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P.O. Box 2793 • Rancho Santa Fe, CA 92067 • (877) 643-3123 • www.gdatf.org • info@gdatf.org

Long-Term Use of Antithyroid Drugs

Antithyroid medications (ATDs) have been prescribed for decades as a treatment option for hyperthyroidism in Graves' disease patients. The U.S. Food and Drug Administration approved propylthiouracil in 1947 and methimazole (brand name Tapazole) in 1950.

In the past, endocrinologists typically prescribed ATDs for a limited period of time. Some doctors used 12-18 months as a benchmark, while others would keep patients on the medication for up to two years. Once the clock ran out, doctors stopped the medication and checked the patient's thyroid function. If levels were in the normal range, the treatment was declared a success. If thyroid levels were still not well controlled (or if the patient became hyperthyroid again after stopping the medication) doctors would recommend radioactive iodine or surgery, which are definitive therapies that result in life-long hypothyroidism.

However, a paradigm shift in recent years – ushered in by new research as well as patient and physician preference – has brought changes to how these medications are used, with more patients remaining on antithyroid medications well past the two-year mark. This new approach has resulted in more patients achieving remission, and many others able to successfully control thyroid levels while taking a low dose of medication.

The topic of long-term use of ATDs has generated a great deal of interest in the patient community, so the Graves' Disease & Thyroid Foundation teamed up with **Dr. Eve Bloomgarden** and **Dr. David Cooper** to present a webinar to help inform patients about this treatment option. (1). Dr. Bloomgarden is a board-certified endocrinologist at Northwestern Memorial Hospital and an assistant professor in the Division of Endocrinology, Metabolism and Molecular Medicine at Northwestern University Feinberg School of Medicine. Dr. Cooper is currently Professor of Medicine at the Johns Hopkins University School of Medicine and Professor of International Health at the Bloomberg Johns Hopkins School of Public Health.

Dr. Bloomgarden kicked off the webinar with an overview of the thyroid, a butterfly-shaped gland that makes thyroid hormones, which are secreted into the bloodstream. Thyroid hormone is involved in energy balance, temperature regulation, metabolism, heart function, muscle function, and cognitive function. "Given that long list of essential functions, it's important that thyroid hormone levels are tightly regulated." Dr. Bloomgarden explained that in our normal state, thyroid hormone production is regulated via a fine-tuned system that operates somewhat like a thermostat. When the body needs thyroid hormone, the pituitary gland secretes a "signal" in the form of

thyroid stimulating hormone (TSH). The TSH binds to the TSH receptor on the thyroid gland, which activates a pathway that tells the thyroid gland to start making thyroid hormones to secrete. Once thyroid hormones get to a normal level, this "turns off" the pituitary gland's signal, and the thyroid stops producing and secreting thyroid hormone.

In Graves' disease, this feedback loop is disrupted when the immune system – which normally generates antibodies against foreign invaders – inappropriately makes antibodies against the TSH receptor. (Named after Irish surgeon Robert James Graves, Graves' disease is one of over 100 autoimmune diseases.) These antibodies are known as thyroid stimulating immunoglobulin (TSI) and Thyrotropin Receptor Antibodies (TRAb). Dr. Bloomgarden called these antibodies "kind of like the ultimate trickster", explaining that they mimic the function of TSH, "but the problem here is that they don't turn off. The antibodies are continuously being made by your immune system." As the thyroid continues to pour out thyroid hormone, even when the pituitary's signal is in the "off" position, the body ends up with too much T4 and T3 circulating in the bloodstream (hyperthyroidism). Patients with hyperthyroidism can experience tremors, heart palpitations, insomnia, shortness of breath, fatigue, muscle weakness, anxiety, irritability, weight loss despite increased appetite, infertility, and menstrual disturbances.

For patients with confirmed Graves' disease, Dr. Bloomgarden provides an overview of the three treatment options for hyperthyroidism (ATDs, RAI, and surgery) and schedules a short-term follow-up visit with the patient to review the treatment options again. The final treatment decision involves weighing risks and benefits of each option, as well as considering other issues, including the patient's desire (and timeline) for a future pregnancy, availability of local expertise (particularly for surgery), and any co-existing medical conditions, such as thyroid eye disease.

