children (VFC) Program is also available to provide vaccines at no cost to eligible children. A child is eligible for this program if he or she is younger than 19 years old and is enrolled in New York State Child Health Plus or Medicaid, is uninsured, underinsured, or is an American Indian or Alaska Native.

During the 2017-2018 flu season, there was also a shortage of oseltamivir (Tamiflu®) capsules and suspensions. Oseltamivir is a neuramidase inhibitor that is FDA-approved for the prophylaxis and treatment of influenza. Pharmacists are eligible to compound the liquid form of the medication under the permission of the State Board of Pharmacy. The pharmacist can annotate on the prescription that an emergency exists and commercial preparation is unavailable. A separate prescription is not required.

Since the passage of executive order no. 176, more than 8,000 New Yorkers aged 2 to 18 have been vac-
cinated. After the order’s passage, there was a nine percent increase in lab confirmed flu. A trend of decline in hospitalizations was seen two weeks after the order was passed.⁵

While all this may be daunting for the typical community pharmacist, we must not forget our responsibilities as patient educators. To prevent contracting the flu, educate your patients to wash their hands with soap and water for at least 20 seconds. If soap and water are not available, have patients use hand sanitizers containing at least sixty percent alcohol. Advise patients to not cough and sneeze into their hands and use a tissue instead. If tissues are not available, advise them to cough into the fold of their arms.⁵ Recommend the flu vaccine to patients even if they have already caught the flu. Patients are often infected with only one strain, but the flu vaccine covers 3 to 4 different strains depending on the vaccine received. Recommend the vaccine even if its efficacy is low. Patients who catch the flu after receiving the flu vaccine experience a less severe course of illness.⁵ As future community pharmacists, our roles have moved beyond standard dispensing. We also serve as educators and immunizers for the good of public health. How will you serve your population next flu season?

**SOURCES:**


Acetaminophen toxicity and n-acetylcysteine

By: Kathleen Horan, PharmD Candidate c/o 2020

During my institutional Introductory Pharmacy Practice Experiential (IPPE) rotation in the emergency department at NYU Winthrop University Hospital in the spring of 2018, I witnessed a variety of interesting cases while shadowing my preceptor, emergency department pharmacist Megan Czuba, PharmD. Among these emergencies, I witnessed a patient experiencing an acetaminophen overdose and was surprised by the gravity of effects that a toxicity caused by such a commonly used medication can have on a patient. After the patient had been stabilized using the widely accepted antidote discussed below, N-Acetylcysteine, my preceptor explained the prevalence of this toxicity as well as other possible treatments available to patients who are afflicted by this toxicity with emphasis on the fact that pharmacists and student pharmacists alike should be aware of the effects that seemingly harmless medications like acetaminophen can have when taken in large doses.

Acetaminophen is the most commonly used analgesic-antipyretic in the United States. It is found not only in common over-the-counter products, such as Tylenol®, FeverAll®, and Mapap®, but also in several over-the-counter and prescription combination products, such as Excedrin®, NyQuil™, Fioricet®, Norco®, and Vicodin®. Because of its prevalence and use in many combination products, it can be easy for patients to accidentally take too much acetaminophen without realizing it. People also sometimes take a high dose of acetaminophen to attempt suicide.1

Acute acetaminophen overdose is defined as a single ingestion of the drug which occurs within a single 8-hour period. The lowest acute doses found to be capable of causing toxicity are 7.5g in an adults and 150mg/kg in children. However, these are relatively conservative standards and it is likely that the actual dose needed to cause toxicity is higher.2

Acetaminophen overdose leads to acetaminophen toxicity, which causes serious health problems and can even lead to death. Some people affected by acetaminophen toxicity are asymptomatic. In symptomatic patients, the symptoms follow a pattern depending on the length of time since overdose. Symptoms in the first 24 hours may include feeling tired and sick, sweating, paleness, nausea, and vomiting. On the second and third day, the symptoms from the first day may go away, however, it is during this time that the liver or kidneys may stop working correctly. Some symptoms during this period include belly pain and decreased urination. After the third day, the original symptoms may return, accompanied by confusion and jaundice. People can die during this stage due to severe poisoning.1

Acetaminophen toxicity is diagnosed by measurement of the serum acetaminophen level using the Rumack-Matthew nomogram (see image below). The nomogram plots the initial concentration versus time of ingestion. In the study in which it was developed, a discriminatory line was originally drawn based on the observations of patients, separating those who developed hepatotoxicity from those who did not. Those who fall at or above the line should be treated for toxicity.2

