T3, or Not T3?
Finding True North in Thyroid Hormone Replacement

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Disclosures

- None

Available Thyroid Hormone Preparations

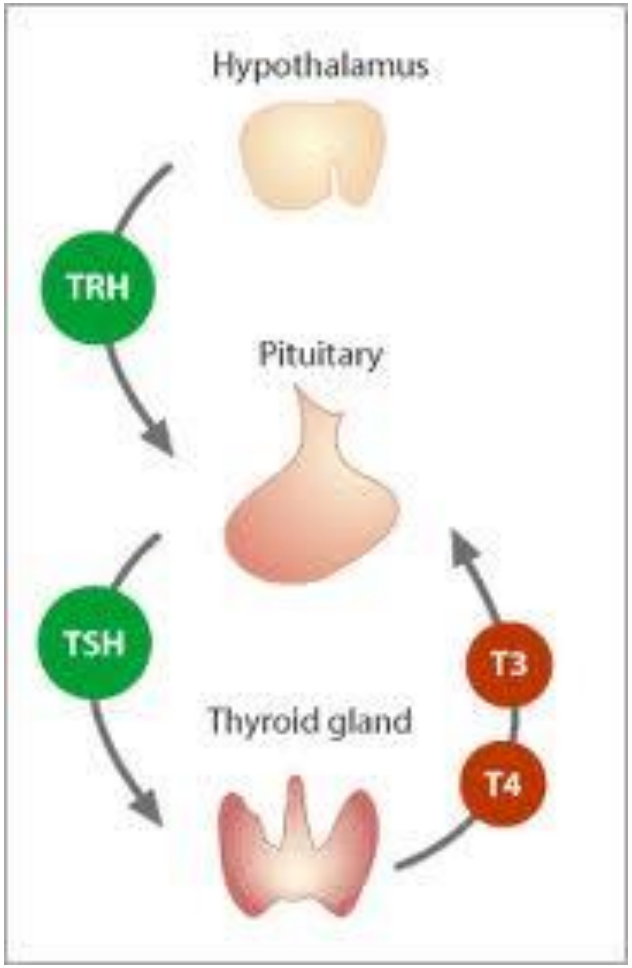
	Half-Life	% T4	%T3
Levothyroxine (LT4)	7 days	100%	--
Liothyronine (LT3)	18 hours	--	100%
Liotrix (LT4 + LT3)	--	80%	20%
Dessicated thyroid extract (DTE)	--	80%	20%

Human thyroid gland produces T4 : T3 ~ 12 : 1

Dosing Thyroid Hormone

- LT4 = 1.6-1.8 mcg/kg/day
  (avg. adult dose 100-125 mcg daily)
- DTE = 60 – 120 mg/day
- Conversion of LT4 to DTE treatment:
  LT4 100 mcg = DTE 60 mg

Regulation of Thyroid Hormone Production



Human Thyroid secretes T4 : T3 at 11: 1 ratio
T4 serum half-life ~ 1 week; T3 serum half-life ~ 18 hours

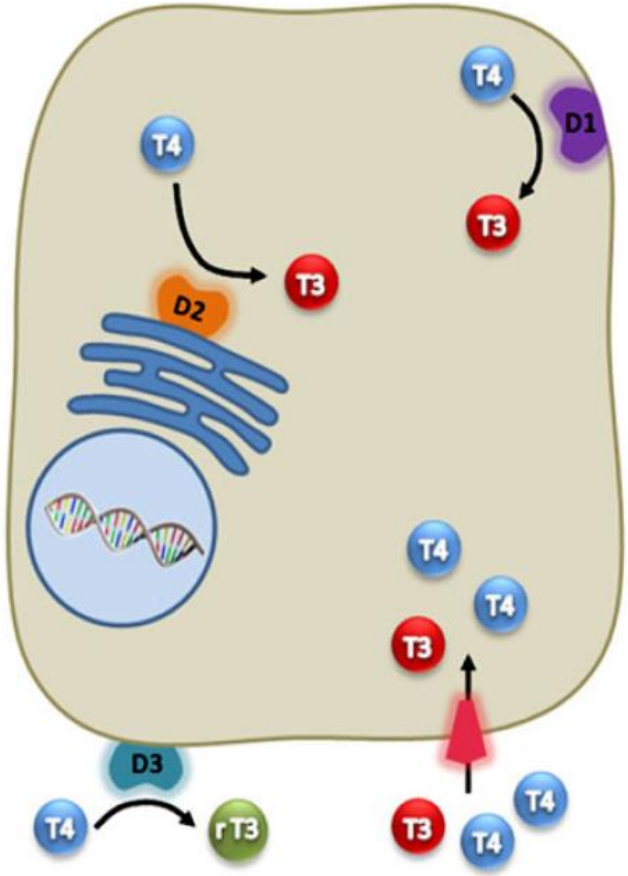
Cellular Transmembrane Transport of Thyroid Hormones

	Location	Specific For
OATP1	All except neurons	T4 & rT3
MCT8	All	T3
MCT10	All except neurons	T4 & T3

