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Title:
Bioidentical Thyroid Replacement Therapy in Practice, delivering a physiologic T4:T3 ratio for improved patient outcomes with the Listecki-Snyder Protocol

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Abstract

Effective thyroid replacement therapy may be elusive to some patients, and compounding pharmacists have an opportunity to deliver more effective therapy. Goodman and Gilman's 12th edition states that the body usually secretes T4:T3 in an 11:1 ratio but cautions against pursuing combined thyroid replacement due to the short half-life of T3 that necessitates multiple daily dosing, no commercial availability and lack of benefit shown in trials[1]. Commercial combinations of T4/T3 such as Armour Thyroid and Nature-Throid have a 4.22:1 T4:T3 ratio. Applying the same concept as bioidentical hormone replacement therapy, compounding pharmacists can deliver an 11:1 ratio using a commercial T4 product and taking into account oral bioavailability of each entity. The short half life of T3 can be remedied by taking the patient's daily T3 dose and dividing it into two time release capsules to be dosed every 12 hours.

Review of Available Literature

Goodman and Gilman cite a meta-analysis[2] that examined 11 studies of combination T4/T3 therapy as a reason not to recommend combination therapy. One study looked at a 10:1 ratio and three looked at 15:1. Most studies only considered decreasing their current T4 and adding a pre-determined amount of T3 in no set ratio.

Of these four studies, many weaknesses were present. One study did not assess body temperature, physical assessment of the patient's skin and physical reflexes[3]. No study assessed all, only some, of the surrogate markers of effective thyroid replacement therapy[3,4,5,6]. All studies did not use extended release or multiple daily dosing of T3[3,4,5,6]. One study used 8 weeks of treatment in each group[4], which may be inadequate to assess effective treatment. The authors of two studies also assessed the patients with lower TSH values were being over-treated, despite values within the normal range[3,4]. However, the treatment group in one study only lost 0.4 kg more then the T4 only group and their heart rate and blood pressure did not differ from baseline[3].

This calls into question the validity of using the TSH level alone to determine adequate treatment of the patient. The TSH suppression observed could be due to the negative feedback mechanism from physiologic replacement of hormone levels. The body needs the thyroid to secrete fewer hormones due to elevated serum T3 and T4 levels and may be tempering its output naturally. The normal range for patients being treated with T4 should be 0.3-3 mIU/L[7], which the trial results data meets.

Although the trials never demonstrated a benefit to combination therapy at a physiological level, two of these four trials showed the patients preferred combination therapy[3,4]. The other two trials did not assess patient preference[5,6]. In one trial, patients preferred combination therapy despite lower TSH levels[3]. The results may be interpreted to mean that a physiologic T4/T3 replacement regimen may be preferred by a patient not satisfied by their current therapy as long as TSH levels are maintained with the normal range of 0.3-3 mIU/L. Considering the quality of life, skin quality, basal temperature and subjective preference of patients currently not receiving satisfactory therapy, use of combination therapy of T4:T3 in an 11:1 ratio may produce more effective therapy in some patients.

Accounting for oral bioavailability

Another question compounding pharmacists may have is how an 11:1 ratio can be delivered to the body. Levothyroxine has an oral bioavailability of about 0.8[1]. Liothyronine (commercial T3) has an oral bioavailability of 0.95[8]. This means that compounding pharmacists can prepare a 13.06:1 ratio of T4:T3 to deliver a blood level of 11:1 to the patient. A commercial T4 source can be substituted based upon the patient's current T4 dose with Armour Thyroid or Nature-Throid. A half dose of the appropriate commercial T4 dosage form can be given every other day if a similar commercial T4 dose is not available. Since T4 has a 9 day half-life[1], every other day dosing should maintain consistent blood levels compared to T3, which is 18 hours[1].

Pharmacokinetics of combination T4/T3 therapy

A subset of patients within a trial receiving combined T4/T3 therapy or T4 therapy alone participated in a 24 hour hormone level monitoring[9]. Based on their methods, patients receiving combined therapy were receiving at least 4:1 T4:T3 or higher based upon the study protocol and oral bioavailability. The study found no differences between the two groups with respect to cardiovascular parameters. Patients reported no adverse effects. The results of the hormone level monitoring are summarized in Table 1.

Compounding pharmacists can minimize the T3 peak by using 12 hour dosing intervals with time release capsules. This may also mitigate the negative feedback loop suppression of TSH that occurs post-dose. 12 hour dosing of time release dosing may help maintain homeostasis within the body and promote even T3, T4 and TSH levels throughout the day in order to provide effective therapy.

Certain patients may receive greater benefit from combination therapy

One subgroup that demonstrated benefit from T3/T4 combination therapy includes athyrotic patients with inadequate TSH suppression. A study found that 15 patients had improved hormone profiles with lower T4 doses when on average administered in a bioequivalent 9.89:1 T4:T3 combination after 9 months of treatment (existing T4 therapy alone first)[10]. The results are summarized in Table 2.