The nomogram used in the United States uses a discriminatory line that was arbitrarily lowered by twenty five percent to increase sensitivity. It is called the “treatment line” or the “150-line,” because it starts at a concentration of 150 μg/mL at 4 hours after ingestion. Use of this line only has a one to three percent failure rate and it should be considered adequate and reliable in assessing acetaminophen toxicity when followed correctly. However, its weakness is that the time of ingestion must be known to make an assessment.2 Some other issues concerning the nomogram are that it is not useful after chronic repeated overdose and that ingestion of sustained-release products or co-ingestion of anticholinergic, salicy-
late, or opioid products may cause delayed elevation of serum levels thereby making interpretation of the nomogram difficult.\(^3\)

N-acetylcysteine is the accepted antidote for acetaminophen poisoning. It is indicated for all patients at significant risk for hepatotoxicity. This includes those who fall above the “treatment line” on the Rumack-Matthew nomogram, patients with an unknown time of ingestion and a serum acetaminophen concentration >10 mcg/mL, and patients with a history of acetaminophen ingestion and any evidence of liver injury. Other possible treatments include the use of activated charcoal, which binds to acetaminophen in the stomach or intestines in order to keep the body from absorbing it and in severe cases, a liver transplant.\(^1\)

**Sources:**

1. Droxia\(^\circledR\) (Hydroxyurea) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; Revised 03/01/2016.


Review of PROTAC - a drug that may alter the future of cancer therapy

By: Yeonah Suk, PharmD Candidate c/o 2020

Despite the $107 billion a year cancer drug industry there is no substantiated cure for cancer. Cancer can be treated by targeting a variety of cellular mechanisms. One innovative approach incorporates the use of proteasome inhibitors in the regulation of programmed cell death. Damaged or inessential proteins must be degraded in order to reconstruct new proteins which are involved in gene expression, cellular division, and detoxification of reactive oxygen species. Ubiquitin binds to the old or damaged proteins which induces proteasome recognition and degradation. When this ubiquitin-proteasome degradation pathway fails, protein aggregation occurs. This may impede the aforementioned cellular activities, leading to cellular degeneration which can be detrimental to healthy cells. However, this very mechanism can also be manipulated to work against cancer cell proliferation. Current technology has developed a new drug model, proteolysis targeting chimeras (PROTAC), that employs this pathway to combat breast cancer.

Estrogen receptor alpha (ERα) is overexpressed in breast cancer cells and promotes estrogen dependent proliferation making it a good drug target. The conventional approach to combating this malignancy is the inhibition of ERα transcription through modulation of receptor conformation by synthetic ligands. The limitation of this method is that there is a high susceptibility of drug resistance. For example, tamoxifen (Soltamox®) is currently used as a treatment for breast cancer because it works as an estrogen receptor antagonist. However, over time, it begins to possess agonist function which results in regrowth of cancerous cells. PROTAC offers a solution because it degrades the target protein directly.

PROTAC consists of three components including a stabilized peptide which binds to ERα, a linker, and a hydroxyproline-containing pentapeptide which is recognized by E3 ubiquitin ligase. When a complex is formed, the E3 ubiquitin ligase that is recruited binds ubiquitin and targets the protein ERα, leading to its degradation through the previously described proteasome pathway. PROTAC’s advantage is its ability to target a broad range of proteins and thus, has been applied to create more peptide based PROTACs that selectively degrade multiple protein targets including ERα and estrogen-related receptor alpha. This potential treatment pathway was pursued because peptide modulators show greater potential than PROTACs in certain respects, such as expediting the necessary drug-to-target protein interactions which is challenging for small molecules, like unmodified PROTACs, to achieve on their own.

Currently, PROTAC conjugation with peptidomimetic estrogen receptor modulator (TD-PERM) is being tested to determine whether it can increase PROTAC’s effects. This combined development is named TD-PROTAC and it executes three characteristic actions. TD-PROTAC selectively activates the ubiquitination and subsequent degradation of ERα by a proteasome dependent pathway, reduces the transcription of ERα related genes which provide anti-proliferative properties, and signals apoptosis of ERα positive cancer cells with almost no cell toxicity toward cells that do not contain ERα. To evaluate this drug’s ability to carry out protein degradation, a study conducted at Shenzhen Graduate School of Peking University in Shenzhen, China by Dr. YanHong Jiang, analyzed ERα levels via immunoblotting after treatment with various groups, a control, and TD-PROTAC. Results showed that the control peptides did not exhibit an ability to degrade ERα. This verifies that both the ERα and ubiquitin binding groups are essential to adequately degrade ERα, both of which are moieties present in TD-PROTAC. 4

TD-PROTAC also prevents signalling of certain receptors. In the same study conducted by Dr. Jiang, polymer-
ase chain reaction analysis was used to examine the mRNA levels of pS2 which is a gene that ERα regulates via transcription. Results showed that TD-PROTAC treated cells displayed significant down regulation of pS2 gene expression revealing the multi-faceted approach TD-PROTAC has in combating breast cancer. Additionally, the effect TD-PROTAC has on other receptors must be assessed due to the risk of harming non cancerous cells, as well as producing severe side effects. Consequently, the effects TD-PROTAC has on vitamin D receptors, embryonic kidney cells and cells that do not contain ERα were also tested. Results demonstrated clinically insignificant degradation of the aforementioned groups, indicating that TD-PROTAC selectively targets ERα positive breast cancer cells.

