

Wilson's Syndrome and T3 Therapy

A Clinical Guide to Safe and Effective Patient Management

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The opportunity to permanently improve energy and temperature, reduce excess weight, enhance well-being and restore normal metabolism is compelling and achievable with cyclic T3 therapy.

Denis Wilson, MD, identified Wilson's syndrome as a disease state in 1990.^{1,2} The syndrome is characterized by consistently low body temperature taken by mouth with a mercury thermometer for a full five to six minutes at three, six and nine hours after rising, in combination with the related symptoms described below.

Symptoms

The symptoms of Wilson's syndrome are the same as those associated with low thyroid function, including chilliness; fatigue; easy weight gain; fluid retention; dry eyes;

dry skin; dry hair or hair loss; weak, brittle unhealthy nails; constipation and concentration impairment. Other possible associated symptoms include insomnia, headaches, irritability, anxiety and panic attacks, depression, premenstrual syndrome, irregular periods, low sexual desire and low self-esteem.³

Table 1. Two-Day Compensating Schedule for Doses of T3.

Day	Dose (in µg)	Temp.	Temp.	Temp.
7/1	7.5	97.2	97.6	97.8
7/2	7.5	97.3	97.8	97.6
7/3	15	97.8	98.0	97.8
7/4	15	97.8	98.0	97.6
7/5	22.5	98.0	97.8	98.0
7/6	22.5	97.4	97.8	98.0
7/7	30	98.2	98.4	98.2
7/8	30	98.4	98.6	98.4
7/9	37.5	98.4	98.6	98.2
7/10	37.5	98.6	98.6	98.6*
7/11	30	98.6	98.6	98.8
7/12	30	98.3	98.8	98.6
7/13	30	98.8	98.6	98.8
7/14	22.5	98.8	98.8	98.6
7/15	22.5	98.6	98.8	98.6
7/16	22.5	98.4	98.8	98.6
7/17	15	98.2	98.4	98.6
7/18	15	98.4	98.6	98.4
7/19	15	98.4	98.6	98.6
7/20	7.5	98.6	98.6	98.6
7/21	7.5	98.4	98.6	98.6
7/22	7.5	98.6	98.4	98.6
7/23	Nothing for the next two weeks			

* Thermoregulation achieved

Patients Most Likely To Be Affected

While the majority (up to 80%) of patients are women, men can develop the condition as well. It is more common among individuals whose ancestors have sustained repeated famines, such as the Native American, Irish, Welsh and Russian populations.¹ Individuals who have fasted for prolonged periods or severely restricted their caloric intake are at great risk for Wilson's syndrome as well. This is especially true if, after these dietary restrictions, the individual regains greater than 10% of his/her initial weight. Many individuals develop the symptoms (chilliness, fatigue, weight gain) after pregnancy or after a prolonged period of stress (childbirth, divorce, death of a loved one, surgery, prolonged job stress).

Diagnosis

A normal serum thyroid-stimulating hormone in combination with oral temperatures averaging consistently below 98.2°F with the symptoms described above confirms the diagnosis of Wilson's syndrome. Temperatures should be taken 15 or more minutes away from cold or warm drinks or food, and away from smoking, showering and exercise.

Temperatures are not to be taken during menstruation, ovulation, concurrent treatment with pain or fever-lowering medications or periods of illness when low-grade or full fevers may be present.

Causes of Low Body Temperatures

In Wilson's syndrome, although circulating blood levels of thyroid-stimulating hormone, thyroxin (T4) and triiodothyronine (T3) or liothyronine are within normal limits, conversion from T4 to T3 in the liver and at the cell-membrane receptor sites (periphery) is impaired. Since T3 is the biologically active form of thyroid hormone,

the patient presents with persistent hypothyroid symptoms in spite of normal lab values. Additionally, a period of stress and starvation induces the conversion of T4 into the biologically inert stereoisomer called *reverse T3*. Reverse T3 is a mirror image of T3 and fits well into T3 cell-membrane receptor sites upside down. Once bound to these receptors, reverse T3 prevents T3 from binding, thus preventing thyroid activation at these receptor sites.