One review states that T4 therapy alone can leave patients with normal TSH levels but still exhibit symptoms of hypothyroidism[11]. Due to distribution differences and polymorphisms, some tissues may not be receiving adequate T3 allowing these symptoms to persist. The review authors state that T4 alone must be given at supraphysiologic doses in order to normalize T3 and TSH levels in 25-32% of hypothyroid patients[11]. The review of 15 trials concluded that hypothyroid patients with underlying autoimmune diseases, athyroid patients or patients submitted to radioiodine therapy, patients lacking T3 production, patients with enzymatic D2 (responsible for T3 tissue delivery) polymorphisms and depressed patients may benefit from combined T3/T4 therapy.

Conclusion

Compounding pharmacists have an opportunity to provide a higher level of patient centered care to patients that are not satisfied with their current hypothyroid therapy. Although the studies have not proven a benefit quantitatively for every hypothyroid patient, some patients have been able to benefit from a more physiologic regimen compared to T4 alone. Additionally, patients have preferred the combination therapy when surveyed, despite lower TSH levels. The trials did not report adverse cardiac events or other health concerns, other than lower TSH levels, from this therapy.

By working with the patient and physician to get a prescription for 13.06:1 T4:T3, the pharmacist can deliver the 11:1 T4:T3 ratio to the bloodstream, which is how the thyroid gland delivers these hormones. By delivering the daily dose of T3 in two time release T3 capsules per day, better homeostasis may be maintained. Table 3 contains a list of suggested formulas to consult for how to compound the T3 and the corresponding dose of T4 in order to deliver the physiologic 11:1 T4:T3 to the patient's bloodstream. It may be useful to provide physicians with a copy of this table to facilitate dosing.

Continuing to monitor the patient's symptoms and TSH is always recommended when changing their current regimen. It is important to give changes to hormone therapy time,

approximately three months, to take effect and balance before evaluating them. Most studies used 90 days as their point of evaluation for this reason. Also, consider reducing the amount of commercial T4 since the active T3 may mitigate the need for maintaining the same T4 dose. In order to mitigate adverse effects, work with the doctor to ensure safe and effective hormone levels.

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Table 1:
Summary of 24 Hour Monitoring of Thyroid Hormone levels[9]

	T4/T3 Combined Therapy	T4 therapy alone
Free T3 Levels	Peak within 4 hours after taking the 0800 dose. Gradual decline to meet and maintain T4-only group's T3 levels	Relatively constant throughout the day with mild decline.
Free T4 Levels	No post dose peak, level maintained throughout the day.	Moderate peak within two hours post dose administration. Level maintained throughout the day 6 pmol/L higher than T3.
TSH Levels: Both groups exhibited circadian rhythms with a nocturnal rise	Moderate decrease from baseline, 5 mIU/L, with a building level from 5-13 hours post dose until maintaining a consistent level near 6 mIU/L.	Lower level maintained consistently around 1 mIU/L throughout the day.

Table 2:
Comparison of athyrotic patients unresponsive to T4 therapy alone after switching to combined T4/T3 therapy for 9 months[10]

	T4 Dose (mcg)	Free T4 (nmol/L)	Free T3 (nmol/L)	TSH (mIU/L)
T4 Only[a]	153.3	170.6	1.3	12.88
T4/T3 combined	117.5	124.3	2.26	1.22

[a]T4 only values were measured at baseline after at least 9 months of T4 therapy before converting to T4/T3 therapy
[b]All values were significantly lower ($P<0.01$)[10]

Table 3:
Suggested formulae to deliver 11:1 T4:T3 to the bloodstream based upon oral bioavailability and commercially available T4 strengths

Daily T4 Dose (mcg)	Commercial T4 Strength (mcg)	Daily T3 Needed for 13.06:1[a] (mcg)	BID T3 dose per per capsule (mcg)	T3 1000:1 for #60 #1 caps (g)	Methocel E4M (g)	Microcrystalline Cellulose (g)
12.5[b]	25	0.96	0.48	0.029	6	8.251
25	25	1.91	0.96	0.057	6	8.223
37.5[b]	75	2.87	1.44	0.086	6	8.194
44[b]	88	3.37	1.68	0.101	6	8.179
50	50	3.83	1.91	0.115	6	8.165
56[b]	112	4.29	2.14	0.129	6	8.151
62.5[b]	125	4.79	2.39	0.144	6	8.136
68.5[b]	137	5.25	2.62	0.157	6	8.123
75	75	5.74	2.87	0.172	6	8.108
87.5[b]	175	6.70	3.35	0.201	6	8.079
88	88	6.74	3.37	0.202	6	8.078
100	100	7.66	3.83	0.230	6	8.050
112	112	8.58	4.29	0.257	6	8.023
125	125	9.57	4.79	0.287	6	7.993
137	137	10.49	5.25	0.315	6	7.965
150	150	11.49	5.74	0.345	6	7.935
175	175	13.40	6.70	0.402	6	7.878
200	200	15.31	7.66	0.459	6	7.821
300	300	22.97	11.49	0.689	6	7.591

[a]13.06:1 T4:T3 is used orally to adjust for bioavailability needed to deliver 11:1 T4:T3 to the bloodstream
[b]Indicates use of commercial T4 product every other day