Breast cancer is a highly prevalent disease and is the fourth leading cause of cancer related death in the United States. Sixty-six percent of all breast tumors express ERα and of these, seventy percent respond to hormone therapy which indicates that PROTAC’s ability to selectively and effectively degrade estrogen receptors as well as impede their transcription is promising in the future of breast cancer therapy.

**SOURCES:**

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Assessing the current treatment recommendations for Graves’ disease

By: Natalie Rodriguez, PharmD Candidate 2019 Philadelphia College of Pharmacy, University of the Sciences and Stacey Gorski, Assistant Professor of Biological Sciences

PRESS SUMMARY

The most common cause of hyperthyroidism, or an overactive thyroid, is an autoimmune disease known as Graves’ disease. In patients with Graves’ disease, the immune system attacks the thyroid gland and causes it to overproduce thyroid hormones. The increased level of hormones causes patients to experience rapid heart rates, tremors, weight loss, sweating, increased appetites, and oftentimes, Graves’ ophthalmopathy—a condition where the eyes appear to bulge from the head. Currently, there are three main treatment options for Graves’, including anti-thyroid drug therapy, radioiodine treatment and a sub-total or total thyroidectomy. Though all are viable treatment options, there is a great deal of uncertainty regarding the safety and effectiveness of each treatment. An analysis of the available literature appears to support total thyroidectomy as the most safe and effective form of treatment, despite most US Graves’ patients undergoing anti-thyroid drug therapy instead.

ABSTRACT

Graves’ disease, the most common form of hyperthyroidism, is an autoimmune disease that generally affects more women than men. The primary cause is production of thyroid-stimulating receptor antibodies, which aberrantly overwork the thyroid gland, and cause excessive production of essential hormones, triiodothyronine (T3) and thyroxine (T4). These two hormones are primarily responsible for regulating heart rate, growth and development, body temperature and most importantly, metabolism. The exact mechanism of Graves’ pathogenesis is still not fully understood, but both genetic and environmental factors clearly play a role. Currently, there is no cure for Graves’ disease; however, there are several treatment options, all with varying degrees of effectiveness and skepticism. Here, we investigate and compare the three primary recommended treatment options: anti-thyroid drug therapy, radioiodine therapy and a partial or total thyroidectomy. When administered properly, all treatment options make Graves’ disease a manageable disease with a good prognosis.

INTRODUCTION

Graves’ disease, first discovered by Robert Graves in the 1800’s, is a thyroid autoimmune disorder, in which the thyroid gland aberrantly produces thyroid hormones as a result of autoantibodies attacking thyroid cells. It is the most common form of hyperthyroidism, and generally affects women ten times more frequently than men. Graves’ disease affects approximately ten million people in the United States, many of whom go undiagnosed for several years. Graves’ disease occurs as a result of both genetic and environmental factors. Though not fully understood, it is believed that human leukocyte antigen complexes (HLA) are the main genes involved in this disease. Stress and smoking are two large environmental factors that also play a role in the development of this disease. The most common signs and symptoms are weight loss, tremors, irritability, increased heart rate, heat intolerance, frequent bowel movements and difficulty sleeping. Additionally, a major sign of Graves’ disease is Graves’ ophthalmopathy—swelling around the eyes. Graves’ disease patients can also have goiters, or enlarged thyroid glands. People with Graves’ disease are also at risk for developing other autoimmune diseases, such as Addison’s disease, rheumatoid arthritis, type I diabetes, pernicious anemia or lupus.
The thyroid gland lies right below the Adam's apple and sits in front of the trachea. When looking at the cellular architecture, the basolateral sides of thyroid cells are found next to capillaries, allowing for iodine entrance into the cell and hormones out into the bloodstream. Inside the cells, there is a large concentration of thyroglobulin, which is required for the production of thyroid hormones. Both thyroglobulin and iodine will leave the thyroid cells, travel through the apical membrane and enter the follicular lumen, where hormone synthesis and storage occurs. Once hormone synthesis is complete, T3 and T4 are sent out through the basolateral membrane and into the bloodstream.

