Common Thyroid Dilemmas

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Conflicts of Interest

- No speaking or consulting
- No conflicts relevant to this talk
- Research money to institution for clinical trial in pituitary disease:
  - Pfizer
  - Chiasma
  - Corcept
  - Novo-nordisk
  - Novartis
Thyroid Anatomy
A 53 year old man comes in for his yearly physical. His only known health problem is GERD. A good friend of his was just diagnosed with hypothyroidism and now feels much better on treatment. He has no complaints and feels well. He asks if his thyroid would typically be checked as part of his physical exam.

- A. Yes, it should, almost all guidelines support it
- B. No, there is no reason to screen an asymptomatic patient for thyroid disease
- C. There may be a role for selective screening, but not in this patient
- D. He has gained 5 pounds, since last year, this is a good reason to screen him
You perform thyroid function tests as part of yearly, routine blood work in a 74 year old woman. She has no history of cardiac disease of any kind. She feels cold and constipated. Her TSH comes back at 7mIU/L. Her Ft4 is normal. You should:

A. Check TPO antibodies and consider treatment based on her symptoms

B. Withhold treatment and recheck levels in one year with a plan to treat if her TSH rises above 10 mIU/L because current guidelines recommend this

C. Consider treatment due to the fact that her ischemic heart disease risk will be lowered by treatment

D. Withhold treatment because it may raise her cardiac risk
You check thyroid function tests at the request of an asymptomatic 40 year old patient. Her TSH comes back at 0.22 mIU/L (normal 0.35-4.5). You perform a FT3 and FT4 and they are normal.

- A. She has subclinical hyperthyroidism. Repeat the level in 2-3 months
- B. She has subclinical hyperthyroidism and should have a radioactive iodine ablation
- C. She has subclinical hyperthyroidism. There is not enough evidence to state whether these labs are associated with any clinical risks or not.
- D. She needs an MRI of the pituitary gland.
A 36 year old female comes to the office. She has Hashimoto’s thyroiditis, diagnosed as a teenager. Her TSH was 35 mIU/ml at diagnosis. She is currently on generic levothyroxine and her TSH is 1.1 mIU/ml. She feels very tired all the time and is napping frequently. She has done a great deal of research on her thyroid condition and requests armour thyroid. You should:

A. Prescribe armour immediately
B. Question her closely about possible sleep apnea
C. Tell her there is no role for armour thyroid in the treatment of hypothyroidism
D. Suggest cytomel instead (T3 or triiodothyronine)
Objectives

- Discuss whom to screen for thyroid dysfunction
- Discuss when you might treat subclinical hypothyroidism and clinical outcomes associated with the condition
- Discuss when you might treat subclinical hyperthyroidism and clinical outcomes associated with the condition
- Discuss the treatment of hypothyroidism and the use of alternate thyroid hormone preparations
- Revisit the questions
Screening for thyroid dysfunction

- Current recommendations from the US Preventive Task force are not helpful
  - In non-pregnant, asymptomatic adults, no official recommendation
  - Insufficient evidence to balance benefits and harms of screening
  - ?
  - This discussion does not include pregnancy, a time of intensive screening
Percentage of Euthyroid, Subclinical and Hypothyroid Patients Reporting Symptoms

60% euthyroid have ≥ 1 symptom
15% ≥ 4 symptoms

R5. Clinical scoring systems should not be used to diagnose hypothyroidism. Grade A, BEL 1

Canaris et al.
# Current Screening Recommendations

<table>
<thead>
<tr>
<th>Organization</th>
<th>Screening recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>College of American Pathologists (13)</td>
<td>Women ≥50 year of age should be screened “if they seek medical care;” all geriatric patients should be screened on admission to the hospital and at least every 5 years</td>
</tr>
<tr>
<td>American Academy of Family Physicians (9)</td>
<td>Patients ≥60 years of age should be screened</td>
</tr>
<tr>
<td>American College of Obstetrics and Gynecology (14)</td>
<td>Women in “high-risk groups” (those with autoimmune disease or a strong family history of thyroid disease) should be screened starting at 19 years of age</td>
</tr>
<tr>
<td>American College of Physicians (12)</td>
<td>Women ≥50 years of age with an incidental finding suggestive of symptomatic thyroid disease should be evaluated</td>
</tr>
<tr>
<td>U.S. Preventive Services Task Force (10)</td>
<td>Insufficient evidence for or against screening</td>
</tr>
<tr>
<td>Royal College of Physicians (11)</td>
<td>Screening of the healthy adult population unjustified</td>
</tr>
<tr>
<td>American Association of Clinical Endocrinologists/ American Thyroid Association (5)</td>
<td>Aggressive case finding</td>
</tr>
<tr>
<td>Latin American Thyroid Society (6)</td>
<td>Aggressive case finding</td>
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American Association of Clinical Endocrinologists: Aggressive Case Finding

<table>
<thead>
<tr>
<th>Screening for Hypothyroidism</th>
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<tbody>
<tr>
<td>Autoimmune disease</td>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td>First Degree Relatives</td>
<td>Psychiatric disease</td>
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<tr>
<td>Anemia</td>
<td>Cardiovascular disease</td>
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<tr>
<td>Genetic disorders (Down or Turner's)</td>
<td>Pulmonary hypertension</td>
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<tr>
<td>Neck radiation</td>
<td>Medications</td>
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<tr>
<td>Thyroid surgery</td>
<td>Osteoporosis</td>
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<tr>
<td>Abnormal exam</td>
<td>Pituitary disease</td>
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</tbody>
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A. Yes, it should, almost all guidelines support it
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Subclinical vs. Clinical Thyroid Disease