Identification of either poor conversion or receptor sites blocked with inert reverse T3 is just one of the many ways low temperature and fatigue can evolve into chronic problems. Adrenal insufficiency (especially abnormally high or low cortisol with low dehydroepiandrosterone (DHEA) causes these symptoms as well. If a patient is adrenal insufficient, giving the patient cyclic T3 could aggravate his/her adrenal insufficiency. It is safest to first

screen patients with a circadian salivary cortisol and DHEA (test before administering T3 therapy).³

Other causes of thermoregulation impairment (low temperatures) include growth-hormone deficiencies; malnutrition (low total caloric intake); hypoglycemia; essential fatty acid deficiencies; and low estrogen, testosterone, progesterone, adrenaline or neurotensin.² Therefore, a complete endocrine and dietary assessment of each patient is indicated before embarking on T3 therapy as the sole intervention in thermoregulation.

T3 Therapy Administration, Regulation and Monitoring

Wilson emphasizes a dosage schedule that raises T3 doses on a daily basis.¹ However, in my clinical experience, it is most efficient and safest to begin dosing patients with

Table 2. One-Day Compensating Schedule for Doses of T3.

Day	Dose (in µg)	Temp.	Temp.	Temp.
7/1	7.5	97.2	97.6	97.8
7/2	15	97.3	97.8	97.6
7/3	22.5	97.8	98.0	97.8
7/4	30	98.8	98.0	98.6
7/5	37.5	98.6	98.8	98.4*
7/6	30	97.4	97.8	98.6
7/7	30	98.6	98.4	98.6
7/8	22.5	98.4	98.6	98.4
7/9	22.5	98.4	98.6	98.6
7/10	15	98.6	98.6	98.6
7/11	15	98.6	98.6	98.6
7/12	7.5	98.4	98.6	98.6
7/13	7.5	98.4	98.7	98.6
7/14	Nothing for the next two weeks			

* Thermoregulation achieved

what I call a two-day compensating schedule (see Table 1). (In this context, compensating means that the patient reaches and maintains an average temperature of 98.6° F in two days.) It raises the dose by 7.5 µg every two days. Each day the proper dose is taken exactly every 12 hours and then raised after two days at each given dosage. The standard dose cycle begins at 7.5 µg, one every 12 hours, and then increases the dose by 7.5-µg intervals every two days. Our starting dose pack peaks at 37.5-µg capsules. Once this dose is reached, the patient tapers down to 30 µg, then 22.5 µg, then 15 µg, then 7.5 µg, taking each dose once every 12 hours for three days throughout this weaning-down cycle. This dose pack contains a total of 44 capsules, ten for each dosage (one every 12 hours for the two days going up and the three days going down) except the four capsules at the 37.5-µg peak dose.

Features of the Two-Day Compensating Schedule

With the dose at 7.5-µg intervals, features of the two-day compensating schedule are as follows:

1. One every 12 hours, two days up and three days down;
2. Gradual dose increases;
3. Less chances of side effects as dose rises;
4. Compensation (reached 98.6°F) on the second day;
5. Missing of the one-day compensator.

Table 3. Commonly Prescribed Dose Increments (in Micrograms) Taken as One Capsule Every 12 Hours.