### Iodine Uptake

When TSH binds to its appropriate receptor on the basolateral side of a thyroid cell, a sodium-iodide symporter (NIS) is stimulated and brings in one iodide and one sodium molecule. The direct binding of TSH to its receptor regulates the expression of NIS and how much iodine is transported into the cell. If there is a high concentration of TSH and more receptors are being stimulated, more symporters will be present on the surface, leading to increased iodine uptake. If there is no TSH present, the NIS will incorporate itself intracellularly, thus preventing iodine from entering the cell (Figure 1).

Once iodine is transported into the cell, it is exported into the follicular lumen through another membrane transporter on the apical side, pendrin. When iodine enters the lumen, it reacts with thyroglobulin, a protein found in the thyroid, and undergoes organification and oxidation reactions with hydrogen peroxide and thyroid peroxidase (TPO), creating two tyrosine residues, monoiodotyrosine (MIT) and diiodothyrosine (DIT). These two tyrosine residues will later combine with the help of TPO and hydrogen peroxide to form triiodothyronine (T3) and thyroxine (T4), both bound to thyroglobulin.

Once these two hormones are produced, they are then macropinocytosed back into the thyroid cell and the thyroglobulin is deiodinated by iodotyrosine dehalogenase, DELHAL1, and the resulting free T3 and T4 are exported out the basolateral side through the MCT8 transporter into the blood. The thyroglobulin remaining in the cells will then be reused and the cycle will continue (Figure 1). T3 is the primary hormone that is taken up by cells, and T4 is generally found more concentrated in the blood. The final mechanism for thyroid hormone production is the deiodination of T4 to T3, to be used by the cells.

### Graves’ Disease Thyroid Function

In Graves’ disease, for reasons that are still unclear, thyroid receptor-stimulating antibodies (TRAb), also known as thyroid-stimulating immunoglobulins (TSI), are produced and bind to the same receptor as TSH, essentially tricking the thyroid into overexpressing the NIS transporter. This causes a massive influx of iodine into the cells, thus leading to a rapid increase in the production of thyroid hormones. With increased T3 and T4 levels, the cells increase metabolism and the patient will develop Graves’ disease. Diagnostically, Graves’ disease patients will have low TSH and increased T3 and T4 levels. The reason for decreased levels of TSH is due to the increased hormone levels, which create a negative feedback, inducing the pituitary gland to inhibit TSH secretion.

### Treatments

Currently, there is no cure for Graves’ disease, however, there are three viable treatment options to help reduce thyroid function and decrease the signs and symptoms of this disease. The first type of treatment is anti-thyroid drug therapy (ATD), which inhibits the mechanisms for iodine uptake in the cell, thus decreasing hormone production. In the second treatment, radioiodine therapy, the thyroid absorbs radioactive iodine (RAI), emitting beta particles, killing thyroid tissue. Finally, a thyroidectomy is a treatment in which the patient can have the entire or part of the gland removed, to decrease hormone production. All three treatments, though very different in their mechanisms, work to achieve the same goal of decreasing hormone production, with hopes of attaining euthyroidism, the state of a normal thyroid gland.
Anti-thyroid drug therapy

Anti-thyroid drug (ATD) therapy is generally the first line of treatment for Graves' disease patients. Presently, there are two primary medications, methimazole (MMI) and propylthiouracil (PTU), that are used to help reduce the production of thyroid hormones, with the desired outcome of attaining euthyroidism. Anti-thyroid drug therapy is noninvasive and cost effective. Additionally, no hospitalization is required, however, life-long follow up with an endocrinologist and several blood tests are essential in order to ensure that the treatment is regulating T3 and T4 production appropriately. Both MMI and PTU have the same primary mechanism—blocking the organification, or incorporation, of iodine into thyroglobulin. This prevents the activity of TPO and hydrogen peroxide, thus inhibiting the formation of MIT and DIT, which are critical to the formation of T3 and T4. These two anti-thyroid drugs can also act more downstream and block the coupling of MIT and DIT, by further inhibiting TPO and preventing the direct formation of the hormones (Figure 2). The main concerns regarding anti-thyroid drug therapy are the low remission rates, high relapse rates and development of hypothyroidism. Additionally, long-term use of these medications may prove harmful because they suppress the body's ability to fight infections. Therefore, treatment duration is not recommended for more than eighteen months.

Figure 2. The effects of anti-thyroid drugs on iodine transport and hormone production. Anti-thyroid drugs work to inhibit the actions of iodine within the thyroid cells to prevent hormones from being produced.

