List of Clinical Studies for you to Take to Your Doctor

How to use this information:

How to look at a study:

1) Adding T3 (Cytomel or Liothyronine) to your current T4 (Levothyroxine or Synthroid) dose
   1) Effects of Long-Term Combination LT4 and LT3 Therapy for Improving Hypothyroidism and Overall Quality of Life (Link)
   2) Combination treatment with T4 and T3: Toward Personalized Replacement Therapy in Hypothyroidism? (Link)
   3) Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients. (Link)
   4) DIO2 Thr92Ala Reduces Deiodinase-2 Activity and Serum-T3 Levels in Thyroid-Deficient Patients. (Link)
   5) Hypothyroid Patients Encoding Combined MCT10 and DIO2 Gene Polymorphisms May Prefer L-T3 + L-T4 Combination Treatment - Data Using a Blind, Randomized, Clinical Study. (Link)

2) Using Tirosint instead of Levothyroxine
   1) Retrospective Study of Patients Switched from Tablet Formulations to a Gel Cap Formulation of Levothyroxine: Results of the CONTROL Switch Study. (Link)
   2) Tablet levothyroxine (L-T4) malabsorption induced by proton pump inhibitor: a problem that was solved by switching to L-T4 in soft gel capsule. (Link)
   3) Pharmacokinetic equivalence of a levothyroxine sodium soft capsule manufactured using the new food and drug administration potency guidelines in healthy volunteers under fasting conditions. (Link)
   4) Oral liquid formulation of levothyroxine is stable in breakfast beverages and may improve thyroid patient compliance. (Link)
   5) Levothyroxine Tablet Malabsorption Associated with Gastroparesis Corrected with Gelatin Capsule Formulation. (Link)
   6) A novel formulations of L-thyroxine (L-T4) reduces the problem of L-T4 malabsorption by coffee observed with traditional tablet formulations. (Link)

3) Why Levothyroxine and Synthroid are not equivalents
   1) Generic vs Name Brand L-Thyroxine Products: Interchangeable or Still Not? (Link)
   2) Generic and Brand-Name L-Thyroxine are not Bioequivalent for Children with Severe Congenital Hypothyroidism. (Link)

4) Using T3 for Depression
   1) T3 augmentation of SSRI resistant depression. (Link)
   2) Liothyronine for Depression: A Review and Guidance for Safety Monitoring. (Link)
3) T3 augmentation of antidepressant treatment in T4-replaced thyroid patients. (Link)
4) Low T3 syndrome in psychiatric depression. (Link)
5) Triiodothyronine (T3) supplementation in major depressive disorder. (Link)
6) Polymorphisms in the brain-specific thyroid hormone transporter OATP1C1 are associated with fatigue and depression in hypothyroid patients. (Link)

5) Using T3 for Bipolar Disease
   1) The use of triiodothyronine as an augmentation agent in treatment-resistant bipolar II and bipolar disorder NOS. (Link)
   2) The use of triiodothyronine (T3) in the treatment of bipolar depression: A review of the literature. (Link)
   3) Thyroid Functions and Bipolar Affective Disorder. (Link)
   4) Adjunctive thyroid hormone treatment in rapid cycling bipolar disorder: A double-blind placebo-controlled trial of levothyroxine (L-T4) and triiodothyronine (T3). (Link)

6) Using T3 for Chronic Pain
   1) Higher Prevalence of “Low T3 Syndrome” in Patients With Chronic Fatigue Syndrome: A Case-Control Study (Link)
   2) Fibromyalgia and chronic widespread pain in autoimmune thyroid disease (Link)
   3) T3-Induced Recovery from Fibromyalgia by a Hypothyroid Patient Resistant to T4 and Desiccated Thyroid (Link)

7) Using T3 for Weight Loss
   1) Metabolic Effects of Liothyronine Therapy in Hypothyroidism: A Randomized, Double-Blind, Crossover Trial of Liothyronine Versus Levothyroxine (Link)
   2) Thyroid hormones and changes in body weight and metabolic parameters in response to weight loss diets: the POUNDS LOST trial. (Link)
   3) The effects of triiodothyronine on energy expenditure, nitrogen balance and rates of weight and fat loss in obese patients during prolonged caloric restriction. (Link)
   4) Effect of Short-Term Thyroxine Administration of Energy Metabolism and Mitochondrial Efficiency in Humans (Link)

8) Switching to NDT
   1) Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: a randomized, double-blind, crossover study. (Link)
   2) The History and Future of Treatment of Hypothyroidism (Link)
   3) Safety review of liothyronine use: a 20 year observational follow up study (Link)

9) Value of Reverse T3 testing
   1) Reverse T3 levels in affective disorders. (Link)
   2) T3/rT3-ratio is associated with insulin resistance independent of TSH. (Link)
   3) Lowering of T3 and rise in reverse T3 induced by hyperglucagonemia: altered thyroid hormone metabolism, not altered release of thyroid hormones.
4) Reverse T3 does not reliably differentiate hypothyroid sick syndrome from euthyroid sick syndrome. (Link)
5) Conversion of Thyroxine (T4) to triiodothyronine (T3) in athyreotic human subjects (Link)
6) Association between increased levels of reverse triiodothyronine and mortality after acute myocardial infarction. (Link)
7) The importance of reverse triiodothyronine in hypothyroid children on replacement treatment. (Link)
8) Serum T3 and reverse T3 concentrations: indices of metabolic control in diabetes mellitus. (Link)

10) Why LDN can help with Hashimoto’s
1) Low dose Naltrexone for induction of remission in inflammatory bowel disease patients. (Link)
2) Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. (Link)
3) Safety and tolerability of low dose naltrexone therapy in children with moderate to severe Crohn’s disease: a pilot study. (Link)
4) Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis. (Link)
5) Therapy with the opioid antagonist naltrexone promotes mucosal healing in active Crohn’s disease: a randomized placebo-controlled trial. (Link)

11) Using Victoza and Saxenda for Weight Loss
1) Liraglutide for weight management: a critical review of the evidence (Link)
2) The Effect of Liraglutide on Weight Loss in Women with Polycystic Ovary Syndrome: An Observational Study (Link)
3) Short-term administration of the GLP-1 analog liraglutide decreases circulating leptin and increases GIP levels and these changes are associated with alterations in CNS responses to food cues: A randomized, placebo-controlled, crossover study (Link)
4) Early Weight Loss with Liraglutide 3.0mg Predicts 1-Year Weight Loss and is Associated with Improvements in Clinical Markers (Link)

12) DIO2/DIO2 Genetic Defect impacts your Ability to Convert Thyroid Hormone
1) Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients. (Link)
2) DIO2 Thr92Ala Reduces Deiodinase-2 Activity and Serum-T3 Levels in Thyroid-Deficient Patients. (Link)
3) Hypothyroid Patients Encoding Combined MCT10 and DIO2 Gene Polymorphisms May Prefer L-T3 + L-T4 Combination Treatment - Data Using a Blind, Randomized, Clinical Study. (Link)
4) A Common Variation in Deiodinase 1 Gene DIO2 Is Associated with the Relative Levels of Free Thyroxine and Triiodothyronine. (Link)
5) Genetics of Thyroid Function and Disease. (Link)
How to use this information:

Doctors practice what is known as evidenced-based medicine which means that they tend to only follow recommendations that have been proven to be effective through clinical studies. Your Doctor should be reading these studies to keep up with the new and emerging literature but you will find that this isn’t always the case. Due to high patient workloads and various other reasons, Doctors don’t always have the time to see the most recent research. We also know, from other studies, that most Doctors are behind the new research by about 12-20 years or so (give or take depending on the person).

This information serves as a way to help you speak the “language” of your Doctor. If you can approach your Doctor and provide them with articles which highlight specific areas you are looking into, they should take a look at this information. If they are unwilling to look at these literary studies (provided below), then you probably would want to seek out a second opinion (find more information on how to do this in the video section).

The best way to use this information is to provide your Doctor with studies relating to the specific area that you are trying to treat.

For instance:

If you want your Doctor to add T3 medication to your current T4 medication then you would print out just the articles in that section and bring them in to have a discussion with your Doctor.

If you want your Doctor to add T3 medication to your regimen to treat your depression then you would want to bring in articles that support this treatment.

Do your best to avoid bringing in articles from ALL topics as this may simply overload your Doctor.

Also, it is helpful if you can prepare your Doctor before your visit to let them know that you want to explore some new studies or clinical research to see if they would fit into your treatment plan.

Using this language will help to avoid confrontation during your visit and prevent a “hostile visit”.

Doctors are well-meaning and have the best intention in mind when treating patients, but they can become defensive if they suspect you are trying to force them to treat you in a certain way.

The best way to be successful in presenting this information is to let your Doctor know that you’ve found research that supports a certain treatment and you want to explore that information further with their assistance.
Consider this sample dialogue:

(Initial visit)

You: As you know, I've been working with your for _______ (insert length of time) and, while I've been improving, I am still suffering from _______ (insert symptoms or problems such as weight gain, fatigue, brain fog, etc.). With that in mind I've been doing some personal research and have found some new information that seems very promising. I was wondering you could take a look at it and if we could discuss the pros and cons of these therapies during our visit.

Doctor: Sure, I would be happy to take a look. (No doctor will refuse literature or clinical research as they know that a physician is always learning!).