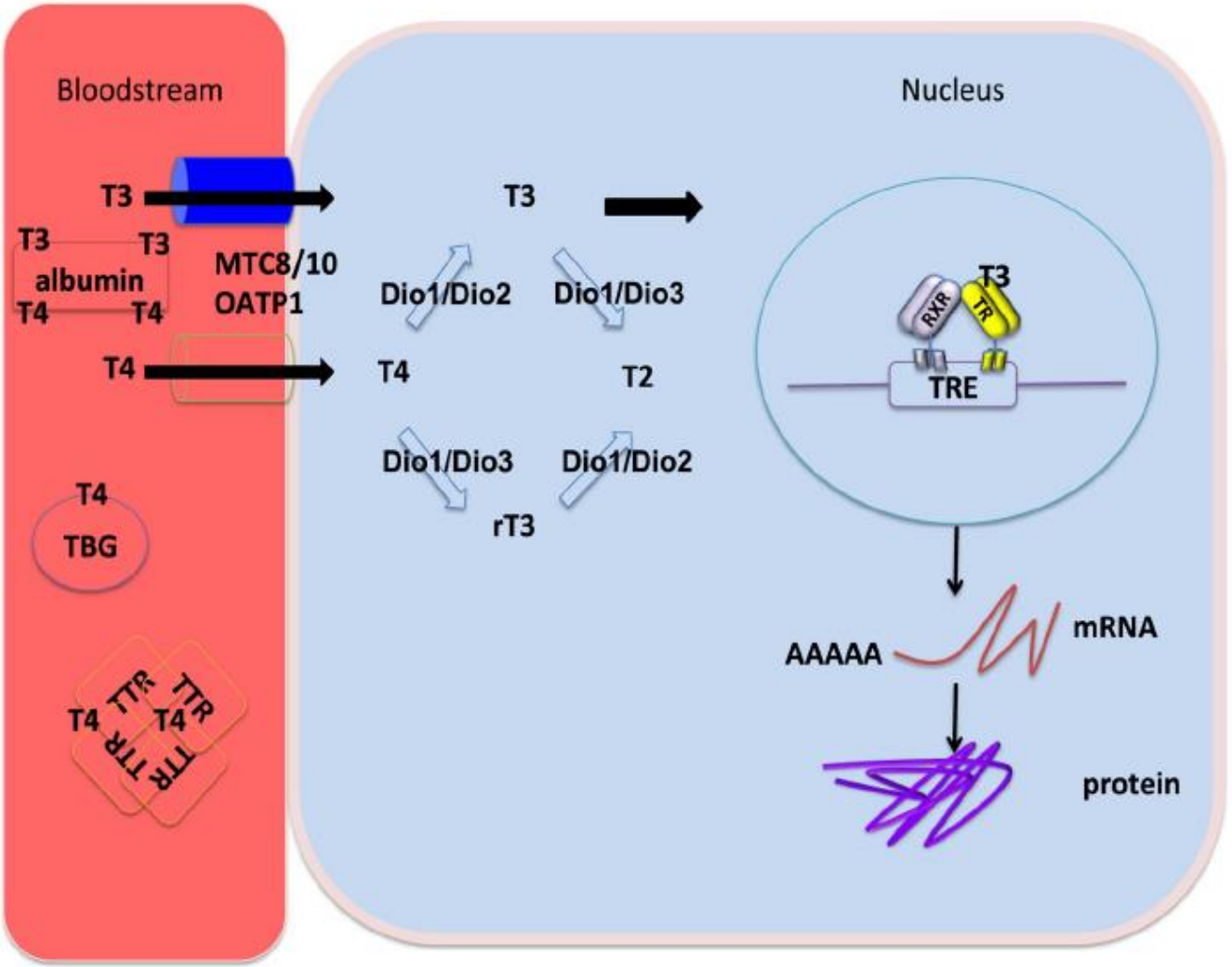
Deiodinases (DIO's)

	Location	Role
DIO1	Cell membrane/ cytosol	T4-to-T3 and rT3, largely to circulation
DIO2	Endoplasmic Reticulum (ER) (EXCEPT Neurons)	T4-to-T3, to nuclear receptor ("activation")
DIO3	Largely cell membrane/cytosol	T4-to-rT3 and T3-to-T2 ("inactivation")

Cellular Localization of DIO's



Cellular Transport & Activation of Thyroid Hormones



Mainstream Dogma: LT4 Alone Is Best

Mainstream Principles of Treating Hypothyroidism

Burch et al. ***JCEM*** 2014; 99: 2077-2085

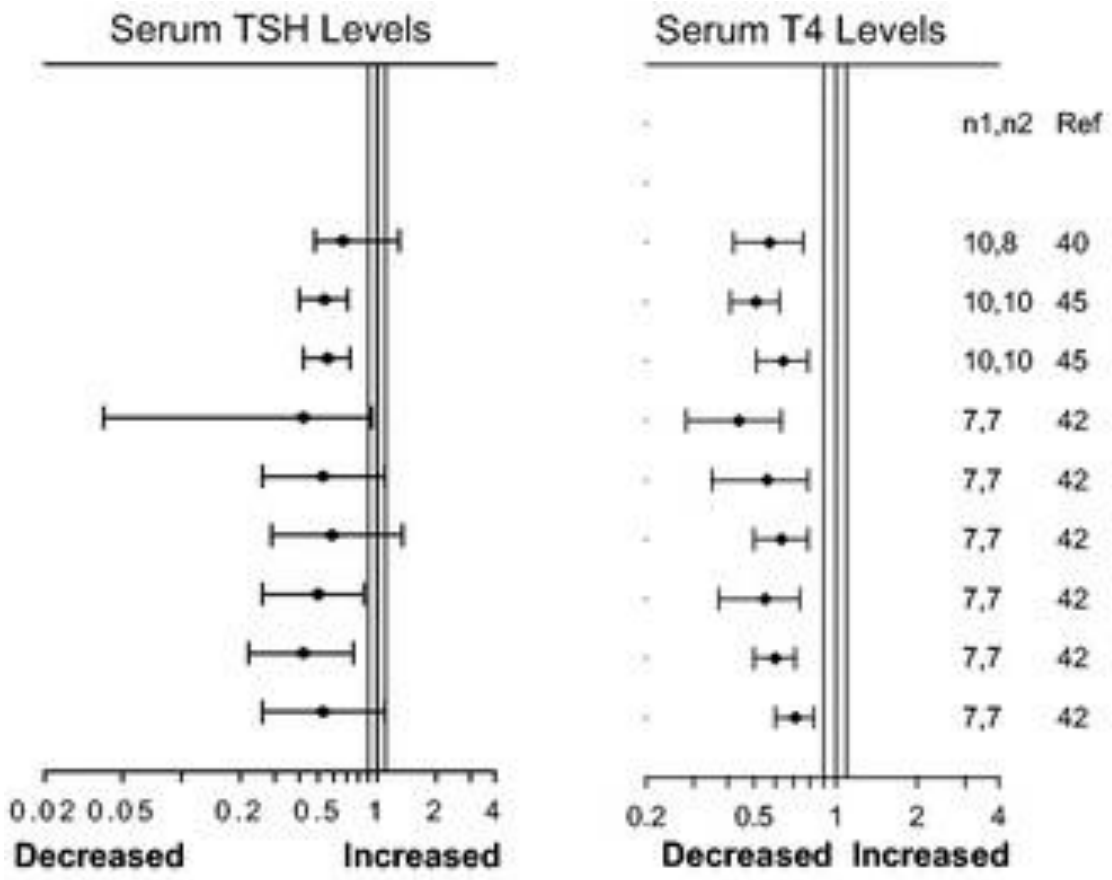
- Do not treat symptoms if TSH/FT4/TPO are normal (99%)
- Always treat if TSH > 10 mIU/ml (99%)
- Selectively treat TSH 5 – 10 mIU/ml (79%)
- Use LT4 as first-choice treatment (99%)
- Monitor therapy with TSH only (60%)