7.5
15
22.5
30
37.5 (24-hour production)*
45 (begins supersaturation)
75
82.5
90
97.5
105 (> often causes side effects)
112.5
120
127.5
135

* ≥ 37.5 µg causes T4 suppression and greater risk of side effects

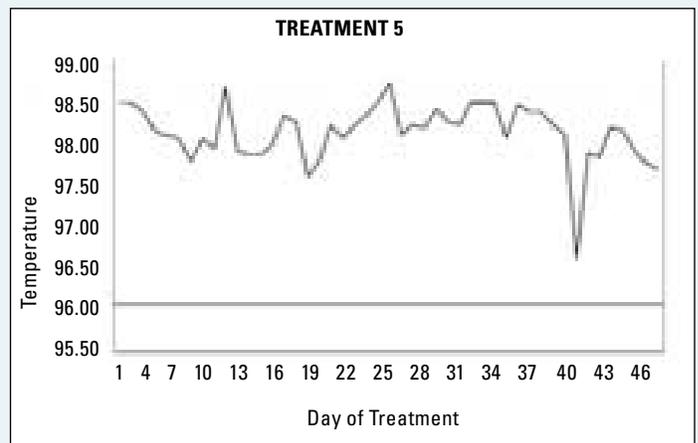
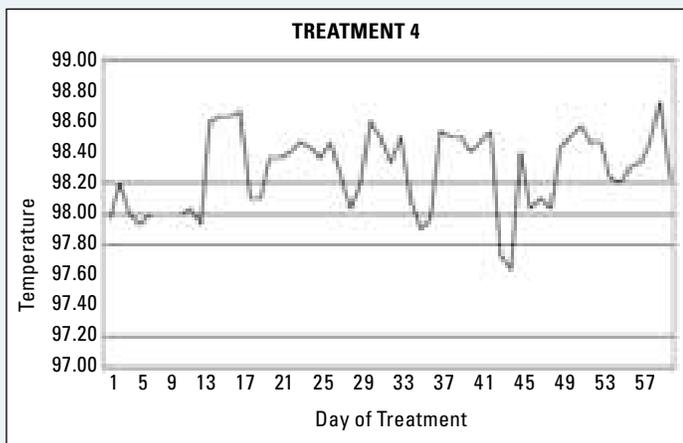
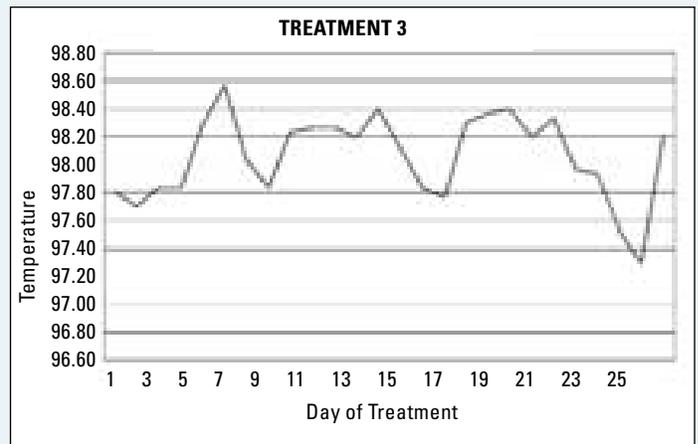
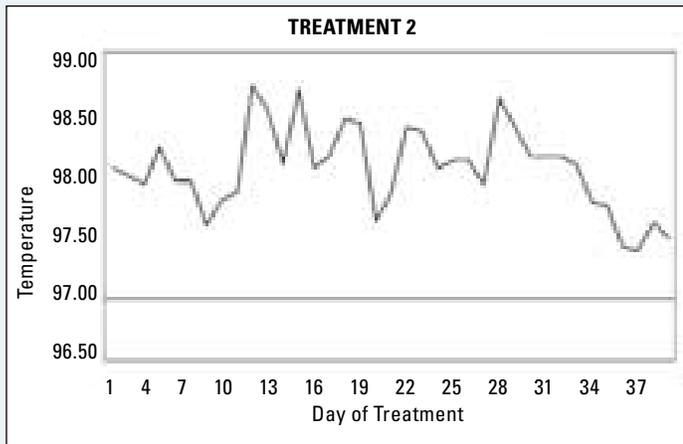
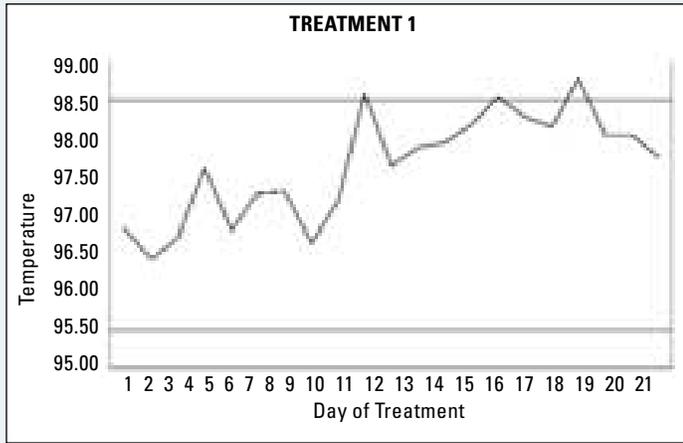
Maintaining a Patient Log