You: Ok great, I've printed out a list of studies that I wanted you to take a look at (hand them studies). It seems that based on these studies that some people have done very well with these newer therapies. If you think that they fit my situation, can we explore a trial of these therapies? If they don’t work or I experience negative side effects we can go back to what was working for me.

Doctor: Yes, I will take a look at these studies for our next appointment.

This dialogue will allow you to present your information in a very non-threatening and informative way and should pave the path to a great follow up discussion.

At this point, you can discuss the desired therapy that you are looking into after your Doctor has had time to evaluate the clinical studies that you provided.

Once your Doctor is on board with your therapy you can go to the video section to determine how to start with your new treatment which will walk you through the process.

Below you will find the link to various clinical studies for a given therapy or treatment. Some topics have more clinical studies than others, but I would recommend that you bring at least 2-3 different studies to your Doctor for the given therapy you are looking to start. This way it’s not too overwhelming for your Doctor and you can always come back with more later if necessary.

It’s also very helpful if you at least look over the studies as well, so that you can come up with responses to common objections or questions your Doctor may have.

How to look at a study:
Each link provides information on a group of people who underwent a certain therapy or treatment. You’ll usually find 4 main categories:

- **Objectives**: The objective is the goal of the study and is usually phrased as a question. An example would be: “Does adding T3 medication to T4 medication help patients?” The goal of the study is to then answer this question. This information is a quick way to figure out if the study is helpful for you.

- **Methods**: The method section contains information to explain how the information from the study was gathered. For instance: Was the information gathered directly from patients or was it a study which look at other studies?

- **Results**: This section will go over values, numbers, lab tests which correlate with their findings. This usually does not include a thought process as to why it occurs but rather just includes all of the results in an objective way.

- **Conclusion**: The conclusion contains the opinion of the author of the study based on the results of the study. So, for instance, if the results section showed that patients taking T3 medication have a higher free T3, the author may explain that in the conclusion section and say why they believe that to be the case. The conclusion has a lot of information that you can read very quickly about the study.

It’s not important for you to understand every aspect of the study (so don’t stress about that), but it’s helpful for you to have some basic idea of what you are reading. I will also provide you with an interpretation of the study in a paragraph form under each study as well.

List of clinical studies support various therapies:

1) Adding T3 (Cytomel or Liothyronine) to your current T4 (Levothyroxine or Synthroid) dose

T3 is the active thyroid hormone and it can be added to your existing dose of thyroid hormone. Patients who take T3 in addition to T4 often feel much better, experience more weight loss, have more energy and so on. Most physicians feel more comfortable using T4 because that’s all that they are used to prescribing. T3 can be safely added to your existing dose of levothyroxine or Synthroid in small or medium doses and may help many people. Studies in this section (and in the depression section) show that up to 25-50mcg per day is safe in the majority of patients! T3 can be safely dosed based on your TSH.

Common objections from your doctor:

- “T3 is not stable” - T3 is stable but it has a shorter half-life than T4 (the half-life of T3 is about 1 day). Your body produces T3 each and every day at a ratio of 20:80 (T3:T4), which means that 20% of the hormone produced by your thyroid gland is T3 and 80% is T4.

- “T3 is not safe” - T3 is very safe as long as it is dosed appropriately.
- “T3 suppresses the TSH” - T3 is about 3-4x more powerful than T4 at suppressing the TSH which simply means you need a smaller dose.
- “T4 is more stable” - T4 has a longer half-life of 6 days but it is not more stable, your body just processes it slower than T3.
- “T4 is safer” - T4 is not necessarily safer than T3, they are just different in how they work in your body. It is, however, easier to overdose on T3 compared to T4.
- “T3 causes heart problems” - T3 will not cause heart problems unless you take too much of it. The studies below show that you can be on T3 medication long-term without an increased risk of heart problems. As long as your TSH is not suppressed (very low) it will not cause heart problems.

Studies:

- **1) Effects of Long-Term Combination LT4 and LT3 Therapy for Improving Hypothyroidism and Overall Quality of Life** ([Link](#))
  - This 6 year study showed that patients who take LT4 + LT3 medication and NDT have no adverse events (no hospitalizations for heart problems, or excess thyroid hormone) and patients who take these medications report feeling “excellent, very good or good” compared to those who take LT4 alone. This is a great study to show your Doctor as it is over 6 years in length and shows that LT4 + LT3 is both safe and effective in many patients. It also shows that NDT is safe and effective as well.
  - Conclusion: This is the only retrospective study reported to use long-term (mean 27 months) thyroid replacements with combination therapy and to compare between the two forms of therapy: synthetic and natural. For patients undergoing either therapy, we did not identify additional risks of atrial fibrillation, cardiovascular disease, or mortality in patients of all ages with hypothyroidism.

- **2) Combination treatment with T4 and T3: Toward Personalized Replacement Therapy in Hypothyroidism?** ([Link](#))
  - This study is important because it is directly from the Endocrine Society which outlines that is important for each person to have an individualized thyroid medication regimen. If your doctor is treating you with a 'one-size-fits-all' approach then you may want to show them this study. You can print out the entire document and show it to him/her. This study includes over 95 references and is from a very reputable organization which helps determine treatments for patients with endocrine diseases.
  - Conclusion: Further prospective randomized controlled studies are needed to clarify this important issue. Innovative formulations of the thyroid hormones will be required to mimic a more perfect thyroid hormone replacement therapy than is currently available.
3) **Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients.** ([Link](#))
   - 16% of patients in this study were found to have the rs225014 SNP out of 552 patients. Patients who had this SNP were found to experience a worse quality of life when compared to those without the SNP on T4 only thyroid medication. These patients also experienced depression, anxiety and other mental health conditions more frequently. This same group of patients had a significant improvement in these symptoms after starting T4 + T3 combination medication. It’s important to note that those with this SNP didn’t have any changes to their thyroid hormone levels even though they did better on T4 + T3 therapy. This means that you may still improve when switching medications even if your lab tests are so-called “normal”.
   - Conclusion: Our results require replication but suggest that commonly inherited variation in the DIO2 gene is associated both with impaired baseline psychological well-being on T(4) and enhanced response to combination T(4)/T(3) therapy, but did not affect serum thyroid hormone levels.

4) **DIO2 Thr92Ala Reduces Deiodinase-2 Activity and Serum-T3 Levels in Thyroid-Deficient Patients.** ([Link](#))
   - This study looked at 140 patients without a thyroid and checked their baseline lab tests for TSH, Free T3, Free T4 and also for the D2 protein. It was found that patients with the DIO2 SNP had lower intracellular free T3 and serum T3 levels even though they had a normal TSH. This shows us that it’s important for all thyroid patients on T4 medication (if it isn’t working) to have their free T3 and free T4 levels evaluated. Low free thyroid hormones may be an indication of this SNP and may be a sign that they need T3 + T4 combination medication.
   - Conclusion: Thyroidectomized patients carrying Thr92Ala are at increased risk of reduced intracellular and serum T3 concentrations that are not adequately compensated for by LT4, thus providing evidence in favor of customized treatment of hypothyroidism in athyreotic patients.

5) **Hypothyroid Patients Encoding Combined MCT10 and DIO2 Gene Polymorphisms May Prefer L-T3 + L-T4 Combination Treatment - Data Using a Blind, Randomized, Clinical Study.** ([Link](#))
   - This study shows that up to 48% of people on thyroid medication prefer combination therapy with T4 + T3 thyroid medication (meaning you are NOT alone!). This randomized, cross-over study looked at 45 patients with Hashimoto’s thyroiditis with a normal TSH on T4 thyroid medication. The researchers then placed these patients on either T4 medication or T4 + T3 medication and asked them which treatment they preferred. Patients with the DIO2 SNP preferred the LT4 + LT3 combination medication at a rate of about
60%. This study shows the importance of SNP testing and normal thyroid lab tests in patients with Hashimoto’s thyroiditis. Patients also experienced more weight loss when switching from T4 only to T3 + T4 therapy.

- Conclusion: The present study indicates that the combination of polymorphisms in DIO2 (rs225014) and MCT10(rs17606253) enhances hypothyroid patients’ preference for L-T4 + L-T3 replacement therapy. In the future, combination therapy may be restricted or may be even recommended to individuals harbouring certain polymorphisms.

2) Using Tirosint instead of Levothyroxine

Tirosint is a T4 only thyroid medication which has the fewest inactive ingredients of all T4 formulations. It’s ideal to use T4 medication if you have a normal free T4 and TSH but you are experiencing symptoms such as headaches, rashes, and intestinal upset. Simply switching from Levothyroxine to Tirosint or from Synthroid to Tirosint is an option that works for many people. This is particularly true if you are a patient which is sensitive to supplements, medications, fillers, dyes, preservatives, foods and so on. This is also a great option for many patients because their Doctors usually won’t put up much resistance if you are simply switching from a T4 medication to another T4 medication.

Common objections from your Doctor:
- “Tirosint is expensive” - Tirosint is more expensive than generic Levothyroxine but coupon codes (found on their website) can reduce the payment down to a reasonable $35 per month. This money is worth it if it allows you to get your life back.
- “Tirosint isn't better than Synthroid or Levothyroxine” - Tirosint contains the same active ingredient but with fewer fillers, dyes, preservatives and additives. The lack of these additives make it much more tolerable for many patients.
- “Tirosint isn't stable because it’s a liquid” - Quite the opposite! Tirosint is more stable in liquid form than the tablet form of levothyroxine because it is easily absorbed by the intestinal tract.