% = Endocrinologists' response to U.S. national survey

Rationale for LT4-Only Replacement

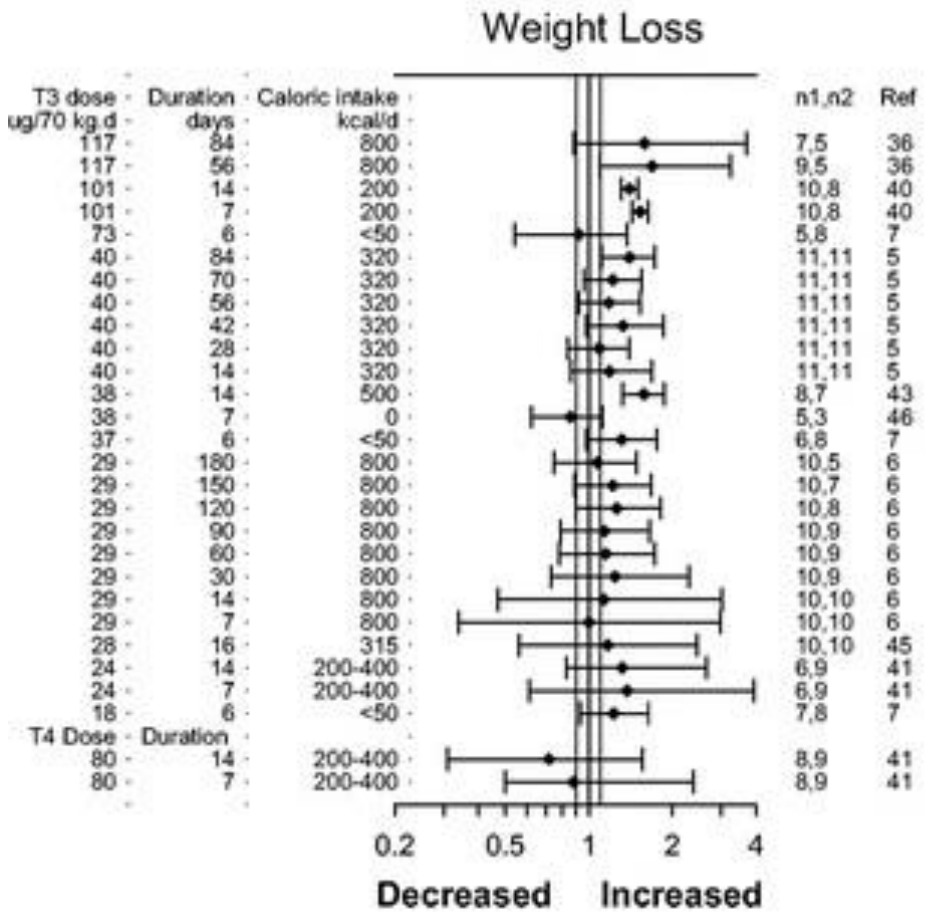
- LT4 is a pro-hormone
  (Safety)
- Generics are very affordable
- Head-to-head studies comparing LT4 vs LT4 + LT3 or DTE show equivalency
  (Non-inferiority)