Patients are instructed to keep a written temperature log that must include the following: date, dose, pulse, three temperature readings followed by daily average temperature and comments concerning any symptom improvements, as well as any negative or positive side effects. Even if the patient does not reach an average temperature of 98.6°F by the 37.5-µg dose, we usually instruct the patient to wean back down to zero. While the patient could use the remainder of the dose pack to continue to cycle upward and then refill the dose pack to complete the cycle, we find this method safer. The 37.5 µg of T3 every 12 hours represents the level of tissue saturation with T3. Doses over 37.5 µg every 12 hours are often well tolerated without side effects. Allowing patients to take higher doses of 60 µg and 90 µg on their first cycle increases the chances of first-cycle overdoses or taking

the medicine at too high or too low a dose without physician supervision. It is safer and ultimately more efficient to dose the patient with a 37.5-µg cycle and then meet with the patient to review both his/her log of symptoms and temperature response, increasing the dose cycle as indicated. Using this method approximately 10% of the population compensates by reaching a temperature of 98.6 and maintains that temperature during the weaning of the dose. It takes an average of three to five cycles to completely correct temperatures.

Thermoregulation after Five Cycles of Slow-Release T3 in a 51-Year-Old Woman

These tables represent sequential T3 cycles ending with improved thermal regulation.



Thermoregulation Variations

On review of the temperature log, you will note that in some cases a patient's temperature ends up lower than when he/she originally started. These patients have other thermoregulating problems such as adrenal insufficiency that T3 therapy is exacerbating. In these cases, evaluate the entire endocrine, dietary and lifestyle aspects of the case carefully.

In reviewing other patient logs, you will note that the temperatures of some patients rise significantly on the first day of a new dose and then fall on the second day at the

same dose. These are one-day compensators who will reach 98.6° F more easily by raising their dose by 7.5- μ g intervals every day rather than every two days. These patients will wean down their dose every two days. The one-day compensating dose schedule is shown in Table 2.

Features of the One-Day Compensating Schedule

With the dose at 7.5- μ g intervals, features of the one-day compensating schedule are as follows:

1. One every 12 hours, one day up and two days down;
2. Rapid dose increases;
3. Greater chance of side effects as dose rises;
4. Identification of the one-day compensator.

Other patients will compensate (reach and maintain an average temperature of 98.6°F) at a certain dose and then relapse in their temperature as their dose is lowered. On the next cycle, once compensation is achieved, use the patient's lowered temperature as a guide to increase the dose to the next 7.5- μ g increment. At this next highest increment, hold that dose for five to seven days or even longer on subsequent cycles before weaning down. The patient's temperature may stay captured or again relapse. If it relapses, again raise the dose. You may end up "stair-stepping" a patient from an initially compensated dose of 60 μ g down to 52.5 μ g and then 45 μ g, then up to 52.5 μ g for one week, then down to 45 μ g, 37.5 μ g, and 30 μ g. If he/she relapses again at 30 μ g, you increase the dose to 37.5 μ g, recapture the temperature and hold the dose at 37.5 μ g for five to seven days before beginning to wean again. Each successive cycle usually becomes easier with less "stair-stepping," and often the dose does not have to go as high as in previous cycles.