Studies:

- **1) Retrospective Study of Patients Switched from Tablet Formulations to a Gel Cap Formulation of Levothyroxine: Results of the CONTROL Switch Study.** ([Link](#))

  - This study shows that patients who switched from levothyroxine to Tirosint were able to reduce their dose and had more compliance in taking their medication all without impacting the TSH. Patients taking Tirosint also reported an improvement in hypothyroid symptoms without increasing their dose. This is a great study to show your Doctor if they don’t believe Tirosint is any different from levothyroxine.
or Synthroid. In addition, this study also highlights that Tirosint may be an option for patients who constantly have to alter their dose because of their TSH. Tirosint is more consistently absorbed and offers more stable TSH levels compared to levothyroxine.

○ Conclusion: The results of CONTROL Switch support a strategy of switching patients who may experience tolerability or efficacy problems with standard levothyroxine tablets to the levothyroxine gel cap formulation.

● 2) Tablet levothyroxine (L-T4) malabsorption induced by proton pump inhibitor; a problem that was solved by switching to L-T4 in soft gel capsule. (Link)

○ This is a case study which shows that Tirosint is not affected by gastric blocking medications whereas levothyroxine is. For instance, levothyroxine the tablet has to have near perfect conditions in order to be completely absorbed. Tirosint, on the other hand, can be taken with meals and with other medications and is still absorbed much better than levothyroxine. If you take other medications and have a consistently high TSH then switching to Tirosint may solve the problem.

○ Conclusion: Confirming in vitro studies conducted by other authors, the soft gel capsule L-T4 is negligibly affected by changes in gastric pH compared to tablet L-T4.

● 3) Pharmacokinetic equivalence of a levothyroxine sodium soft capsule manufactured using the new food and drug administration potency guidelines in healthy volunteers under fasting conditions. (Link)

○ This is a simple study which shows that Tirosint (gel capsules) are equivalent to levothyroxine tablets. This study can be shown to your Doctor if they don’t think that Tirosint is stable or that it has been well-tested.

○ Conclusion: The levothyroxine soft capsule formulated with the stricter new potency guideline set forward by the Food and Drug Administration met equivalence criteria in terms of rate and extent of exposure under fasting conditions to the reference tablet formulation. Clinical doses of the capsule formulation can be given using any combination of the commercialized strengths.

● 4) Oral liquid formulation of levothyroxine is stable in breakfast beverages and may improve thyroid patient compliance. (Link)

○ Tirosint is different from levothyroxine in that it can be taken with food without any absorption issues. Levothyroxine absorption, on the other hand, if taken with food, is dramatically reduced. This makes Tirosint a great option for those who have scheduled which don’t allow for a 30-60 minute wait to eat after taking their thyroid medication.

○ Conclusion: The results of the study demonstrated that T4 is stable in all beverages after 20 min incubation. Demonstration of T4 stability is a prerequisite
for a thorough evaluation of the effect of breakfast beverages on the bioavailability of T4 given as oral solution and for a better understanding of the reasons underlying a decreased T4 bioavailability administered as solid formulations.

● 5) Levothyroxine Tablet Malabsorption Associated with Gastroparesis Corrected with Gelatin Capsule Formulation. (Link)
  ○ This case study shows that Tirosint is the preferred thyroid medication in cases of gastroparesis. Gastroparesis is a condition in which the intestinal tract slows down and it reduces absorption of food, medications and hormones. This is a good study to show your Doctor if you have any sort of gastrointestinal issue (gastroparesis, IBS, IBD, acid reflux, chronic constipation, etc.) and want to switch from levothyroxine to Tirosint.
  ○ Conclusion: Changing to a gelatin capsule formulation quickly corrected her thyroid function assays. This case suggests that gastroparesis may affect absorption of levothyroxine tablets and the gelatin capsules may be an effective alternative therapy.

● 6) A novel formulations of L-thyroxine (L-T4) reduces the problem of L-T4 malabsorption by coffee observed with traditional tablet formulations. (Link)
  ○ This is a small case study showing that Tirosint can be taken with coffee without impacting absorption. If you are someone who needs to drink coffee then using Tirosint may help improve your absorption compared to levothyroxine.
  ○ Conclusion: In the two volunteers, the L-T4 loading test showed that coffee influenced L-T4 pharmacokinetics minimally. Soft gel capsules can be used in patients who are unable/unwilling to change their IH of taking L-T4.

3) Why Levothyroxine and Synthroid are not equivalents

Levothyroxine and Synthroid are both T4 only medications. Synthroid is the brand name while levothyroxine is the generic version. Doctors and patients believe that these medications are completely identical. Studies have shown that this isn’t the case and that certain people do better on one version over the other. This creates a unique opportunity for patients who don’t tolerate one version who can then switch to another version. This is a simple and easy switch and your physician should not oppose to making this small change. If they do, you can show them these studies which clearly show that there is a difference. Another common problem is that the pharmacy may be allowed to switch your medication from brand name to generic without your consent. So, if you do better on more over the other, be sure that you are getting that version from your doctor. You can have your doctor write “dispense as written” on the medication to ensure that you get the proper medication.
Common objections from your Doctor:
- "They are both the same medication" - These medications contain the same active ingredient but differ in inactive ingredients which alters how they are processed and absorbed by the body.
- "Synthroid is more expensive than levothyroxine" - Synthroid is slightly more expensive than levothyroxine, but, with coupon sites such as goodrx.com, it's possible to get your Synthroid for about $10 per month (compared to the $4 of generic levothyroxine).
- "There is no difference in these medicines" - Studies show that there are slight differences in these patients which tend to be exaggerated in certain patients. If you don’t tolerate levothyroxine then switching to Synthroid may be a simple switch that helps you feel better.

Studies:

1) **Generic vs Name Brand L-Thyroxine Products: Interchangeable or Still Not?** ([Link](#))
   - This study highlights the differences among Synthroid and levothyroxine and how physicians should choose a medication based on the patient and be willing to switch from Synthroid to levothyroxine based on the success of the patient with either medication. It also states that patients need to be aware that the pharmacy may change their medication without them knowing and to be on the lookout for such an event.
   - Conclusion: Shortcomings of the traditional pharmacokinetic method resulted in a modification of the process to correct for endogenous T\textsubscript{4}, but concerns remained that potentially clinically significant differences in a LT4 dose of 12.5% or more might not be recognized with the pharmacokinetic approach in products designated as bioequivalent by the pharmacokinetic standard.

2) **Generic and Brand-Name L-Thyroxine are not Bioequivalent for Children with Severe Congenital Hypothyroidism.** ([Link](#))
   - This study showed that levothyroxine and Synthroid result in different serum TSH levels in certain patient populations. This was primarily performed in children with congenital thyroid problems but the logic can be extended to other patient groups. If you are having trouble with one medication then switching to the other may be a potential option.
   - Conclusion: Synthroid and an AB-rated generic l-T4 are not bioequivalent for patients with severe hypothyroidism due to CH, probably because of diminished thyroid reserve. It would therefore seem prudent not to substitute l-T4 formulations in patients with severe CH, particularly in those <3 yr of age. Our results may have important implications for other severely hypothyroid patients in whom precise titration of l-T4 is necessary.
4) Using T3 for Depression

T3 in the form of liothyronine or Cytomel can be used to treat treatment-resistant depression in both hypothyroid patients and patients without thyroid disease. This section is very important because much of the research done in this area is from psychiatrists who have used T3 in non-hypothyroid patients in high dosages. Many of the studies show that dosages ranging from 25mcg to 50mcg are not only safe for patients but also very effective at treating depression. If you have a normal TSH, are taking levothyroxine and experiencing depression, then these studies may be helpful to show to your doctor to see if they would be willing to use T3 to treat the depression.

Common objections from your Doctor:
- “T3 isn’t safe to use for depression” - T3 is very safe to use, even in high doses, as long as thyroid lab tests are monitored every 8 weeks.
- “Anti-depressants are better than T3” - Anti-depressants may work for some people, but not for everyone. Besides, T3 can be safely added to your current dose of anti-depressants and has been shown to be safe to use with all different types of anti-depressants including SSRI’s, SNRI’s, TCA’s and MAO’s.
- “You need to see a physiatrist to diagnose T3 because I’m not comfortable” - This may actually be a good thing! Psychiatrists don’t have years of low-level knowledge clouding their judgement and may be more likely to prescribe T3 to you for depression. Even if you are using T3 for depression it may still help with your thyroid and other hypothyroid symptoms.

Studies:

- 1) T3 augmentation of SSRI resistant depression. ([Link](#))
  - This study looked at 12 people (low number) and added T3 to their current SSRI medication. Of the 12 people, 1 dropped out due to side effects from the T3, but the other 11 experienced a reduction in their depressive symptoms without any negative side effects. The average dose in the study was 40-45mcg of T3 taken every day. This study shows that T3 can be added to existing anti-depressants without negative side effects and can help even those without thyroid abnormalities.
  - Conclusion: T3 augmentation resulted in improvement of mood scores. The responders’ rate of 42% in our study is comparable to the response rates reported using T3 or lithium to augment tricyclic antidepressants or other combination strategies used to treat resistant depression. Even though one patient withdrew prematurely due to side effects, the remaining 11 patients tolerated the addition of T3 very well. With the availability of T3, a viable, safe,
inexpensive and effective augmentation treatment, the recent trend of replacing T3 with other novel strategies appears unwarranted.