Impact of LT3 Therapy on Serum TSH & FT4



Kaptein et al, JCEM 94(10):3663-3675; 2009

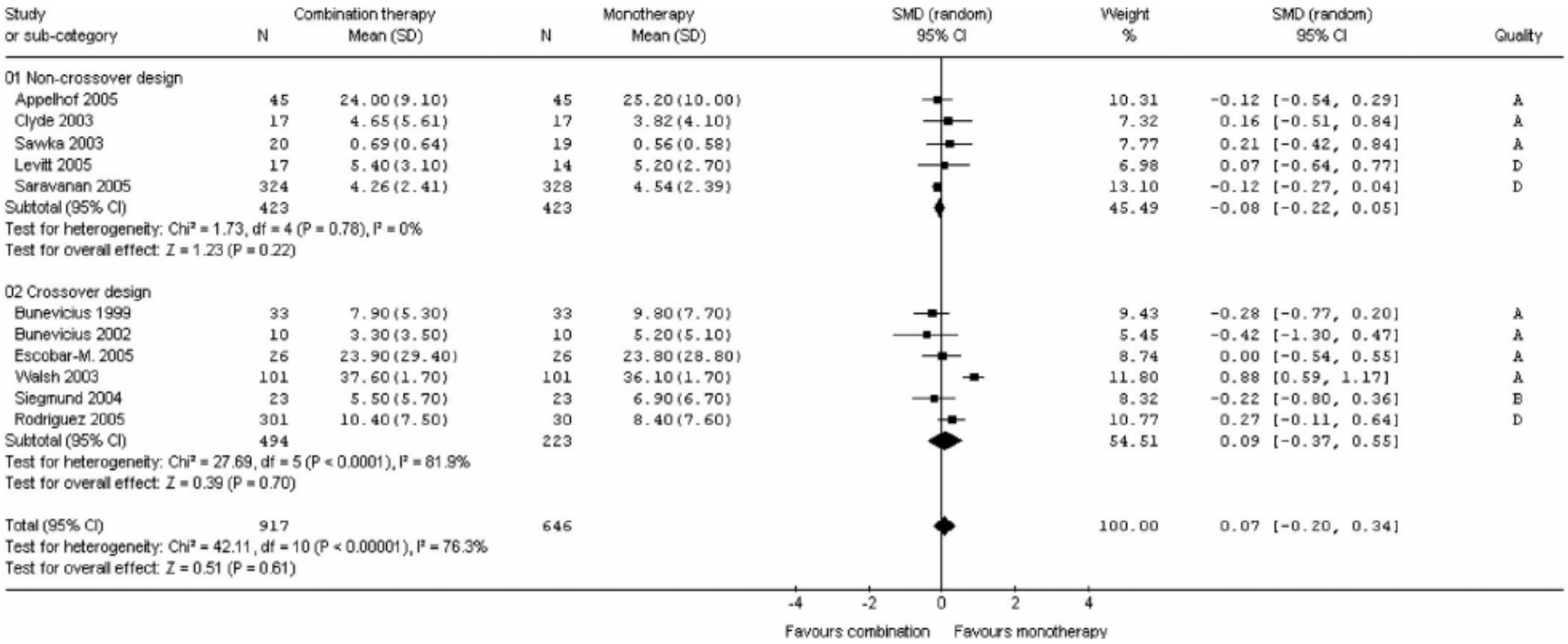
Impact of LT4 vs LT3 on Weight Loss



Kaptein et al, JCEM 94(10):3663-3675; 2009

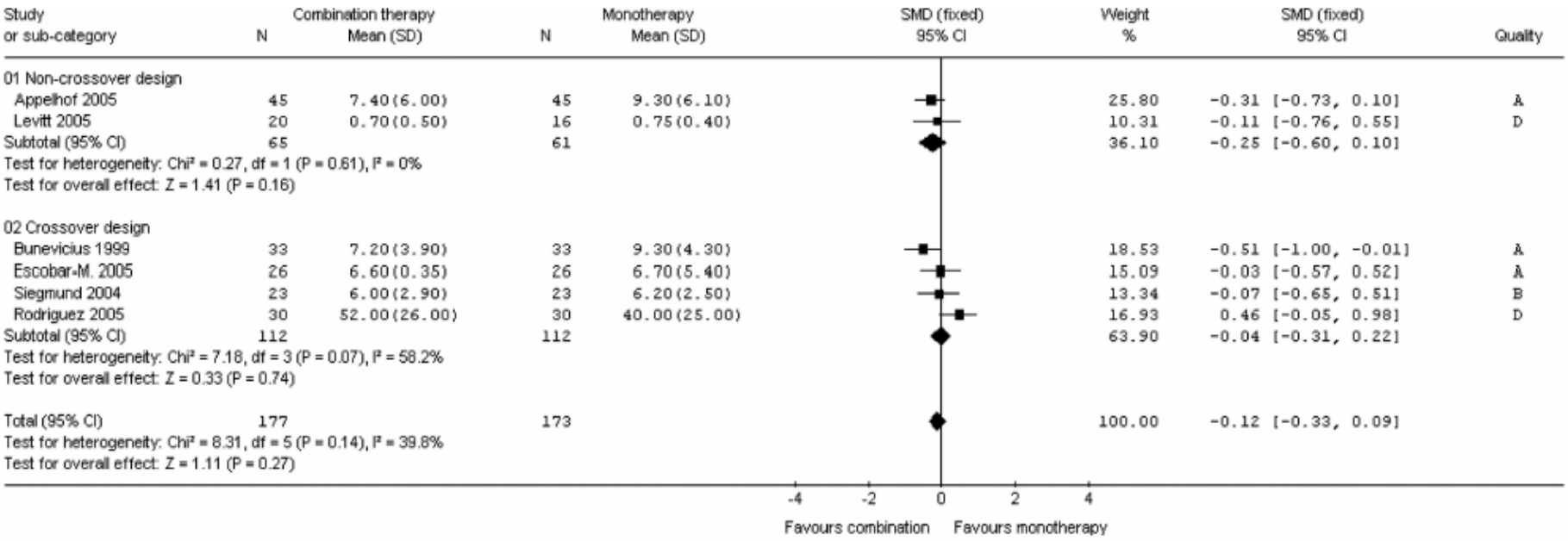
LT4 vs. LT4 + LT3 Effect on Depression Meta-analysis

Grozinsky-Glasberg et al. ***JCEM*** 2006; 91: 2592-2599



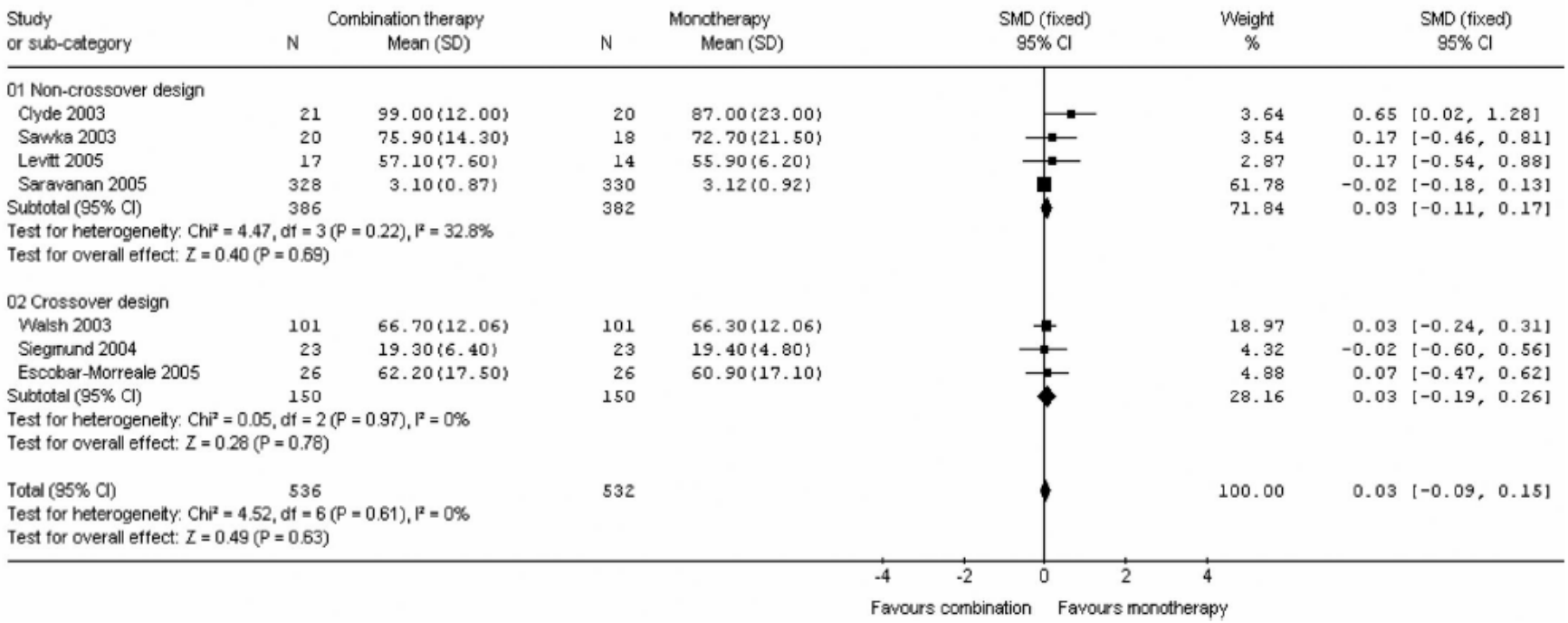
LT4 vs. LT4 + LT3 Effect on Fatigue Meta-analysis