Maximum Dosing

It is rare for cycles of T3 to require doses of greater than 90 μ g to 105 μ g every 12 hours. However, rare cases may require dosing up to 120 μ g to 135 μ g. When doses are this high, suspect additional causes of thermoregulation impairment outlined above. The chances of side effects significantly increase with these higher doses. Table 3 lists the usually prescribed dose increments taken as one capsule every 12 hours.

Additional Benefits

In addition to the benefits of improved energy, better concentration, weight loss and enhanced general well-being, correcting thyroid metabolism improves the functioning of all tissues, organs and metabolic pathways. Many patients report fewer incidences of colds and flu after successful cyclic T3 therapy, since one's ability to maintain surveillance over bacteria, viruses and cancer cells is reduced with lower temperatures. Broda Barnes, MD, has wonderfully elucidated the role of optimizing circulating thyroid hormone in preventing heart disease, cancer, hypertension (although a relative contraindication for cyclic T3 therapy), arthritis, headaches including migraines, menstrual disorders, infertility, skin disorders (recurrent impetigo,

cellulitis, erysipelas, acne, eczema, lupus, psoriasis), emphysema, chronic obstructive pulmonary disease, obesity and premature aging, as well as enhancing treatment outcome.⁴

Hypothyroidism Misconstrued as Wilson's Syndrome

In hypothyroidism, the patient's laboratory values are abnormal, with high thyroid-stimulating hormone and low T4 and/or low T3. The patient's thyroid gland has lost its organ-reserve capacity to produce adequate levels of T4 and T3. Serum and/or total T4 and T3 are low and thyroid-stimulating hormone levels correspondingly rise. These patients need to take thyroid replacement continually and are at greatest risk for developing the array of complications noted by Barnes. It is medically contraindicated to take them off their continuous dosing of thyroxin or glandular thyroid, replacing this with cyclic T3. However, hypothyroid patients may also be poor converters of T4 into T3 and neither T4 replacement nor glandular thyroid will optimize these patients' health status. Many hypothyroid patients taking synthroid continue to present with fatigue, low temperatures, obesity and additional thyroid deficiency symptoms despite normal lab values. A February 1999 study in the *New England Journal of Medicine* reported that patients with hypothyroidism experienced improved mood and neuropsychological function when treated with a combination of T4 and T3.⁵

Cycling Safely

After weaning patients down on a T3 cycle, it is absolutely essential to instruct them to discontinue T3 for two weeks before starting a new cycle. Prolonged, extended dosing with high levels of T3 suppresses endogenous production of T4 from the thyroid gland. This therapy is designed to cure thyroid conversion and utilization impairment and in so doing restore the thyroid gland to optimal production of T4 and T3. The last thing we want to do is weaken endogenous long-term T4 production. Furthermore, continuous very excessive doses of T4 and T3 have been linked to osteoporosis.

Thyroid Medication and Osteoporosis

Although there is no clear evidence showing that normal replacement dosing with continuous T4 or T3 causes osteoporosis, there are multiple studies that correlate an increased incidence of osteoporosis with hyperthyroidism, thyrotoxicosis, and thyroid overdosing in hypothyroidism.⁶⁻⁸ It is therefore prudent to avoid dosing patients for extended periods of time at a dose that significantly suppresses thyroid-stimulating-hormone levels below the normal reference range. Mild thyroid-stimulating-hormone suppression does not apparently affect bone density.⁹⁻¹²

Contraindications

There are few contraindications to the use of cyclic, time-released T3. They include allergic reactions, a recent heart attack or recent/unstable congestive heart failure

and weight loss with normal labs and no thyroid-related symptoms or low temperatures. Other relative contraindications include hypertension, unstable rapid arrhythmias (paroxysmal supraventricular tachycardia, atrial fibrillation with a rapid ventricular response; paroxysmal ventricular tachycardia; or frequent, coupled premature ventricular contractions) and adrenal insufficiency.