MMI, also known as Tapazole, is currently the most commonly used anti-thyroid drug treatment and has a very high potency and long half-life. As a result, it requires lower doses per day. Generally, most adult patients will receive 15-30mg of the drug for mild to moderate Graves’ disease. In patients with severe Graves’ disease, doctors will prescribe up to 60mg of MMI, which is taken in three doses, separated approximately eight hours apart. Although today MMI is more commonly used, it is generally not administered to pregnant women, specifically during the first trimester. Though past research states that MMI passes through the placental barrier more readily than PTU, newer findings suggest that the levels are very similar and as a result, there is still uncertainty as to which drug should be administered to this vulnerable patient group. Recently, Andersen, SL, and Laurberg, P demonstrated in their article, “Managing hyperthyroidism in pregnancy: current perspectives” that birth defects are more severe in pregnant women treated with MMI in the first trimester, compared to those treated with PTU. Fetal birth defects found with MMI treatment included esophageal and gastrointestinal atresias, abdominal wall defects and ventricular wall defects, while PTU defects were preauricular sinus, fistulas and cysts—further validating the preference of PTU in the first trimester. There are several minor side effects associated with MMI treatment in non-pregnant adults as well; these include urticaria, or skin rash, nausea, and drowsiness. Some severe side effects, though rare, include agranulocytosis and leukocytopenia.

PTU was the primary drug of choice for Graves’ disease patients in the United States until 2010, when the Food and Drug Administration issued a black box warning due to severe hepatotoxicity. PTU, though less commonly used today, has an additional mechanism of action that inhibits the deiodination of T4 to T3, preventing cells from taking up additional thyroid hormones. In contrast to MMI, PTU is less potent and has a shorter half-life, ne-
Radioiodine Therapy

Radioiodine therapy (RAI) is a form of nuclear medicine that entails ingesting a radioactive iodine pill, [131]I. This treatment is very cost-effective and easy to administer. [131]Iodine is absorbed almost exclusively by the thyroid gland, which greatly limits the likelihood of radiation transmission to other parts of the body. Once an [131]I pill is ingested, it travels through the gastrointestinal tract and is absorbed into the bloodstream, where it works its way to the thyroid gland. [2]When [131]I enters thyroid tissue, it works by emitting β particles that slowly cause shrinking and destruction of the thyroid cells (Figure 4). [19]Today, many endocrinologists, specifically in the United States, are advocating for RAI therapy to be the primary treatment for Graves’ disease patients, especially pediatric patients. [20]However, most primary care physicians continue to use radioiodine as second line treatment instead, if anti-thyroid drug therapy fails. [11]When receiving RAI treatment after anti-thyroid drug therapy, MMI or PTU medications must be discontinued at least three days prior to the onset of RAI therapy. Following RAI, patients can return home, but it is advised to avoid prolonged, close contact and to stay approximately six feet away from others, especially infants and pregnant women, to prevent radiation exposure. Most radiation leaves the body within the first two days, predominantly through urine. [21]Currently, there is debate as to whether patients should receive a calculated dose of RAI catered to their specific needs, or if fixed doses prove to be more effective. With proper dosing, partial or complete thyroid destruction is possible, leading to euthyroidism; however, hypothyroidism is the far more common outcome. [11]In some cases, especially in patients treated with lower levels of RAI, relapse can occur, leading to recurrence of hyperthyroidism. Due to the uncertainty with measured doses, attaining euthyroidism is very difficult, and as a result, continued follow up is necessary to ensure proper thyroid function. Some side effects of RAI, though transient, include a metallic taste in the mouth, nausea and swollen salivary glands. [22]Additionally, RAI can temporarily worsen Graves’ ophthalmopathy. [23]Radiation treatment is not administered to patients who are pregnant or planning to become pregnant and generally is not given to children under the age of five. [19-22]

Thyroidectomy

A subtotal or total thyroidectomy is the least common treatment for Graves’ disease patients. Thyroidectomies are typically only considered for very young patients, women planning to become pregnant, those with large goiters, severe ophthalmopathy, relapse from radiation, or patients with malignancies on the thyroid. [2,24]For many years, subtotal thyroidectomies were the favored surgical option, because only part of the thyroid tissue is removed, with hopes that the remaining portion can provide an adequate hormone supply for the body. [25]In most cases, euthyroidism is not achieved, and the patient can either relapse or be rendered hypothyroid, calling for replacement hormone therapy, and constant follow up by an endocrinologist. [13]Most recent studies, however, have shown that doctors are now more commonly performing total thyroidectomies, removing the entire gland, and providing long-term replacement hormone therapy (Figure 6). [25]Total thyroidectomies are now preferred to subtotal thyroidectomies because subtotal requires more postoperative regulation due to fluctuations in hormone levels, whereas total thyroidectomies prove more effi-
cient due to easy postoperative treatment. Additionally, it was originally thought that subtotal thyroidectomies carried less risk of complications compared to total thyroidectomies, but recent research disproves this theory.\textsuperscript{25,26} Some complications of thyroidectomies include hypoparathyroidism, hypocalcemia and laryngeal nerve injury. These complications can lead to low calcium uptake by the body, causing muscle twitches and a decrease in bone growth. Laryngeal nerve injury, one of the more common complications, can make patients incapable of lengthening their vocal cords, preventing them from producing higher pitched sounds. Many of these complications, however, can be prevented with an experienced surgeon.\textsuperscript{25, 27, 28}