Dr. Bloomgarden explained that ATDs interfere with the synthesis of thyroid hormone, not the release of pre-formed thyroid hormone. "The thyroid…can actually store a decent amount of thyroid hormone, so starting PTU or methimazole is not going to result in immediate control of your thyroid levels, but it will certainly start to cool down the process and block the production of new thyroid hormones." She also noted that ATDs might also play a role in immune suppression, but they are not curing the underlying autoimmune problem.

Dr. Bloomgarden explained that ATDs can be used as a front-line therapy or on a short-term basis to "cool the patient down" prior to RAI or surgery. Methimazole (brand name Tapazole) is preferred over PTU. In 2010, the FDA came out with a recommendation to limit the use of PTU to a few clinical scenarios because of the risk of liver dysfunction. These scenarios include the first trimester of pregnancy (if treatment is needed), during thyroid storm, and in some patients who experience a mild rash with methimazole. Methimazole can be taken once per day, while PTU is typically split into 2-3 doses throughout the day. For both medications, the starting dose depends on the severity of hyperthyroidism, and is typically lowered over time, with guidance from

laboratory testing. “We’re trying to give you the lowest dose needed to control your levels,” Dr. Bloomgarden explained. She also noted that the supplement Biotin can interfere with thyroid function tests, so recommends that her patients stop taking vitamin supplements 2-7 days prior to having lab tests completed.

Dr. Bloomgarden noted that side effects to ATDs are dose-dependent, with larger doses more likely to result in side effects. Rash is the most common side effect in methimazole, with one study reporting that around 6% of patients experienced this issue. Other side effects include nausea, joint pain, and itching.

Major side effects, although rare, include liver dysfunction (more common with PTU than with methimazole) and agranulocytosis, which is a dangerous lowering of white blood cell count that occurs in 0.2% to 0.5% of patients treated with ATDs. Agranulocytosis is potentially life-threatening, as it puts the patient at risk for a severe infection, but typically resolves after the medication is stopped. “Part of starting one of these medications is counseling about this risk and what to do.” Dr. Bloomgarden gives her patients a copy of the “Methimazole Rules” at every visit, which states that patients who experience fever or sore throat while taking antithyroid medications should stop the medication, contact her office, and get lab testing done immediately to rule out agranulocytosis. (Please consult with your own doctor about procedures for reporting potentially serious side effects.)
Dr. Bloomgarden’s approach to dealing with minor side effects can involve lowering the dose or stopping medications for a few days. For cases of itching or rash, the medications might be re-started in conjunction with an antihistamine like Claritin or Zyrtec. However, Dr. Bloomgarden noted that some patients prefer not to continue with the medications because of side effects, and for those patients, she will “switch gears” and recommend one of the other available treatment options.

In the next section of the webinar, Dr. Cooper then shared some of the research that has informed the recent paradigm shift on long-term use of antithyroid medications, beginning with some historical context on treatment options for Graves’ disease, and some of the early scientific papers on antithyroid drugs. In 1967, Dr. John Eager Howard from Johns Hopkins School of Medicine and Hospital noted during a lecture for the American Medical Association: *“The approach to the therapy of thyrotoxicosis is to control the disease for a lifetime if need be with a drug such as propylthiouracil until spontaneous remission occurs.”* As Dr. Cooper noted, “This is not a new idea that we’re talking about today. This is something that’s been around for decades and decades.”

Dr. Cooper noted that studies in the 1990s on the appropriate duration of antithyroid therapy were typically designed to compare shorter periods of time, such as 6 versus 18 months or 12 versus 24 months. However, more recent research has found that longer duration of treatment increases the chances of remission (defined as having normal thyroid hormone levels for one full year after the discontinuation of antithyroid medications).