● **2) Liothyronine for Depression: A Review and Guidance for Safety Monitoring.** ([Link](#))
  ○ This study looked at several studies done over the last 50 years (known as a meta analysis) and evaluated if T3 was effective at treating depression as an ‘add-on’ agent. Over 10 studies were evaluated in this study which all showed a similar finding: that T3 is helpful in treating depression. Importantly, this study also showed that doses as high as 50mcg per day can be effective and do not cause any negative side effects as long as the TSH is checked and monitored to be in the low-normal range. This is a great study to show your doctor because it comprises many other smaller studies into one.
  ○ Conclusion: With appropriate baseline and follow-up safety monitoring, liothyronine augmentation can be a safe and effective treatment for unipolar depression. Larger studies of longer duration assessing liothyronine efficacy with serotonin norepinephrine reuptake inhibitors and multimodal antidepressants are needed.

● **3) T3 augmentation of antidepressant treatment in T4-replaced thyroid patients.** ([Link](#))
  ○ This small study evaluated 9 patients (another small study) but showed that 7 out of the 9 patients tolerated and noticed improvement when taking T3 medication for depression. While the study only included a small number of people, it’s important to note that the majority (> 75%) of the patients in this study preferred to be on T3 medication for their depression. It’s also important to note that this study was done on hypothyroid patients who were already taking T4 medication! So, it shows that patients who are still depressed while taking LT4 may benefit from the addition of T3 to their regimen.
  ○ Conclusion: These results are consistent with a report of differential effects for T3 versus T4 augmentation in depressed patients free of thyroid disease. The results have implications for the treatment of depression in the presence of thyroid disease and for the mechanism of thyroid hormone potentiation of antidepressants.

● **4) Low T3 syndrome in psychiatric depression.** ([Link](#))
  ○ This study found that there was a high percentage of depressed patients who were found to have low T3 upon laboratory testing even though they did not have a diagnosis of hypothyroidism. This study highlights the connection between free thyroid hormone levels and how to use those tests to determine if T3 may be effective at treating depression. If you have low free T3, and you suffer from depression, and you are taking levothyroxine and you are still depressed, then you may be a prime candidate for LT3 therapy in addition to your LT4.
Conclusion: The depression might constitute an illness having the same relation to low T3 as found in the low T3 syndrome previously described in euthyroid sick subjects. The present findings, besides describing low T3 syndrome in psychiatric patients without systemic illnesses, suggest the possibility of subgrouping in clinical psychiatric depression which may have a broader clinical significance.

5) **Triiodothyronine (T3) supplementation in major depressive disorder.** ([Link](#))

- This article is incredibly important because it shows that T3 can be used to treat depression in the absence of hypothyroidism! What this implies is that T3 plays an important role in regulating your mood and certain patients may need higher than normal T3 levels to treat their depression. If you have hypothyroidism (or not) T3 may be a viable option to help treat your condition. In addition, this study shows that the use of 25-50mcg of T3 per day can be safe and effective at treating depression. This is important because most Endocrinologists only use 5-10mcg per day. You can take this study to your Doctor to show them that the use of higher doses is safe and effective at treating certain conditions including depression.

- Conclusion: Data support the use of T3 augmentation (25-50 μg/d) for the treatment of depressive symptoms in some patient populations without thyroid hormone abnormalities who do not respond to an adequate trial of a tricyclic antidepressant or a selective serotonin reuptake inhibitor. Monitoring for adverse effects and conditions that may be exacerbated by T3 augmentation is recommended.

6) **Polymorphisms in the brain-specific thyroid hormone transporter OATP1C1 are associated with fatigue and depression in hypothyroid patients.** ([Link](#))

- This study shows the connection between a certain SNP (the OATP1C1 SNP) and depression and fatigue among thyroid patients. This SNP plays a role in transport of T4 across the blood brain barrier. It’s plausible (though not confirmed) that hypothyroid patients with this SNP need to be treated with T3 only medication to allow crossover from the bloodstream to the brain. Using T4 only thyroid medication alone may result in a normal TSH but with consistent depression and fatigue in certain patients.

- Conclusion: OATP1C1 polymorphisms are associated with fatigue and depression, but do not explain differences in neurocognitive functioning or appreciation of LT4–LT3 combination therapy. Future studies are needed to confirm these findings.
5) Using T3 for Bipolar Disease

T3 Medication (including Cytomel and Liothyronine) can also be used as a standalone therapy to treat bipolar disorder. Bipolar disorder is an incredibly difficult to treat condition which can impact your mood and your behavior. T3 can be added to your existing medication or simply be used by itself. A large percentage of patients who use T3 medication for bipolar disorder notice a dramatic reduction in their symptoms or a near complete resolution in their symptoms. To get this benefit you may need higher than normal doses (50mcg per day) but if you can provide your Doctor with the studies listed below (especially a psychiatrist) you can convince them to try it out. If you are using T3 for bipolar disorder you will also notice other beneficial effects such as weight loss, a reduction in depression, and so on.

Common objections from your Doctor:

- “T3 is dangerous” - T3 is not dangerous and it can be safely dosed based on the TSH and still provide much improvement to those who use it!
- “There are better medications for bipolar disorder available” - If the “better” medications were working then you wouldn’t still have symptoms. T3 can also be safely added to those medications to augment their efficacy or used by itself as a complete bipolar disorder medication.
- “You need to see a psychiatrist to get prescribe it” - You may actually have more luck getting a psychiatrist to prescribe T3 over a primary care physician, especially if you show them the studies listed below.
- “Insurance doesn’t cover that medication” - Almost all insurances cover T3 medication, or you can pay the cash price which shouldn’t be more than $15-20 per month.

Studies:

- 1) The use of triiodothyronine as an augmentation agent in treatment-resistant bipolar II and bipolar disorder NOS. (Link)
  
  ○ This study took patients who had used and failed on average 14 different medications for bipolar disorder and put them on T3. 84% of patients experienced improvement and 33% experienced a complete remission of their symptoms. The average dose used in this study was 90.4mcg per day and very few experienced negative symptoms on this higher than normal dose. This study highlights the value of using high T3 doses to completely resolve bipolar disorder.
  
  ○ Conclusion: A high percentage of bipolar II and bipolar NOS patients with treatment resistant depression improved on T3. Despite the use of higher than usual doses in many of the patients, the medication was well tolerated. Augmentation with supraphysiologic doses of T3 should be considered in cases of treatment resistant bipolar depression.
The use of triiodothyronine (T3) in the treatment of bipolar depression: A review of the literature. (Link)

This study looked a series of studies which evaluated the use of T3 to treat bipolar depression. The researchers found that the studies showed an improvement in 56% of patients, 75% of patients and 89% of patients (depending on the studies) and also showed that T3 was superior to placebo. The total number of patients evaluated in all studies was 353 patients which is a decent number. This study also showed that T3 can be safely used with other bipolar and antidepressant medications.

Conclusion: The few available studies are small and flawed. They do show promising results. We found many clues suggesting that T3 could augment and accelerate treatment response not only with antidepressants, but also with lithium and perhaps with other treatment options, that it might protect against rapid cycling bipolar disorder, as well as against relapse during the first few years of treatment.

Thyroid Functions and Bipolar Affective Disorder. (Link)

This study highlights the connection between patients with bipolar disorder and the rate at which these patients also have hypothyroidism. One issue that this study points out is that many patients with bipolar disorder have subclinical hypothyroidism which is tricky to identify and treat which may be why so many patients are not treated correctly. The study also highlights the connection between even small changes to thyroid function and how it impacts the outcome of bipolar disease progression. This study shows that T4 medication can be used to treat bipolar disorder (but from my experience T3 is superior to that of T4).

Conclusion: Even minor perturbations of the HPT axis may affect the outcome of bipolar disorder, necessitating careful monitoring of thyroid functions of patients on treatment. Supplementation with high dose thyroxine can be considered in some patients with treatment-refractory bipolar disorder. Neurotransmitter, neuroimaging, and genetic studies have begun to provide clues, which could lead to an improved understanding of the thyroid-bipolar disorder connection, and more optimal ways of managing this potentially disabling condition.

Adjunctive thyroid hormone treatment in rapid cycling bipolar disorder: A double-blind placebo-controlled trial of levothyroxine (L-T4) and triiodothyronine (T3). (Link)

This study looked at patients with rapid cycling bipolar disorder and placed them in 3 different treatment groups: those given T4 medications, those given T3 medication, or placebo. The group taking T4 medication had the biggest improvement whereas the placebo and T3 group didn’t show an improvement in symptoms. Much of the discrepancy in this study has to do with the dosages used, but you can clearly see that T4 is better than nothing and can still be an effective tool for treating bipolar disorder.
Conclusion: The findings in this first double-blind study directly comparing the effects of L-T4 and T3 therapy against placebo provide evidence for the benefit of adjunctive L-T4 in alleviating resistant depression, reducing time in mixed states and increasing time euthymic. Adjunctive T3 did not show statistically significant evidence of benefit over placebo in reducing the time spent in disturbed mood states.