Grozinsky-Glasberg et al. ***JCEM*** 2006; 91: 2592-2599



LT4 vs. LT4 + LT3 Effect on QOL
Meta-analysis

Grozinsky-Glasberg et al. ***JCEM*** 2006; 91: 2592-2599



Combination LT4 + LT3 Treatment: The Mainstream View

- Bunevicius et al NEJM 1999: RCT of LT4 + LT3 demonstrated improved symptoms with combination Rx vs LT4 alone
- Since then:
  - 10 additional similarly designed trials with negative results
  - 7/10 did not report undesirable effects; 3/10 identified
    - < TSH
    - ↑serum indicators of bone remodeling
    - ↑atrial arrhythmias
- Take-Home Point: Can't advocate routine administration of LT4 + LT3 (by extension, "natural" thyroid hormone is variable T4 + T3)

Summary: The Case for LT4-Only Replacement

- Supply the pro-hormone and let target tissues activate T4-to-T3 based on requirement
- Most studies comparing LT4 vs. LT4+LT3 show non-inferiority
- Persistent symptoms, in the face of normal TSH, spell "NYT"
  (**n**ot **y**our **t**hyroid)

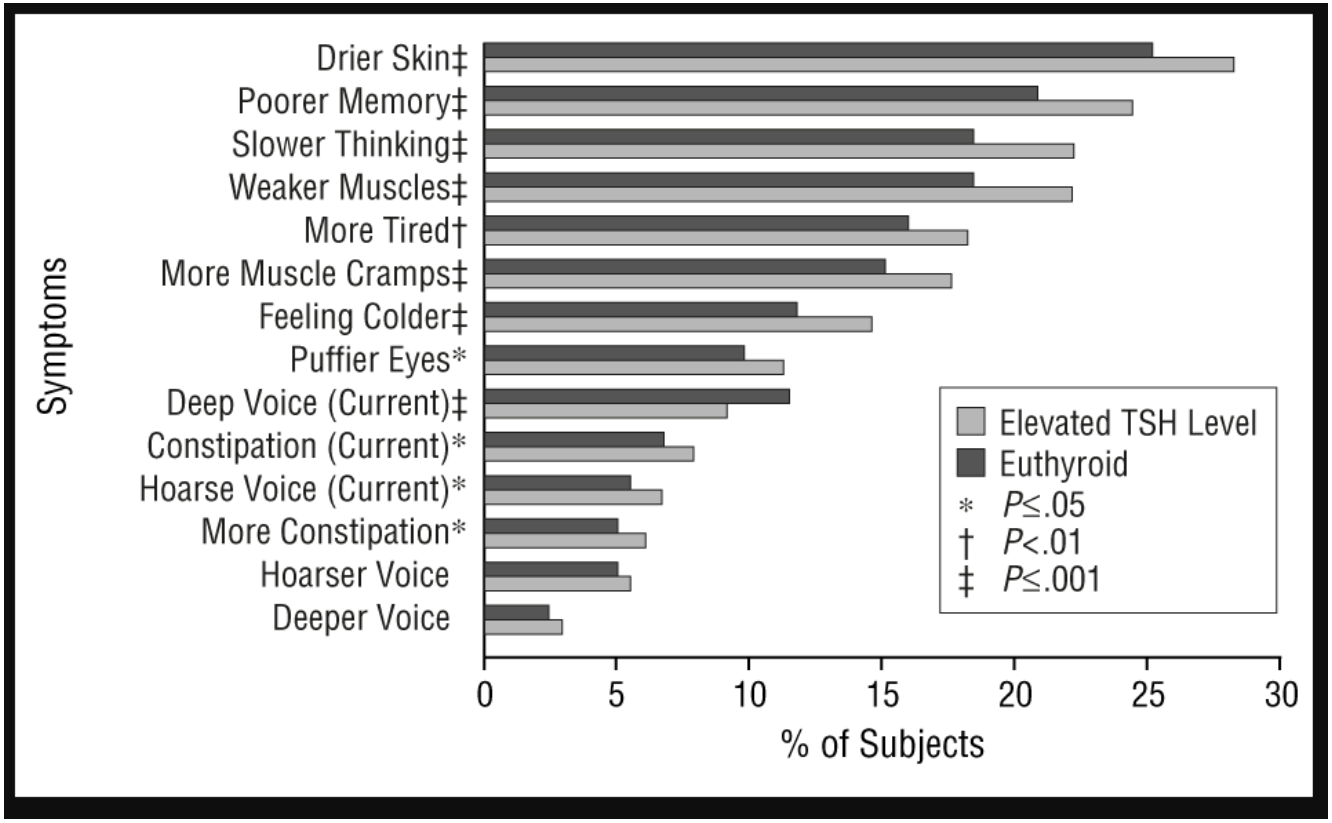
"…Dessicated thyroid hormone possess no uniquely desirable properties, and should, therefore, be retired to the place that it has earned in medical history."

--Stephen Smith, M.D., ***Archives of Internal Medicine***, 1984

But I Don’t Feel Right on LT4!