Patients with a lower chance of remission are those who have an enlarged thyroid,

very high thyroid or antibody levels, a history of prior relapses, and severe thyroid eye disease. Dr. Cooper noted that according to the "old paradigm", these patients were not considered good candidates for antithyroid medications and were typically referred to RAI or surgery. (For patients with severe eye disease, RAI is not recommended, due to an increased risk that the eye issues will worsen.)

Dr. Cooper further explained that patients taking antithyroid medications typically fall into one of three groups: those who see a steady decline of antibodies and enter remission, those whose antibodies remain continually elevated, and those who cycle between periods of high and low antibodies. Dr. Cooper noted that patients who are good candidates for long-term, low-dose methimazole include children, patients with eye disease, patients wishing to avoid radioactive iodine or surgery, and those with mild disease on low-dose therapy who have a history of relapses.

Dr. Cooper reviewed a 2015 study from Villagelin, et. al., where patients received either radioactive iodine or low-dose methimazole after a relapse. On average, those on low-dose methimazole had better control of thyroid levels and lower body weight. In addition, more of the patients on long-term methimazole saw an improvement in their eye problems, while more of the radioactive iodine patients had a worsening of eye problems. (2)

Dr. Cooper noted that a 2016 study of insurance claims data found that in 2005, radioiodine and antithyroid drugs were used with similar frequency – but since then, "Radioiodine has taken a nosedive, and antithyroid drugs are now clearly the predominant treatment for Graves' disease." Dr. Cooper speculates that this trend is driven by patients, although said that "many doctors now prefer antithyroid drugs as well." (3)

This paradigm shift was reflected in updated treatment guidelines from the American Thyroid Association, which were published in 2016. (4) The new guidelines explain that measurement of TRAb "aids in predicting which patients can be weaned from the medication, with normal levels indicating greater chance for remission", with a recommendation that, "*If methimazole is chosen as the primary therapy for GD, the medication should be continued for approximately 12-18 months, then discontinued* ***if thyroid function and TRAb levels are normal at that time****.*" (Emphasis added). The guidelines also note that for patients with measurable antibodies, "C*ontinued low-dose MMI treatment for longer than 12-18 months may be considered in patients not in remission who prefer this approach*."

Dr. Fereidoun Azizi is one of the seminal researchers on the safety and effectiveness of long-term ATD use, and Dr. Cooper shared the results of his latest study, which followed 59 patients who had taken methimazole for a minimum of 14 years – and up to 24 years. Of those who stopped at year 14, only 19% relapsed. Of those who continued for the full 24 years, all maintained negative (normal) antibody levels, and there were no adverse effects noted. The mean dose decreased over time, down to 2.5 mg per day at year 24. (5)
The absence of adverse effects is important, as one concern under the "old

paradigm" was that the risk of side effects would increase with increased duration of treatment with ATDs. However, we now know that side effects tend to occur within the first 90 days of treatment and are less likely to appear with longer-term use. (One exception is vasculitis, a rare inflammation of the blood vessels that can occur years after treatment and affects the lungs and kidneys, requiring immediate treatment along with discontinuation of ATDs. Vasculitis is much more common with PTU than with methimazole.) It's also important to note that if a patient begins a new course of antithyroid drugs after coming out of remission, the patient will have the same risk of side effects early in the course of treatment as those who are starting the medication for the first time.

Dr. Cooper concluded his talk by highlighting potential new therapies for Graves' disease. "There are some treatments that are around the corner that actually get at the cause of Graves' disease." These potential treatments include monoclonal antibodies that block the TSH receptor, small molecules that inhibit the activation of the TSH receptor, and other immunosuppressants, which are often used as treatment used for rheumatoid arthritis and other diseases.

At the conclusion of the presentations, Dr. Bloomgarden and Dr. Cooper took questions – and our attendees had a lot of them! Following are a few of the highlights:

Is methimazole safe during pregnancy? Dr. Bloomgarden noted that methimazole is not safe to take during the first trimester, due to risks to the developing fetus. (PTU is the preferred medication during the first trimester.) She also noted that as pregnancy progresses, the need for medication can often be reduced, or in some cases, eliminated. Dr. Bloomgarden explained that reproductive planning is a critical issue to discuss ahead of time when considering treatment options.