Drug Interactions

Thyroid can thin blood, especially at higher doses. Patients on warfarin sodium (Coumadin®) or other anticoagulants may develop an increase in prothrombin time requiring a lowering of their anticoagulant therapy while taking thyroid medication. Drug-drug interactions may occur with other anticoagulants, oral hypoglycemic agents (increased requirements), insulin (increased requirements), estrogens and oral contraceptives (increased thyroid requirement), tricyclic antidepressants (enhanced effects), cardiac glycosides (potential toxicity and reduced dose) and cholestyramine (decreased T3 and T4 absorption). Several drugs, including cimetidine, ranitidine, glucocorticoids, amiodarone and beta-receptor antagonists, have been reported to increase the hepatic metabolism of T4 into reverse T3 by inhibiting 5'-desiodinase, the hepatic microsomal enzyme catalyzing the conversion of T4 into T3.¹³

Side Effects

In general, although most patients tolerate T3 well, certain patients are idiosyncratically sensitive to T3, even at low doses. Given enough T3, anyone may exhibit one or more of the following side effects: headaches, jitteriness, anxiety, irritability, nervousness, sweating, rapid heart rate, irregular heart rhythm, insomnia, restlessness, easy bleeding and menstrual irregularities. Side effects and overdosing symptoms are best neutralized with a small dose of T4, 12.5 µg to 25 µg. Beta-blockers may be necessary to control excessive sympathetic nervous system activity or cardiac glycosides may be necessary if congestive heart failure develops.

The Value of the Compounding Pharmacist and Slow-Release T3

Triiodothyronine is only available through compounding pharmacists. It is synthetically manufactured and received by the pharmacist as pure USP-grade powder. Micronized T3 is mechanically blended for six hours with microcrystalline cellulose as a filler, then hydroxypropylmethylcellulose (grade E4M) is used as a slow wetting agent in proper proportions related to the finished microgram dose (Jon Fenrich, RPh; Don West, RPh, oral communication, May 24, 1999). Other blending methods may be used as long as the powders are very thoroughly mixed due to the small amounts of active ingredient involved in each dosage level; this complex releases T3 slowly to minimize high peak levels associated with immediate-release tablets (Jon Fenrich, RPh; Don West, RPh, oral communication, May 24, 1999).

Cytomel,® the pharmaceutically manufactured form of T3, is not slow released. By weight, T3 is three to four times more active than T4. The half-life of T3 is 2.5 days, compared with 7.5 days for T4. A molecule this biologically active, released continually throughout the day, is best delivered gradually in a slow-release form.

This significantly reduces the occurrence of side effects compared to prescribing 25 µg to 100 µg of Cytomel once daily.

Patient questions are frequent in the management of T3. The compounding pharmacist plays a crucial role in patient education and the effective dosing of the medication. Most pharmacists make available patient information sheets, temperature logs and additional educational literature. The integrated role of the physician and pharmacist in patient management is crucial in order to optimize the outcome for Wilson's syndrome patients.

Prognosis

The opportunity to permanently improve energy and temperature, reduce excess weight, enhance well-being and restore normal metabolism is compelling and achievable with cyclic T3 therapy. The variables affecting thermoregulation are complex, yet thyroid conversion/receptor problems are high on the list of possibilities. Cyclic T3 therapy, delivered safely and effectively, remains one of the most effective adjuncts in restoring normal body temperature and metabolism. A full endocrine, dietary and lifestyle assessment aids the pharmacist and clinician in targeting an optimal treatment regime, enhancing the prognosis for a larger number of patients.

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