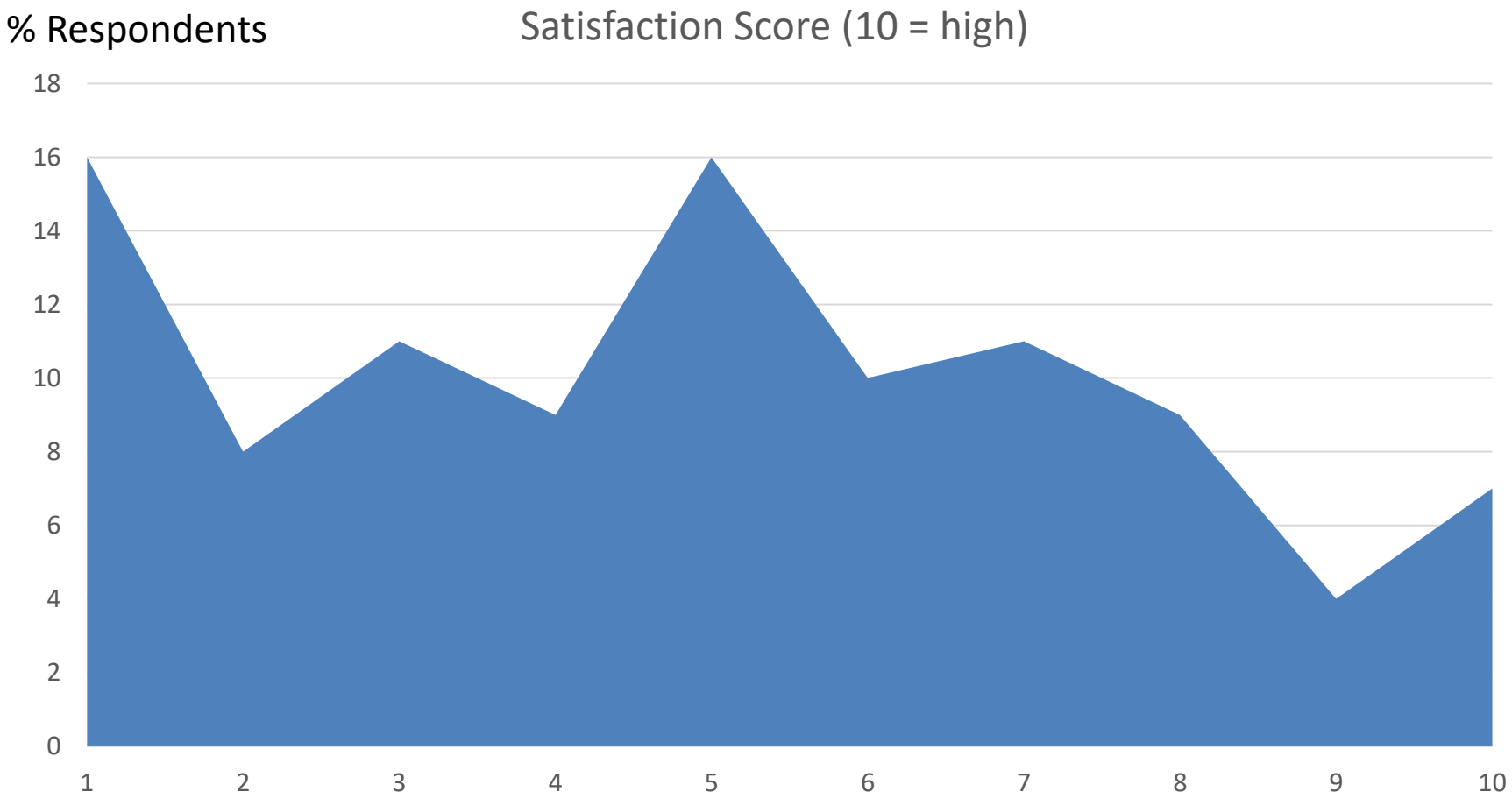
Prevalence of Persistent Symptoms in Treated Hypothyroidism (n = 1525)

Canaris et al. ***Arch Int Med*** 2000; 160:526-534



Patient Satisfaction Survey: LT4 Users (n = 6,949)

Peterson et al. ***Thyroid*** 2018; 28: 707-721



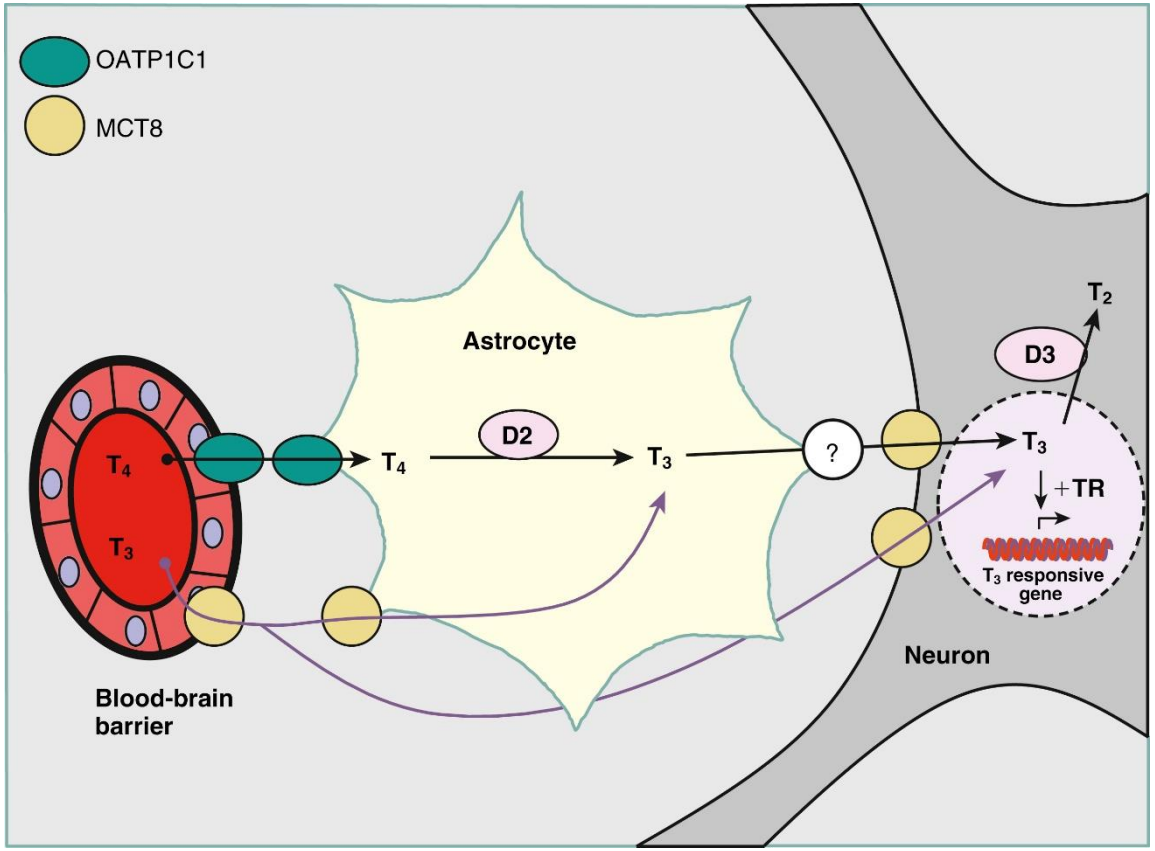
Patient Satisfaction Survey: DTE Users (n = 3,239)

Peterson et al. ***Thyroid*** 2018; 28: 707-721

Rationale for DTE

- Patient preference (“natural” vs. “artificial”)
- Persistent symptoms of hypothyroidism in many patients, on optimal LT4 replacement
- Impaired CNS conversion of T4 to T3 in some patients
- Higher T3 content to CNS, if using DTE or LT3