All three treatments have the same common goal: attaining euthyroidism. However, it is very unlikely that any treatment will achieve this goal long-term. Anti-thyroid drug therapy can transiently achieve euthyroidism, however, once taken off medication, the patient will usually relapse or be rendered hypothyroid.\textsuperscript{33} Radiation therapy has had much controversy due to the limited amount of research and though a common treatment option recommended by endocrinologists, this treatment frequently results in hypothyroidism due to excessive destruction of the thyroid.\textsuperscript{34} This is primarily due to the uncertainty of how to accurately calculate a dose specific to each patient, making it extremely difficult to administer the perfect regimen of RAI that will achieve euthyroidism. As a result, most primary care physicians will use fixed doses, which in some cases will not be enough to treat the patient, keeping them at a hyperthyroid state. Consequently, RAI therapy can result in both hypothyroid or hyperthyroid states, calling for additional follow up and treatment. In a study comparing different fixed doses of RAI it was found that higher doses proved more effective than lower ones—71.4% of patients treated with 370 mega-becquerel (MBq) were rendered hypothyroid after one treatment, while over 30% of patients treated with 185 MBq required additional doses.\textsuperscript{34} Subtotal thyroidectomies can also be extremely difficult to regulate. Individual surgeons use different techniques to determine how much of the thyroid to remove, and as a result, several outcomes can occur. In subtotal thyroidectomies, patients can transiently achieve euthyroidism, but eventually develop hyperthyroidism or hypothyroidism several months later. Over 60% of subtotal thyroidectomy patients are rendered hypothyroid and about 15% remain in a hyperthyroid state, requiring additional treatments.\textsuperscript{27} Although anti-thyroid drug therapy, RAI and subtotal thyroidectomies can prove successful in treating Graves’ disease, each treatment will result in maintaining some functionality of the thyroid gland, calling for regular thyroid function tests. Total thyroidectomies, regardless of the patient’s situation, will always result in a definitive state of the thyroid—hypothyroidism, thus calling for thyroid-replacement hormone therapy for the remainder of the patient’s life.\textsuperscript{12}

Although no treatment option can ultimately achieve permanent euthyroidism, other factors should be considered when deciding on a treatment plan. While anti-thyroid drug therapy and RAI treatment are considered cost-effective, the varying results require life-long follow-up, and if hypothyroidism results, thyroid-hormone re-
placement therapy. Furthermore, if the patient relapses and becomes hyperthyroid, another treatment is required. ATD patients also require many blood tests in order to regulate the patient’s liver function and blood cell counts, as a means to prevent serious side effects. Thyroidectomies are expensive to conduct and difficult to find an experienced surgeon. When comparing total and subtotal thyroidectomies, In, H et al, found that total thyroidectomies offer the more cost effective treatment. Although subtotal thyroidectomies, in theory, seem to be the best treatment option, more often than not, they result in hypothyroidism or hyperthyroidism, requiring life-long follow up, constant thyroid regulation and depending on the patient’s situation, either thyroid-replacement hormones or additional treatment. The uncertainty in outcomes and the inevitability of hypothyroidism makes subtotal thyroidectomies less appealing. We analyzed recent literature and found that the majority of studies conducted between 1990-2017 tend to prefer total thyroidectomies to subtotal thyroidectomies (Figure 6). While total thyroidectomies are expensive to conduct, they also offer a definitive outcome, with minimal follow-up. Since there is no chance of relapse, total thyroidectomy patients are administered life-long thyroid hormone replacement medications, such levothyroxine for the remainder of their lives. When looking at all treatment options, more likely than not, a patient will eventually be rendered hypothyroid. Thyroid levels after ATD, RAI and subtotal thyroidectomies are more difficult to regulate due to thyroid function fluctuations and as a result, more monitoring of the patient is required until stabilization occurs, thus calling for more doctor’s visits and lab tests. Total thyroidectomies, however, offer a definitive outcome, making it easier to stabilize a patient more quickly, calling for less follow up.