Is there any role for methimazole when thyroid hormone levels are stable without medications, but antibodies are still elevated? Dr. Bloomgarden said that she will typically not use methimazole patients with normal thyroid hormone levels, as this runs the risk of hypothyroidism.

What percentage of patients eventually turn hypothyroid after long-term use and why? Dr. Cooper noted that this effect was recognized many decades ago. He estimated that this occurs in around 15-20% of patients, noting that the vast majority of patients in remission stay normal. This effect could be due to antibodies infiltrating the thyroid and causing destruction. Dr. Cooper also noted that it's important for patients in remission to continue having their thyroid levels monitored. This is important in terms of catching a potential relapse into hyperthyroidism – and also for ensuring those who do start to become hypothyroid receive treatment in a timely manner.

Is there anything specific I can do to lower my antibodies? Dr. Bloomgarden cautioned patients to not smoke, and to allow time for the treatment to work. But other than that, there are no supplements or diet proven to reduce the antibodies.
My levels are normal, but I'm still symptomatic. What can I do? Dr. Bloomgarden noted that there is a quality

of life impact with Graves' disease that can be hard to pinpoint. She typically recommends investigating for other reasons for the symptoms to ensure that the patient is getting proper treatment. "We look at sleep, diet, exercise, and mood." She also noted that it's important to make sure that thyroid levels aren't "at the edges of the normal range".

What are some of the factors that might influence a patient to stop using antithyroid drugs and pursue definitive therapy? Dr. Cooper noted that some patients do tire of years of frequent blood tests and doctor visits and elect to pursue definitive therapy – while others tire of the cycle of remission and relapse. He noted that most patients do well with radioactive iodine and surgery.

Can your body become resistant to the effect of antithyroid drugs? In short, no. Dr. Cooper pointed to the Azizi study referenced earlier where patients were well controlled on 2.5 mg/day and noted that he has patients who only take 2.5 mg 3 days per week and are well controlled.

The webinar was produced by the Graves' Disease & Thyroid Foundation with a grant from the County of San Diego Community Enhancement Program, and was originally broadcast on February 6, 2021. If you would like to view the program in its entirety, please visit the GDATF's YouTube channel at https://www.youtube.com/user/GravesAndThyroid/videos.

(1) Bloomgarden, E. and Cooper, D. (2021, 6 February). *Long-Term Use of Antithyroid Drugs*. [Webinar] https://www.youtube.com/watch?v=WJjSzjFyNU4&t=2s

(2) Villagelin, et. al. "Outcomes in Relapsed Graves' Disease Patients Following Radioiodine or Prolonged Low Dose of Methimazole Treatment". Thyroid. 2015 Dec;25(12):1282-90. doi:10.1089/thy.2015.0195. Epub 2015 Oct 20. Accessed at https://pubmed.ncbi.nlm.nih.gov/26414885/. October 19, 2021.

(3) Brito, et. al. "Antithyroid Drugs-The Most Common Treatment for Graves' Disease in the United States: A Nationwide Population-Based Study". Thyroid. 2016 Aug;26(8):1144-5. doi: 10.1089/thy.2016.0222. Epub 2016 Jul 5. Accessed at https://pubmed.ncbi.nlm.nih.gov/27267495/. October 19, 2021.

(4) "2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and other causes of Thyrotoxicosis." Ross, Burch, et al., DOI: 10.1089/thy.2016.0229. Accessed at https://www.liebertpub.com/doi/full/10.1089/thy.2016.0229. October 19, 2021.

(5) Azizi, F., Abdi, H. & Amouzegar, A. Control of Graves' hyperthyroidism with very long-term methimazole treatment: a clinical trial. BMC Endocr Disord 21, 16 (2021). https://doi.org/10.1186/s12902-020-00670-w. Accessed at https://bmcendocrdisord.biomedcentral.com/articles/10.1186/s12902-020-00670-w