6) Using T3 for Chronic pain

By chronic pain I am referring to two conditions: Fibromyalgia and Chronic Fatigue Syndrome. Both of these conditions, while different, may have the same underlying cause: low T3. The studies here are designed to show you that there is a connection between your thyroid and chronic pain, especially in the muscles. If you are suffering from chronic pain, and you are taking T4 medication like Synthroid or Levothyroxine, you should seriously consider adding T3 to your regimen! Patients who do this experience a significant drop in their pain levels and a dramatic improvement in their quality of life.

Common objections from your Doctor:
- “Chronic pain is not caused by the thyroid” - Chronic pain is caused by many different conditions but your thyroid is one well known cause of chronic pain. It doesn’t mean that your pain is necessarily caused by your thyroid, but there is a high likelihood that it is contributing.
- “It’s safer to use narcotics and pain medications” - Pain medications negatively impact the thyroid and lead to worsening thyroid function! In addition, pain medications carry far more risk of overdose and harm than thyroid medications.
- “Thyroid hormone for pain is not well studied” - While it is true that this connection is emerging and new, the data and studies still show that there is a connection. And, when you consider that treating your thyroid is so safe and that other alternatives for treating pain are dangerous, it makes using thyroid hormone a very good option.

Studies:

● 1) Higher Prevalence of “Low T3 Syndrome” in Patients With Chronic Fatigue Syndrome: A Case-Control Study (Link)
  ○ This study looked at 98 patients with chronic fatigue syndrome and found that patients with CFS exhibited lower free T3 levels but normal free T4 levels. This indicates that people with CFS, most likely due to inflammation, have trouble converting T4 to T3 which may make chronic pain syndromes worse. This study also showed that patients with low T3 exhibited higher rT3 levels which can be tested in the serum and this picture was similar to euthyroid sick syndrome seen in patients who are very ill in the hospital. This study could be useful to show your
Doctor that low T3 is not a normal condition and it is associated with various conditions including chronic fatigue syndrome. If you aren’t aware, patients with CFS (chronic fatigue syndrome) have muscular pain in various areas on their body.

○ Conclusion: Low circulating T3 and the apparent shift from T3 to rT3 may reflect more severely depressed tissue T3 levels. The present findings might be in line with recent metabolomic studies pointing at a hypometabolic state. They resemble a mild form of “non-thyroidal illness syndrome” and “low T3 syndrome” experienced by a subgroup of hypothyroid patients receiving T4 monotherapy. Our study needs confirmation and extension by others. If confirmed, trials with, e.g., T3 and iodide supplements might be indicated.

• 2) Fibromyalgia and chronic widespread pain in autoimmune thyroid disease (Link)

○ This study is useful because it shows that there is a clear connection between hypothyroidism (in this case Hashimoto’s thyroiditis) and fibromyalgia. In fact, Hashimoto’s thyroiditis (untreated) is a known cause of fibromyalgia and chronic widespread pain. I would use this study to help your Doctor understand that there is definitely a connection between these two conditions and that treating the thyroid may impact your pain levels.

○ Conclusion: The gradual elucidation of these pain pathways is allowing the rational use of pharmacotherapy in the management of chronic widespread pain in autoimmune thyroid disease. This review looks at the current understanding of the prevalence of pain syndromes in autoimmune thyroid disease, their likely causes, present appreciation of the pathogenesis of chronic widespread pain, and how our knowledge can be used to find lasting and effective treatments for the pain syndromes associated with autoimmune thyroid disease.

• 3) T3-Induced Recovery from Fibromyalgia by a Hypothyroid Patient Resistant to T4 and Desiccated Thyroid (Link)

○ This study is a case report which outlines exactly how to use T3 in patients with chronic fatigue and fibromyalgia to help induce recovery. This study is particularly useful in showing your Doctor because it includes the dosages of T3 that were used in this patient, includes information on how to monitor for side effects, and other information which is helpful to the practical application of using T3 for chronic pain. It is only a case study (meaning this was only done on 1 person), but it has very helpful information in it.

○ Conclusion: The main purpose of this case report is to illustrate a clinical observation common to me: that 4 fibromyalgia patients with central hypothyroidism who fail to benefit from T or desiccated thyroid completely recover when they switch to T. Changing status in the patient was evaluated in three ways: a psychiatrist used a depression inventory, a physical therapist performed functional musculoskeletal assessments, and I performed algometer tender point exams and monitored symptoms. I hope the description of the
management of this case provides a protocol that other clinicians will use with fibromyalgia patients similar to the one who is the subject of this report.

7) Using T3 for Weight Loss

T3 is the active thyroid hormone known as triiodothyronine and it can be taken in medication form. It is the most active and most powerful thyroid hormone available because it already comes active. When you take T4 medications like Levothyroxine and Synthroid, your body must activate them in order for them to be used. You can bypass this system by taking T3 directly. As you might suspect, taking T3 directly increases your metabolism which helps with weight loss. Patients taking T3 medication experience more weight loss than compared to people taking T4 because of its effects on your metabolism. The studies below will help your doctor understand why it’s important to use T3 if you are overweight and struggling with hypothyroidism.

Common objections from your Doctor:
- “T3 is not safe for weight loss” - T3 is perfectly safe and it can be dosed based on the TSH so that side effects are minimal. T3 should not be used for weight loss unless you have hypothyroidism, though.
- “T4 is just as good as T3 for weight loss” - T4 is not ideal for weight loss! In people who are already obese, their body will have problems converting T4 to T3 which is why these people do not lose weight when starting thyroid medication.
- “T3 will cause bone loss and heart problems” - This is only an issue if you take doses which completely suppress the TSH. If you use a normal amount to regulate your TSH then there is no issue with bone loss or heart problems.
- “T3 is dangerous” - T3 is not dangerous as long as it is dosed correctly. Most physicians just aren’t familiar with using it.
- “T3 must be dosed several times per day and is hard to regulate” - T3 does not have to be dosed several times per day and many patients do perfectly fine on once a day dosing. If you prefer, you can dose it several times throughout the day but it is not necessary.

Studies:

- 1) Metabolic Effects of Liothyronine Therapy in Hypothyroidism: A Randomized, Double-Blind, Crossover Trial of Liothyronine Versus Levothyroxine (Link)
  - This study is incredibly important because it shows that LT4 medication can be completely substituted out for LT3 medication based on the TSH and patients who switch over have no negative side effects and experience natural weight loss without any other therapies added. Patients who switched over not only lost weight but also experienced improved cholesterol levels as well.
○ Conclusion: The substitution of l-T3 for l-T4 at equivalent doses (relative to the pituitary) reduced body weight and resulted in greater thyroid hormone action on the lipid metabolism, without detected differences in cardiovascular function or insulin sensitivity.

● **2) Thyroid hormones and changes in body weight and metabolic parameters in response to weight loss diets: the POUNDS LOST trial.** *(Link)*

○ This study is important because it shows that your free T3 and total T3 levels can help determine how responsive you will be to weight loss therapies. Patients with high-normal T3 levels lose more weight compared to patients with low-normal T3 levels. By checking your Free T3 and total T3 you can determine how likely you are to lose weight. These numbers can also directly be influenced by using T3 medication either by itself or in combination with your current T4 medication.

○ Conclusion: In this diet-induced weight loss setting, higher baseline free T3 and free T4 predicted more weight loss, but not weight regain among overweight and obese adults with normal thyroid function. These findings reveal a novel role of thyroid hormones in body weight regulation and may help identify individuals more responsive to weight loss diets.

● **3) The effects of triiodothyronine on energy expenditure, nitrogen balance and rates of weight and fat loss in obese patients during prolonged caloric restriction.** *(Link)*

○ This study showed that using T3, after weight loss, resulted in an increase in metabolism as measured by resting energy expenditure and indirect calorimetry. This is important because the main reason that people gain weight after they lose weight is because of metabolic damage. This metabolic damage can be minimized by strategically using T3 medication to blunt the negative effects that weight loss has on your metabolism.

○ Conclusion: Mean weight loss increased by 92 g/d during T3 therapy. T3 significantly increased the metabolic rate as measured by two other independent measures: the resting energy expenditure (REE), measured by indirect calorimetry (fourteen patients), and the sleeping heart rate (six patients).

● **4) Effect of Short-Term Thyroxine Administration of Energy Metabolism and Mitochondrial Efficiency in Humans** *(Link)*

○ This study has to do with LT4 medication but it still shows that using LT4 (much like T3) can also help to promote metabolism to prevent weight gain after weight loss. This is important because it shows that it may be necessary to use thyroid medication in obese patients to help normalize metabolism to promote weight loss.

○ Conclusion: Together, the results suggest that T4, although less metabolically active than T3, reduces skeletal muscle efficiency and modestly increases resting
metabolism even after short-term supplementation. Our findings may be clinically relevant given the expanding application of T4 to treat non-thyroidal conditions such as obesity and weight.