Finally, when considering Graves’ disease treatment options, side effects and complications should be taken into consideration. While anti-thyroid drug therapy may not have many severe side effects, altering white blood cell counts and liver damage can be incredibly detrimental to the patient. There is also a great deal of uncertainty in RAI therapy regarding the chances of developing cancer later in life and as a result of this ambiguity, many patients are skeptical with this treatment option. Thyroidectomies have complications as well, however, with an experienced surgeon the rates of complications are often transient. In an experiment conducted in Italy, 14,934 thyroidectomies were conducted in 42 different endocrine surgery units. Of those 14,934 surgeries, 9,599 of them were total thyroidectomies—1.3% of the patients developed permanent laryngeal nerve injury, and 2.2% developed permanent hypocalcemia. Based on these results, with an experienced surgeon, severe complications are rare, making total thyroidectomies an extremely effective treatment option.

Although there is still a great deal of uncertainty in which treatment option offers the best outcome, many factors can contribute to a patient deciding on a particular treatment. Through a meta-analysis of the recent literature, we found several studies and were able to compare each study’s recommendation for Graves’ disease patients (Figure 7). Although treatment plans vary in countries around the world, there is evidence to support that total thyroidectomies offer the safest and most cost-effective treatment for Graves’ disease patients, with easy post-operative procedures and minimal follow up.

**Figure 7. Literature based comparison of Treatment Options for Graves’ Disease Patients**

 Although diagnosed appropriately, Graves’ disease can be an extremely manageable disease with a good prognosis. Through more research, scientists may soon be able to determine the causes of this disease and further understand the production of autoantibodies that trigger the increased production of T3 and T4.
Recently, Apitope, a drug discovery and development company, launched a phase I clinical trial for the treatment of Graves’ disease. Their approach involves suppressing pathogenic T helper cells with antigen-processing independent epitopes. These synthetic peptides do not require antigen-presenting processing, but allow for IL-10 activation, which induces regulatory T cells and elicits an anti-inflammatory response. By suppressing the immune response, this treatment is working to induce T cell tolerance to the TSH receptor and decrease TRAb production. This treatment option, though still not fully explored and tested, may be a promising and viable long-term treatment option in the near future.

As potential new promising therapies loom in our future, Graves’ disease patients still have several treatment options available to help to control their symptoms. Though presently, no single treatment offers a definitive chance at euthyroidism, there are viable options in helping to manage the disease. Currently, anti-thyroid drug therapy and RAI treatment are more commonly administered to patients, especially here in the US; however, total thyroidectomies may prove to be a more worthwhile option. Although thyroidectomies are expensive, the minimal follow-up, definitive outcomes and low risk of complications prove effective.

**Literature Meta Analysis**

Research articles included for analysis were found searching the PubMed database and were limited to those published between 1990 and 2017. Articles were found using several unique keywords and search terms. For anti-thyroid drug preference, “MMI vs. PTU”, “which ATD is most recommended”, “PTU black box warning”, “PTU or MMI”, “propylthiouracil and methimazole”, and “PTU MMI” were used. For thyroidectomy preference, the following terms were used: “Subtotal AND Total thyroidectomies AND Graves’ disease”, “Subtotal vs. total thyroidectomies in Graves’ disease patients”, “bilateral or total thyroidectomy”, “total vs. subtotal thyroidectomy” and “Surgery AND Graves’ disease” were used. When comparing all three treatment options, the above search terms in addition to “RAI vs. ATD”, “ATD or thyroidectomy”, “RAI or thyroidectomy”, “Graves’ disease treatment options”, “cost-effective AND Graves’ disease treatment” (radioactive iodine OR RAI) AND (anti thyroid drug OR ATD)”, “(anti thyroid drug OR ATD) AND

**Thyroidectomy”, “(radioactive iodine OR RAI) AND Thyroidectomy”, “Graves’ disease treatment AND best outcome”, and “Treatment recommendations for Graves’ disease patients.” were used. A total of 67 references were identified and 53 were used in the analysis.

**SOURCES:**


Puzzle: Blockbuster Oncology Products

By Matthew Kahn, Graphics Editor

ALIMTA
AVASTIN
GLEEVEC
HERCEPTIN
IMBRUVICA
KEYTRUDA
NEXAVAR
OPDIVO
REVLIMID
RITUXAN
TARCEVA
TASIGNA
XTANDI
YERVOY
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Puzzle: Blockbuster Oncology Products

Answers

ALIMTA
AVASTIN
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TARCEVA
TASIGNA
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ZYTIGA
Throughout my time in the PharmD program, my understanding of pharmacy as a profession has evolved and deepened as much as my desire to create awareness, particularly to non-science students, about the diverse role pharmacy plays in various healthcare and non-healthcare settings. I have always had an affinity for writing and look forward to combining my interests in literary composition, editing and pharmacy to produce relevant issues which both pharmacy students and non-pharmacy students alike will find relatable and take an interest in.