Thyroid Hormone Transport in the Brain



Human Knockout Model: Allan-Herndon-Dudley Syndrome (AHDS)

- Severe mental retardation and movement disorders
- X-linked
- Normal TSH, low Free T4, and elevated Free T3
- Defect = ↓ MCT8 expression in brain

LT3 for Refractory Depression

- STAR-D trial, Nieremberg et al Am J Psych 2006
- RCT of 143 patients with depression refractory to 2 or 3 drugs
- Randomized to augmentation Rx with Li or LT3
- 15-24% achieved remission (based on Hamilton depression inventory score)
- Take-Home point: T3 is an effective antidepressant

Randomized Crossover Trial LT4 vs. DTE

Hoang et al. ***JCEM*** 2013; 98: 1982-1990

- 70 subjects, mean age 50
- Hypothyroidism prevalently Hashimoto's; also included postsurgical and postablation
- 16 weeks' DTE followed by 16 weeks LT4 or converse
- Measurements = TSH; free T4; free T3; body weight; symptoms as assessed by questionaires (Beck Depression Inventory, GHQ-12, and TSQ); patient preference for Phase 1 or Phase 2 treatment, at study's end.

Results of Crossover Trial LT4 vs. DTE

Hoang et al. ***JCEM*** 2013; 98: 1982-1990

- No significant differences in TSH, either phase
- 3# weight decrease during DTE phase
- No significant difference in symptom questionnaire scores
- HOWEVER patient preference for LT4, DTE, or no preference (equal) broke down as follows:
  - No preference 32.9%
  - FT4 18.6%
  - DTE 48.6%
- Subgroup preferring DTE scored significantly better on symptom GHQ-12 and TSQ during DTE phase, AND lost the most weight (4#) by study's end.

Thr92Ala-DIO2 Polymorphisms in the Brain: Human Tissue Study

McAninch et al. ***JCEM*** 2015; 100: 920-933

- Background: 12-36% of humans are homozygous for a common polymorphism Thr92Ala point substitution in DIO2
- Cadaveric brain study (19 brains with Thr92Ala polymorphism) compared differences in gene products, nuclear TH binding of T3, and cellular location of DIO2 in wild type vs. Thr92Ala homozygotes
- Identified ↓ ER-based ubiquination of DIO2 in Thr92Ala, and
- ↑DIO2 expression in Golgi, but ↓ in ER
- Differential gene product expression, wild type vs. Thr92Ala reversible with 24 hour exposure to an antioxidant (N-acetylcysteine) implying a role for oxidative stress as a mechanism for the DIO2 location
- No difference in nuclear TH binding of T3

Thr92Ala-DIO2 Polymorphisms in the Brain: Human Tissue Study--Implications

McAninch et al. ***JCEM*** 2015; 100: 920-933

- The common Thr92Ala-DIO2 polymorphism is associated with differential cellular location (Golgi vs. ER), as compared with wild type
- The translocation of expression is associated with different T3-gene product expression, without abnormal T3 binding to the nuclear receptor
- The gene product expression is rapidly restored to wild type with a cellular antioxidant
- Oxidative stress may vary in different persons but may ultimately determine the severity of derangements leading to symptoms

LT4 vs. DTE Double-blind RCT

Carle et al. Eur Thyroid J 2017; 6:143-151

- 45 subjects (42 women) with TPO+ chronic thyroiditis
- TSH at randomization and on treatment normal
- Satisfaction with treatment = main outcome measure
- Grouping based on T4/T3 cellular transport and T4 to T3 DIO polymorphism (grouping followed data collection)

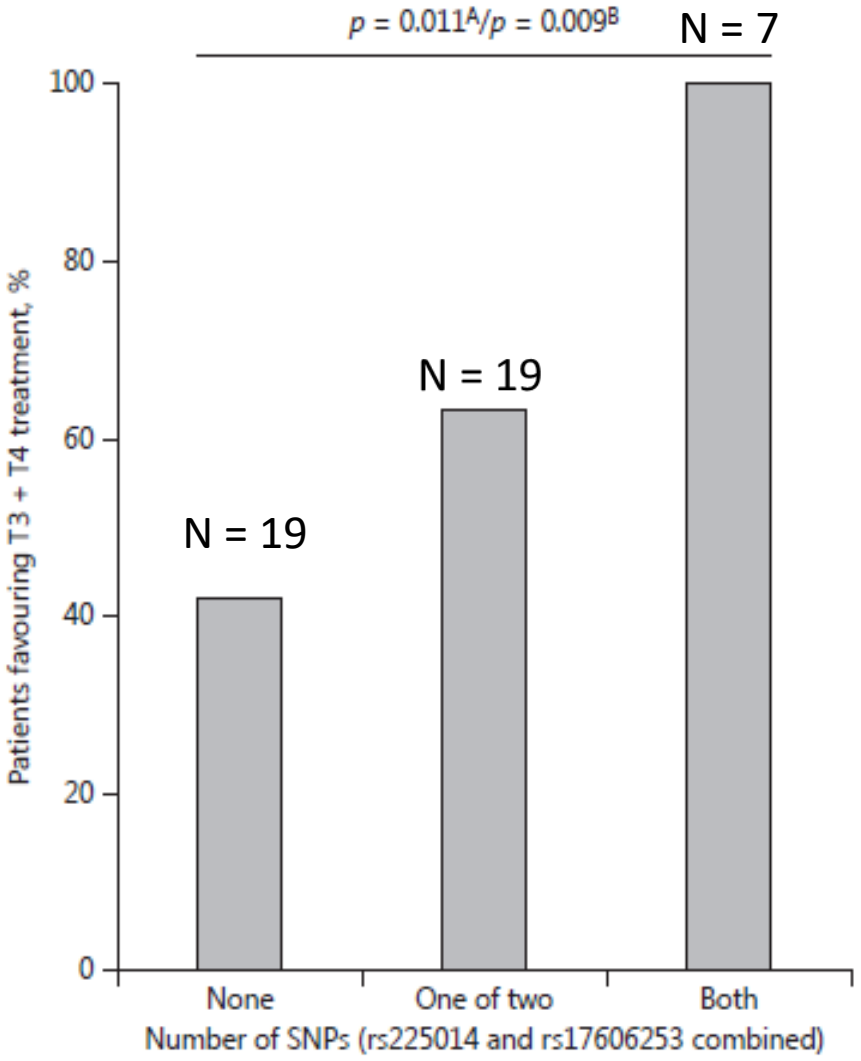
LT4 vs. DTE Double-blind RCT

Carle et al. Eur Thyroid J 2017; 6:143-151

	SNPs, *n* (wild type)	Hetero-zygous, *n* (wild type; 1 SNP)	Homo-zygous, *n* (double SNP)
DIO2			
rs225014	26 (TT)	18 (CT)	1 (CC)
rs225015	23 (GG)	18 (AG)	4 (AA)
rs12885300	14 (CC)	20 (CT)	11 (TT)
rs225011	41 (TT)	6 (GT)	0 (GG)
MCT10			
rs17606253	31 (TT)	13 (CT)	1 (CC)