8) Switching to NDT

NDT stands for Natural Desiccated Thyroid. This thyroid medication is unique in that it is derived from pigs. This medication is created by taking the thyroid gland from pigs, drying it out, crushing it up, and placing it into capsules/tablets. Each ‘grain’ of NDT is standardized to contain 38mcg of T4 and 9mcg of T3. This means that NDT is a combination T4 plus T3 thyroid medication. In addition, it also includes other ingredients including less active thyroid hormones T1 and T2 as well as Calcitonin (all of these hormones are found in thyroid glands). This used to be the most commonly prescribed thyroid medication up until the 1970’s but was replaced by Levothyroxine. Unfortunately, around that same time, patients started to experience worsening thyroid symptoms as dosing was based off of the TSH. NDT is a great way to get combination hormones and many people report great improvement when switching from T4 only medications to NDT.

Common objections from your Doctor:

- “NDT is not safe” - NDT, like other thyroid medications, is perfectly safe as long as it is used correctly! It can become dangerous if you take too much, but this is true of all thyroid medications.
- “NDT levels fluctuate and are not consistent” - This is simply not true and has been perpetuated by Doctors for years. Each grain of NDT contains a set amount of thyroid hormone which is 38mcg of T4 and 9 mcg of T3. The variability between tablets is the same as is seen in levothyroxine and Synthroid.
- “T4 is safer than NDT” - T4 is more stable in the bloodstream when compared to NDT, but it is not safer than NDT. Both medications are perfectly safe provided they are dosed correctly.
- “NDT comes from animals” - That is true, NDT is sourced from pigs (porcine derived) but that isn’t a reason not to use it.
- “NDT can cause heart problems and bone loss” - This is only true if your dose is excessively high enough to cause TSH suppression. If it is dosed correctly then there is no risk of bone loss or heart problems.

Studies:
1) *Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: a randomized, double-blind, crossover study.* (Link)

- This patient looked at 70 different patients and placed them on either Levothyroxine or NDT and then switched them to the other medication after a period of time. They found that when patients were switched to NDT, patients experienced more weight loss and nearly half of them preferred to be on NDT. They lost weight and felt better without any other changes except their thyroid medication. While the number in this study is small, it still highlights the importance of looking at each individual to help determine what they prefer and how they feel.

- Conclusion: DTE therapy did not result in a significant improvement in quality of life; however, DTE caused modest weight loss and nearly half (48.6%) of the study patients expressed preference for DTE over L-T₄. DTE therapy may be relevant for some hypothyroid patients.

2) *The History and Future of Treatment of Hypothyroidism* (Link)

- This is a well thought of paper which outlines the history of thyroid treatment over the last 80 years. This paper shows the trend in how doctors have prescribed thyroid medication over the years and the influences which caused them to change these preferences. NDT used to be the major thyroid medication used prior to the 1970’s and was only replaced when people thought that T4 was more stable. That turned out not to be true and now we are trying to backpedal to figure out the right balance.

- Conclusion: New research suggests mechanisms for the inadequacies of l-thyroxine monotherapy and highlights the possible role for personalized medicine based on deiodinase polymorphisms. Understanding the historical events that affected clinical practice trends provides invaluable insight into formulation of an approach to help all patients achieve clinical and biochemical euthyroidism.

3) *Safety review of liothyronine use: a 20 year observational follow up study* (Link)

- This study isn’t about NDT necessarily, but it does show that you can safely use medications which contain T3 (such as NDT, Liothyronine, and Cytomel) without any issue over a long period of time. This study showed that there is no risk of atrial fibrillation (heart problems) or bone loss when using T3 over a 20 year period.

- Conclusion: No increased risk of fractures or atrial fibrillation in patients taking liothyronine compared to L-thyroxine was demonstrated. There was an increased risk of mental health disorders if liothyronine was used alone.
9) Value of Reverse T3 testing

Reverse T3 is a lab test which can help you and your doctor understand how your body is processing thyroid hormone and if it is being properly activated and utilized by your cells. In order for thyroid hormone to become active it must be converted from T4 to T3. Your body also has another route that it can take which is creating reverse T3 from T4. Your body can only choose one path, so if it chooses the T4 to reverse T3 pathway it will result in decreased free T3 in your serum. You can test to see which path your body is “choosing” by ordering reverse T3. High levels of reverse T3 indicate that your body is not processing thyroid hormone correctly and may mean that you need to add T3 medication to your regimen. The studies below show the clinical value of this test.

Common objections from your Doctor:
- “Reverse T3 has no clinical value” - Reverse T3 cannot be used by itself to determine if you are hypothyroid, but it can be used in conjunction with other thyroid tests to help you understand if your body is metabolizing thyroid hormone correctly.
- “Testing for reverse T3 isn’t covered by insurance” - Reverse T3 testing is absolutely covered by insurance! I’ve never had a problem ordering this test and treating patients with all types of insurance.
- “You only need the TSH” - You do need the TSH but you should also order other thyroid lab tests such as reverse T3, free T3 and free T4.

Studies:

● 1) Reverse T3 levels in affective disorders. (Link)
  ○ 32 patients were evaluated with acute major depressive disorder. These depressed patients were tested for free T3 and reverse T3 and it was shown that those with depression showed a significant rise in reverse T3 and a drop in free T3 levels compared to healthy controls. In addition, these patients had no significant difference in T4 or TSH levels. This study shows that reverse T3 has clinical value and can be used to determine the thyroid status of various patients.
  ○ Conclusion: In the group of patients with acute major depressive disorder, however, a significant increase in reverse T3 levels and a significant decrease in T3 levels, but no significant difference in T4 or TSH levels, were seen in the patients with the most pronounced clinical symptoms as measured by the CPRS. The implications of these findings are discussed.

● 2) T3/rT3-ratio is associated with insulin resistance independent of TSH. (Link)
  ○ This study shows that thyroid metabolism can be assessed with the T3/rT3 ratio and that patients with insulin resistance show an increased reverse T3 and a lower free T3. This means that testing this ratio can help identify early insulin
resistance and help you understand how your body is metabolizing thyroid hormone.

○ Conclusion: Furthermore the T3/rT3-ratio was lower in men compared to women (p for the within-subject effect=0.046) both in the insulin sensitive and the insulin resistant subjects. Here we show that the T3/rT3-ratio, which is supposed to reflect the tissue thyroid hormone metabolism, is significantly increased in insulin resistant subjects. This further supports a link between thyroid function and IR

3) Lowering of T3 and rise in reverse T3 induced by hyperglucagonemia: altered thyroid hormone metabolism, not altered release of thyroid hormones.

○ This study shows that thyroid hormone metabolism is an important predictor of thyroid status in the body. These patients were given a medication (glucagon) which altered thyroid hormone metabolism and resulted in both a decline in free T3 and a rise in reverse t3. These changes alone were caused by the conversion of T4 to reverse T3. This study shows that thyroid metabolism is an important factor when understanding thyroid function!

○ Conclusion: Glucagon infusion induced a significant decline in serum T3 (P less than 0.05) and a marked rise in rT3 (P less than 0.05) whereas saline administration caused no alterations in T3 or rT3 levels. Thus the changes in T3 and rT3 were significantly different during glucagon study when compared to saline infusion. (P less than 0.01 for both comparisons). Since, the release of thyroid hormones is suppressed by exogenous LT4 administration in these subjects; we conclude that changes in serum T3 and rT3 observed following glucagon administration reflect altered thyroid hormone metabolism in peripheral tissues and not altered release by the thyroid gland.

4) Reverse T3 does not reliably differentiate hypothyroid sick syndrome from euthyroid sick syndrome. (Link)

○ A

○ Conclusion: Although reverse T3 may be elevated in the setting of nonthyroidal illness, it is not reliable in distinguishing between the hypothyroid sick patient and the euthyroid sick patient. This is probably because of drug and disease effects on thyroid hormone metabolism as well as the presence of sufficient T4 substrate for conversion to reverse T3 in many hypothyroid sick patients.

5) Conversion of Thyroxine (T4) to triiodothyronine (T3) in athyreotic human subjects (Link)

○ This study shows that the majority of T3 in the body of those without a thyroid is created by conversion of T4 to T3. This is important because it means that this process needs to be evaluated in patients with and without a thyroid. Conversion problems (meaning your inability to create T3 from T4) can be assessed with reverse T3 testing.
Conclusion: In contrast to earlier experiments in humans in which 131I-labeled T3 was not definitively demonstrated in serum after a single intravenous injection of 131I-labeled T4, the present findings are taken to provide conclusive evidence of the extrathyroidal conversion of T4 to T3 in man. These results raise once again the question of the extent to which the metabolic effect of T4 is mediated through the peripheral generation of T3.

6) **Association between increased levels of reverse triiodothyronine and mortality after acute myocardial infarction.**  
(Visited)

Researchers found that high levels of reverse T3 were predictive of early death in those who have had a heart attack. This is important because high reverse T3 can be seen as an adaptive mechanism in the body to slow down metabolism and energy production.

Conclusion: Determination of reverse T3 levels may be a valuable and simple aid to improve identification of patients with myocardial infarction who are at high risk of subsequent mortality.

7) **The importance of reverse triiodothyronine in hypothyroid children on replacement treatment.**  
(Visited)

This study shows the importance of reverse T3 testing in children and gives a great example of how reverse T3 impacts your symptoms. The children with suppressed TSH and high free T4 were found to have high reverse T3 levels. This indicates that the high reverse T3 was acting to block extra thyroid hormone from causing hyperthyroid symptoms. This shows that, even in adults, high reverse T3 may block thyroid hormone at the cellular level and produce hypothyroidism.