I've always loved graphic design, so I was thrilled at the opportunity to be a part of the Rho Chi Post team and contribute to future publications. I'm excited to explore new ways to make the Post even better, and also to be continuously exposed to new ideas in the pharmaceutical field.

It's always interesting to see how the healthcare field evolves and all the advancements in pharmacy come to fruition. I joined the Rho Chi Post because it brings together a variety of these topics with distinguishing perspectives from our peers in pharmacy practice. I am ecstatic to join the team in continuing Rho Chi Post's endeavors in promoting the profession.

The Rho Chi Post allows me to have an appreciation for interactive pharmacy learning as well as the art of writing. With each newsletter, my goal is to provide current information to readers who come across the Post. As an editor, I hope to make the newsletter one-of-a-kind and motivate and influence writers to explore science with their creative talents.

As a member of the Rho Chi Post team, I have a vast appreciation of what it means to be a pharmacist in the rapidly evolving world of healthcare. As a graduate editor, I will continue to bring my passion for science and creativity to the Rho Chi Post.

My two great loves are innovative science and quality writing; the Rho Chi Post is an insightful combination of both. As an editor, I look forward to bringing relevant information and fresh perspectives to the student and faculty of St. John’s University, as well as to making the Rho Chi Post a newsletter that offers something new to every reader.
@ Jonathan Mercado
6th Year, STJ; Finance and Outreach Manager, Staff Writer
The Rho Chi Post breaks barriers for students that want a glimpse of their future and acts as an inspiration to work harder to achieve their goals. It is an embodiment of the motivation and intelligence that drives pharmacy students to be the most informed and capable professionals they can be. I am glad to be a part of that mission and to channel my passion and interests through this newsletter.

@ Gabrielle Flavoni
Graduate Staff Editor
Writing has always been an enormous passion of mine, and I’m blessed to join such an amazing team that encourages me to explore it. As a new Staff Writer for the Post, my goal is to aid others in staying up-to-date about the pharmacy world, while also utilizing a creative outlet to make an impact on those around me.

@ Kathleen Horan
5th Year, STJ; Staff Editor
I have always loved writing, and I hope to couple my passion for writing with my interest in clinical pharmacy by becoming a writer and staff editor for the Rho Chi Post. As a writer and staff editor for the Rho Chi Post, I hope to write and edit informative and interesting articles that relate to the world of healthcare and pharmacy. I am so excited to join this team of student pharmacists and writers.

@ Alex Chu
6th Year, STJ; Staff Writer
With a constantly evolving healthcare field, it is imperative that we keep ourselves up to date with the latest news. This is what led me to join the Rho Chi Post, which constantly comes out with interesting and informative topics. It is an honor to write for the Rho Chi Post, and I wish to contribute innovative and intriguing articles to this newsletter.

@ Anna Chen
5th Year, STJ; Staff Writer
The Rho Chi Post is a fantastic opportunity for future health professionals to keep up with the vastly changing healthcare world. As the pharmaceutical landscape keeps changing, it is crucial that we join the conversation in voicing our opinions and clinical input into current healthcare debates. Healthcare is limitless in possibilities to better patient centered care and I aim to deliver content that is both invigorating and inspiring to both students and practicing professionals.

@ Thanesha Graham
6th Year, STJ; Staff Writer
As a writer for the Rho Chi Post, I have the unique opportunity to convey my knowledge, discoveries and interests to the general public. I will be able to enlighten individuals about issues that will not only impact them, but also their families, and communities. I look forward to supplying this newsletter with valuable and relevant information about the evolving field of pharmacy.
Writing for the Rho Chi Post allows me to bridge the gap between class and the real world. It gives me a reason to focus on topics that are relevant to me as a practicing student pharmacist and explore new medications, laws, and ventures in our evolving profession. This process of researching, teaching oneself, and finally, teaching others is what we will ultimately do as future pharmacists. I am honored for this opportunity to be further exposed to what pharmacy has to offer all while giving back to the community that has taught me so much.
The Rho Chi Post is an award-winning, monthly, electronic, student-operated, faculty-approved publication that aims to promote the pharmacy profession through creativity and effective communication. Our publication is a profound platform for integrating ideas, opinions, and innovations from students, faculty, and administrators.

The Rho Chi Post aims to become the most exciting and creative student-operated newsletter within St. John’s University College of Pharmacy and Health Sciences.

Our newsletter continues to be known for its relatable and useful content.

Our editorial team continues to be known for its excellence and professionalism.

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To maintain a healthy, respectful, challenging, and rewarding environment for student editors.
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