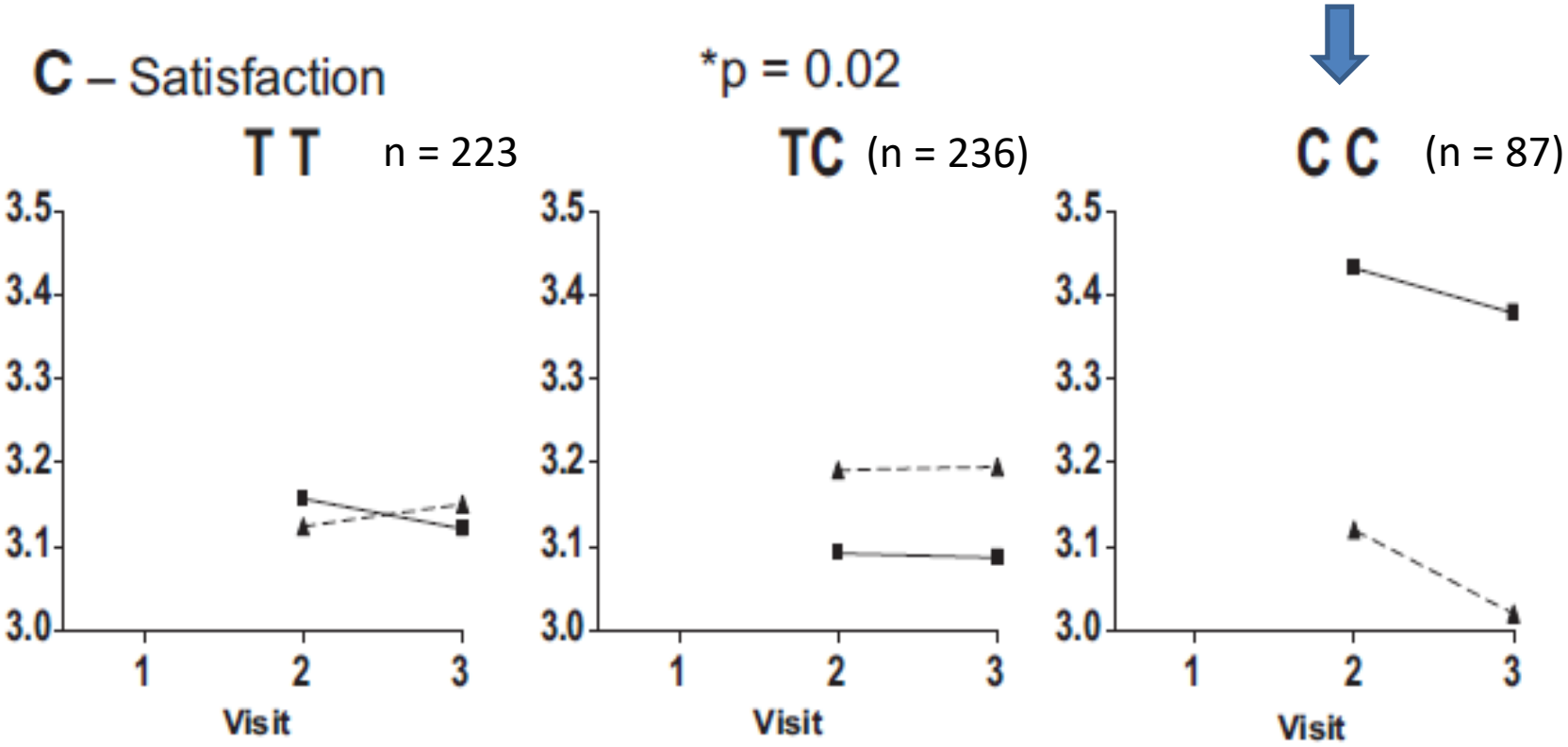
LT4 vs. DTE Double-blind RCT

Carle et al. Eur Thyroid J 2017; 6:143-151



LT4 vs. LT4+LT3 in DIO2 Thr92Ala Polymorphism RCT (n = 556)

Panicker et al. JCEM 2009; 94:1623-1629



Y Axis = Score on GHQ-12
Dashed lines = LT4
Solid lines = LT4 + LT3

Thyroid Societies Expert Panel Recommendations

Jonklaas et al. ***Thyroid*** 2021; 31: 156 - 182

- Clinical trials of DIO2 polymorphisms and effectiveness of LT4-only vs. DTE or LT4 + LT3
- Studies should include patients dissatisfied with current treatment
- Primary outcomes measures should include patient preference
- Placebo-controlled RCT design of trials, and extended length of trials (a year or longer) is important

Practical Considerations with Dessicated Thyroid Hormone

- Human T3:T4 Ratio in thyroidal thyroglobulin ~ 1: 12
- Animal (porcine) T3:T4 Ratio ~ 1:4
- Thus: Serum T4 often low, in dessicated thyroid Rx
- T3 serum levels depends on time from last dose (18 hour half-life)
- Goals of treatment:
  - “Happy pituitary” (i.e., normal serum TSH)
  - “Happy patient”

Conclusions & Recommendations: Levothyroxine vs. Dessicated Thyroid

- Levothyroxine dose-titrated to normal serum TSH should be first recommendation
- Patients with persistent “brain fog” and/or weight gain/difficulty losing weight, can be candidates for dessicated thyroid hormone treatment
- Athyrotic patients (post-thyroidectomy or post-ablation with radioactive iodine) have no thyroidal source of T3, and may stand to benefit the most
- Goal will be normal TSH, knowing that free T4 will likely be “low”
- Up to 20% of patients so treated may have durable response
- If not, recommend reverting to levothyroxine therapy

What a piece of work is a man!
-Shakespeare, ***Hamlet***

“We may never know as much as we think we know.”
--Frank Davidoff, MD, MACP