Conclusion: We suggest that in patients on T4 replacement treatment the peripheral thyroid homeostatic mechanisms produce larger amounts of rT3, thereby preventing high T3 values where serum T4 values are raised. This may explain why the 'overtreated' children showed no clinical evidence of hyperthyroidism. These findings emphasise the protective and selective role of peripheral monodeiodination.

8) **Serum T3 and reverse T3 concentrations: indices of metabolic control in diabetes mellitus.**  
(Visited)

This study highlights the fact that the T3:rT3 ratio is an important indicator of whether or not diabetes is controlled and can be used, along with Hgb A1c, in assessing this. Patients with uncontrolled diabetes (meaning high blood glucose) were found to have low free T3 and high reverse T3. When their blood sugars were controlled free T3 increased and reverse T3 decreased. This study shows that monitoring both levels can help evaluate metabolic function in the body.

Conclusion: Furthermore, significant negative and positive correlations were noted between parameters of metabolic control and serum T3 and rT3 levels.
respectively. Therefore, this study demonstrates that serum T3 and rT3 may be reliable indices of metabolic control in diabetes mellitus.

10) Why LDN can help with Hashimoto’s

LDN stands for low dose naltrexone and is a medication which blocks opioid receptors in the body. It works at a low dose because it only temporarily blocks these receptors which triggers a release of endorphins naturally by the body. The release of endorphins continue throughout the entire day, long after the blockage of the opioid receptors have ended. Endorphins regulate the immune system which may be why LDN helps to treat autoimmune conditions such as Hashimoto’s thyroiditis. Low doses of LDN, ranging from 3.0mg to 4.5mg may help reduce inflammation and improve your symptoms. There are no studies which show that LDN is effective for treating Hashimoto’s thyroiditis, but the studies listed below show that LDN can be effective at treating other autoimmune diseases, are perfectly safe, and may help heal your gut lining.

Common objections from your Doctor:
- “LDN is not well studied” - It is true that LDN does not have very many studies supporting its use for Hashimoto’s, but it has been studied in the setting of Crohn’s disease (another autoimmune disease).
- “LDN isn’t safe” - LDN is very safe, especially at low doses and does not cause negative side effects. If it doesn’t work you can safely stop taking the medication without any harm. It is also relatively cheap (usually around $30-40 per month).
- “LDN hasn’t been proven to work” - LDN has not been proven to work consistently, but approximately 4 out of 10 people do experience significant improvement on this medication. With few side effects and a potential for success, it’s worth the trial.

Studies:

- 1) Low dose Naltrexone for induction of remission in inflammatory bowel disease patients. (Link)
  - 47 patients with inflammatory bowel disease, who failed traditional medications, were given LDN as a trial medication. The addition of LDN induced clinical improvement in 74.5% of patients and complete remission in 25.5% of patients. LDN also helped improved the intestinal lining which may be how it helped reduce the autoimmune component in these patients. While this study was done in patients with inflammatory bowel disease, the same logic can be extended to those with Hashimoto’s thyroiditis. It also showed that this therapy was extremely safe!
  - Conclusion: Naltrexone directly improves epithelial barrier function by improving wound healing and reducing mucosal ER stress levels. Low dose Naltrexone
treatment is effective and safe, and could be considered for the treatment of therapy refractory IBD patients.

- **2) Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels.** ([Link](#))
  - LDN was given to 10 patients with chronic pain. The researchers found that 28.8% of patients had a reduction in their pain, improved their mood, and increased their satisfaction with life. No side effects were reported. This study highlights that LDN can be used to treat patients with hypothyroidism who also have chronic pain.
  - Conclusion: The preliminary evidence continues to show that low-dose naltrexone has a specific and clinically beneficial impact on fibromyalgia pain. The medication is widely available, inexpensive, safe, and well-tolerated. Parallel-group randomized controlled trials are needed to fully determine the efficacy of the medication.

- **3) Safety and tolerability of low dose naltrexone therapy in children with moderate to severe Crohn’s disease: a pilot study.** ([Link](#))
  - This study shows that using LDN is safe in children with Crohn’s and reduced their disease activity. This is a good study to provide if you are trying to use LDN for your child but your doctor is worried about side effects.
  - Conclusion: Naltrexone therapy appears safe with limited toxicity when given to children with Crohn’s disease and may reduce disease activity.

- **4) Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis.** ([Link](#))
  - 60 patients with MS underwent LDN therapy without any negative side effects. Those who used LDN experienced better mental health quality of life.
  - Conclusion: LDN significantly improved mental health quality of life indices. Further studies with LDN in MS are warranted.

- **5) Therapy with the opioid antagonist naltrexone promotes mucosal healing in active Crohn’s disease: a randomized placebo-controlled trial.** ([Link](#))
  - In this study, 78% of patients treated with LDN had a noticeable response when evaluated through endoscopy (which is a procedure similar to colonoscopy). This means that Doctors went inside and looked at the gut lining and it showed that it had improved visually. This is important because it shows that LDN may help to improve the gut lining and may help treat other gastrointestinal diseases. Also, gut dysfunction may be a predisposing cause of autoimmune disease (leaky gut) in many individuals.
  - Conclusion: Naltrexone improves clinical and inflammatory activity of subjects with moderate to severe Crohn’s disease compared to placebo-treated controls.
Strategies to alter the endogenous opioid system provide promise for the treatment of Crohn's disease.

11) Using Victoza and Saxenda for Weight Loss

GLP-1 agonists are a group of medications which help lower insulin, reverse leptin resistance, and help with weight loss. They are, in my opinion, some of the most effective and underrated weight loss medications available on the market. The problem? Most doctors aren’t aware that they are even useful because they were originally designed to treat type II diabetes. The good news is that one of them (Saxenda) was recently FDA approved for weight loss. The only problem is that it is NOT covered by insurance and can be expensive. But, you can still get the benefits of using a GLP-1 agonist by convincing your doctor to prescribe one of the other medications which may be covered by insurance.

Medications in the GLP-1 class include: Byetta, Bydureon, Victoza, Saxenda, Trulicity, and Tanzeum. You can call your insurance company and ask which one they cover and then ask your doctor to prescribe that medication. That way you can take advantage of the weight loss benefits without having to pay out of pocket.

You can obtain the benefits of weight loss by using any of these medications. I recommend using whichever one your insurance covers and if they don’t cover any of them then your best choice is Saxenda. Saxenda will almost always be expensive because insurance companies (at the time of writing this) do not cover it.

Common objections from your Doctor:
- “These medications don’t work” - All GLP-1 agonists are highly effective medications and can be used for weight loss (studies below to prove it).
- “These medications cause pancreatic cancer” - While it is true that initial studies suggested that people who took these medications had a higher incidence of pancreatic cancer newer studies have not shown this to be the case. Plus, if you are using these medications temporarily (for 6 month intervals), then the risk of pancreatic cancer is virtually zero.
- “These medications are not FDA approved” - It is true that most of these medications are not FDA approved for weight loss, but it should be noted that Saxenda is FDA approved for weight loss. Saxenda is the exact same medication as Victoza and the only difference is in the starting and ending dose, otherwise they are identical. So, if Saxenda is FDA approved for weight loss then your doctor shouldn’t have a problem prescribing Victoza which is an identical medication.
- “These medications are used to treat diabetes” - It is true that these medications were designed initially to treat diabetes but they were also found to help diabetic patients lose a significant amount of weight. Since that time newer studies have come out which highlight their effectiveness in weight loss programs.
Studies:

1) Liraglutide for weight management: a critical review of the evidence (Link)
   - This is a basic study which looked at 5 different studies to try and determine if Liraglutide (the active ingredient in both Victoza and Saxenda) works for weight loss. This study found that, on average, people using liraglutide lost between 9 and 13 pounds or 5 to 10% of their body weight without making any other changes other than starting the medication. In addition, most patients only experienced minor stomach issues as negative side effects. This study shows that both Victoza and Saxenda are indeed effective (more so than other weight loss medications) and can help people lose weight. What's important here is not the absolute number, but the fact that it can help. When combined with other therapies such as fasting, diet, and exercise, the weight loss seen is even higher.
   - Conclusion: Liraglutide helps to induce and sustain weight loss in patients with obesity. Its efficacy is comparable to other available agents but it offers the unique benefit of improved glycemic control. Additional studies are needed to determine its long term efficacy and safety profile.

2) The Effect of Liraglutide on Weight Loss in Women with Polycystic Ovary Syndrome: An Observational Study (Link)
   - This study is important because it shows that GLP-1 agonists can be used in patients without type II diabetes. In this study, patients with PCOS were given liraglutide. On average, these women lost almost 20 pounds and experienced a drop in their BMI of 3.2. These results were seen while using liraglutide each day for 27.8 weeks (which is around half of a year). These results are fairly typical in my practice as long as it is dosed correctly. It’s important to realize that this weight loss was seen without adding in other therapies as well.
   - Conclusion: Treatment with liraglutide in combination with metformin and lifestyle intervention resulted in a significant weight loss in overweight and obese women with PCOS, indicating that liraglutide may be an effective alternative for weight loss in this group of patients. However, larger placebo-controlled studies are needed to confirm this.

3) Short-term administration of the GLP-1 analog liraglutide decreases circulating leptin and increases GIP levels and these changes are associated with alterations in CNS responses to food cues: A randomized, placebo-controlled, crossover study (Link)
   - This study is very important in that it shows that liraglutide can help sensitize the body to leptin levels and help reverse leptin resistance. It is well known that leptin resistance leads to weight loss resistance, so treating and reversing it is
incredibly important for long lasting weight loss. In this study, patients who were given liraglutide showed a drop in leptin levels and a reduction in food cravings and desire for food. This is one of the ways that GLP-1 agonists help with weight loss by reducing both appetite and cravings for harmful foods.

○ Conclusion: We demonstrate herein short-term changes to circulating levels of GIP and leptin in response to GLP-1 agonist liraglutide therapy. These findings suggest that liraglutide may alter the circulating levels of hormones important in energy homeostasis that, in turn, influence CNS perception of food cues. This could possibly lead to compensatory changes in energy homeostasis that would over time limit the efficacy of liraglutide to decrease body weight. These novel findings, which, pointing to the potential advantages of combination therapies, may have therapeutic implications, will need to be confirmed by larger and longer-term trials.

● 4) Early Weight Loss with Liraglutide 3.0mg Predicts 1-Year Weight Loss and is Associated with Improvements in Clinical Markers (Link)

○ I’m not a big fan of this study, but I wanted to include it here to help you understand what it means. This study showed that if people lost a significant amount of weight when they started using liraglutide that this was a good sign for long-lasting weight loss. This study does highlight the importance of ‘responders’ vs ‘non-responders’ in that some people do seem to experience more weight loss than others on these medications. That doesn’t mean that they won’t work for you, but it may mean that you need to look at other types of medications within the same class. I’ve seen some people respond very well to liraglutide while others respond better to Byetta and so on. You may have to play around with your medication to find the right type for your body.

○ Conclusion: The early response criterion was clinically useful to identify individuals who would achieve clinically meaningful weight loss at 56 weeks.

12) DIO2/DIO2 Genetic Defect impacts your Ability to Convert Thyroid Hormone

Genetic testing for problems known as SNP’s, or single nucleotide polymorphisms, is becoming more and more common with genetic tests such as 23andme. These tests give you information about your genes and which disease states you may be susceptible to developing in your lifetime. A polymorphism refers to a single change at a specific place in your DNA which may alter the function of the enzyme that your DNA codes for. This small change isn’t always enough to cause a huge problem, but it may cause slight differences among individuals and result in changes such as how you tolerate medications, how you tolerate supplements and so on. There is a very important enzyme in your body known as D2 (Deiodinase type 2) which is responsible for converting T4 into the active T3. Several SNP’s (genetic defects in your body) have been identified which are quite common (up to 15% of people have these) which have been shown to
alter how thyroid hormone is metabolized in the body. Individuals with DIO2 SNP’s do not do well on standard T4 thyroid medications, may be more depressed than other patients and may have lower than normal free T3. If you have a 23andme test (or if you decide to get one) you can show your doctor these studies which may also help you get the right type of treatment. DIO1 is found in the liver, kidney, thyroid and pituitary in humans and is responsible for 30% of circulating T3. DIO2 is found in the skeletal muscle, pituitary, thyroid, heart, central nervous system and brown adipose tissue and is responsible for 70% of circulating T3. Both are important for determining how you will respond to thyroid medications but D2 is more important because it works harder than D1. So, generally, defects in D2 will have more of an impact on your body than defects to D1.

Common objections from your Doctor:
- “Genetic testing isn’t helpful” - Genetic testing is an emerging field and can certainly be helpful in many situations. The presence of a SNP does not necessarily mean you have a disease state, but it can help drive treatment.

Studies:

1) Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients. (Link)
   - 16% of patients in this study were found to have the rs225014 SNP out of 552 patients. Patients who had this SNP were found to experience a worse quality of life when compared to those without the SNP on T4 only thyroid medication. These patients also experienced depression, anxiety and other mental health conditions more frequently. This same group of patients had a significant improvement in these symptoms after starting T4 + T3 combination medication. It’s important to note that those with this SNP didn’t have any changes to their thyroid hormone levels even though they did better on T4 + T3 therapy. This means that you may still improve when switching medications even if your lab tests are so-called “normal”.
   - Conclusion: Our results require replication but suggest that commonly inherited variation in the DIO2 gene is associated both with impaired baseline psychological well-being on T(4) and enhanced response to combination T(4)/T(3) therapy, but did not affect serum thyroid hormone levels.

2) DIO2 Thr92Ala Reduces Deiodinase-2 Activity and Serum-T3 Levels in Thyroid-Deficient Patients. (Link)
   - This study looked at 140 patients without a thyroid and checked their baseline lab tests for TSH, Free T3, Free T4 and also for the D2 protein. It was found that patients with the DIO2 SNP had lower intracellular free T3 and serum T3 levels
even though they had a normal TSH. This shows us that it’s important for all thyroid patients on T4 medication (if it isn’t working) to have their free T3 and free T4 levels evaluated. Low free thyroid hormones may be an indication of this SNP and may be a sign that they need T3 + T4 combination medication.

○ Conclusion: Thyroidectomized patients carrying Thr92Ala are at increased risk of reduced intracellular and serum T3 concentrations that are not adequately compensated for by LT4, thus providing evidence in favor of customized treatment of hypothyroidism in athyreotic patients.

- 3) Hypothyroid Patients Encoding Combined MCT10 and DIO2 Gene Polymorphisms May Prefer L-T3 + L-T4 Combination Treatment - Data Using a Blind, Randomized, Clinical Study. (Link)
  ○ This study shows that up to 48% of people on thyroid medication prefer combination therapy with T4 + T3 thyroid medication (meaning you are NOT alone!). This randomized, cross-over study looked at 45 patients with Hashimoto’s thyroiditis with a normal TSH on T4 thyroid medication. The researchers then placed these patients on either T4 medication or T4 + T3 medication and asked them which treatment they preferred. Patients with the DIO2 SNP preferred the LT4 + LT3 combination medication at a rate of about 60%. This study shows the importance of SNP testing and normal thyroid lab tests in patients with Hashimoto’s thyroiditis. Patients also experienced more weight loss when switching from T4 only to T3 + T4 therapy.
  ○ Conclusion: The present study indicates that the combination of polymorphisms in DIO2 (rs225014) and MCT10(rs17606253) enhances hypothyroid patients’ preference for L-T4 + L-T3 replacement therapy. In the future, combination therapy may be restricted or may be even recommended to individuals harbouring certain polymorphisms.

- 4) A Common Variation in Deiodinase 1 Gene DIO2 Is Associated with the Relative Levels of Free Thyroxine and Triiodothyronine. (Link)
  ○ This study found that the expression of this gene helps people convert T4 to T3 more readily meaning that patients may be “super converts” and do very well on T4 only thyroid medication. In addition, this study also shows that these changes do NOT impact the TSH. If you have this SNP you may be fine using LT4 medication such as Tirosint.
  ○ Conclusion: This study provides convincing evidence that common genetic variation in DIO1 alters deiodinase function, resulting in an alteration in the balance of circulating free T3 to free T4. This should prove a valuable tool to assess the relative effects of circulating free T3 vs. free T4 on a wide range of biological parameters.
5) Genetics of Thyroid Function and Disease. (Link)

- This study clearly shows the link between certain SNP’s and how they influence patients and how well they do on thyroid medication (you can see the image below). If you have your 23andme data you can take it into your Doctor with this study and they should be able to easily see the link between your SNP’s and your preference for certain thyroid medication.
- Conclusion: However, these genes alone account for only a small percentage of the current prevalence of these disorders. Although the advancement of genetic technology has led to many significant findings in the last decade or two, it is clear that we are only just beginning to understand the role of genetics in thyroid function and disease.

Table 3.
Summary of thyroid related genes associated with clinical phenotypes.

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIO2</td>
<td>rs225014/rs12885300</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td></td>
<td>rs225010/rs225012</td>
<td>Mental retardation in iodine deficient areas</td>
</tr>
<tr>
<td></td>
<td>rs225014</td>
<td>Psychological well-being on T4</td>
</tr>
<tr>
<td></td>
<td>rs225014</td>
<td>Preference for T3/T4 over T4 therapy</td>
</tr>
<tr>
<td></td>
<td>rs225014/rs12885300</td>
<td>Bipolar affective disorder</td>
</tr>
<tr>
<td></td>
<td>rs225014</td>
<td>Hypertension/blood pressure</td>
</tr>
<tr>
<td>TSHR</td>
<td>rs1991517</td>
<td>Bone density</td>
</tr>
<tr>
<td></td>
<td>rs1991517</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td></td>
<td>rs10149689/rs12050077</td>
<td>Longevity</td>
</tr>
<tr>
<td>OATP1C1</td>
<td>rs10770704</td>
<td>Psychological well-being on T4</td>
</tr>
<tr>
<td>DIO1</td>
<td>rs11206244/rs12095080</td>
<td>IGF-1</td>
</tr>
</tbody>
</table>

*Phenotypes in italics have conflicting evidence.*