- Subclinical refers to TSH abnormalities in the absence of frank derangement of Ft3 and Ft4
- Subclinical hypothyroidism = high TSH, normal Ft3 and Ft4
- Subclinical hyperthyroidism = low TSH, normal Ft3 and Ft4
- Whether or not “subclinical” is an appropriate term is debatable
- Term implies no clinical consequences
- There may be
  - Hypo: CHF risk
  - Hyper: Afib and osteoporosis risk
Frank, Severe Hypothyroidism - Clinical Signs and Symptoms

- Bradycardia
- Diastolic hypertension
- Narrowed pulse pressure
- Cold intolerance
- Fatigue
- Prolonged QT interval
- Predisposition to ventricular arrhythmia (?)
- Pericardial effusion
What is a normal TSH?

- Historical range is likely contaminated by those with thyroid disease (Hashimoto’s thyroiditis)
- Lab normals are typically 0.35-4.5 mIU/L
- Substantial evidence exists that true, healthy, younger population normal is likely between 0.35-2.5 mIU/L
TSH Population Reference Range

95% Limits

0.3-0.4
1.3-1.4
2.5-3.0
~4-5
10

TSH mIU/L

Reasons for the skew BESIDES AGE

- Euthyroid Outliers - inherent TSH lability
- Measurement of bioinactive TSH isoforms
- TSH receptor polymorphisms - ↓ TSH sensitivity
- Occult autoimmune thyroid dysfunction (AITD)

Clinical Practice Guidelines for Hypothyroidism in Adults: AACE and ATA 2012
Severity of Primary Hypothyroidism by Thyroid Levels

- TSH rises first and abruptly
- Decline of T4 and T3 slower and later

Clinical Practice Guidelines for Hypothyroidism in Adults: AACE and ATA 2012
When to treat Subclinical Hypothyroidism

- Essentially all would advocate treatment for TSH over 10 mIU/ml
- Many would advocate treating in the 4.5-10 mIU/ml range
- Some would advocate treatment in the 2.5-4.5 mIU/ml range with evidence of Hashimoto’s thyroiditis (no guideline support)
- There is some evidence of improvement in lipids, CIMT, and endothelial function even in the lowest range above
- Historically no clear evidence of improved clinical outcomes in treating in any of these ranges
  - Emerging but still confusing data regarding CHF
What is a Normal TSH?

- Reasonable to get TPO antibodies in those with elevated TSH
- If positive, likely have Hashimoto’s and may progress
- Approximately 10% of US population has positive antibodies
- Half of those go on to develop frank hypothyroidism
- 5% of US female population on levothyroxine
- Female to male prevalence diminishes with age
- Are you helping them?
When Should Anti-thyroid Antibodies Be Measured?

- R1. Thyroid peroxidase antibody (TPOAb) measurement should be considered when evaluating patients with subclinical hypothyroidism. Grade B, BEL 1; Downgraded. If positive, hypothyroidism rate of 4.3% versus 2.6% per year. Therefore, may or may not influence the decision to treat.

- Anecdotally, most endocrinologists would use this information
# Autoimmune Thyroid Disease: 20 Year % Probability of Developing Hypothyroidism

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
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<tbody>
<tr>
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<td>1</td>
<td>6</td>
<td>1</td>
<td>6</td>
<td>3</td>
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<tr>
<td>70</td>
<td>4</td>
<td>21</td>
<td>4</td>
<td>21</td>
<td>9</td>
</tr>
</tbody>
</table>

TPOAb (+) with TSH of 3-4 30-60% chance of developing hypothyroidism over 20 years; TPOAb (-), <20%

Sites of Action of Thyroid Hormone on the Heart with Hypothyroidism

Based on Klein and Danzi, In: The Thyroid 2004
Hypothyroidism and the Heart

- Hypertension (Diastolic)
- Diastolic Dysfunction
- Elevated Cholesterol*
- Long Q-T Syndrome
- Serum CK Elevation (*Statin Hazard?)
- Coagulopathy
Best to Date NON RCT--Observational: Benefit of Treatment?

- UK General Practitioner: In ~50% of individuals 40-70 yrs old treated with L-thyroxine, (TSH 4.5-10) hazard ratio cardiac events reduced (0.67, CI 0.49 – 0.92)

- Cleveland Clinic: high risk ASCVD Clinic (TSH 6.1-10 and >10) who were under 65 yrs old and not treated with LT4 had higher all-cause mortality

Arch IM 2012
McQuade, Thyroid 2011
Heart Failure Events by TSH

<table>
<thead>
<tr>
<th>TSH (mlU/L)</th>
<th>Events / Participants</th>
<th>HRs (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.0-19.9</td>
<td>40 / 224</td>
<td>1.86 (1.27-2.72)</td>
</tr>
<tr>
<td>7.0-9.9</td>
<td>54 / 422</td>
<td>1.65 (0.84-3.23)</td>
</tr>
<tr>
<td>4.5-6.9</td>
<td>156 / 1422</td>
<td>1.01 (0.81-1.26)</td>
</tr>
</tbody>
</table>

Until RCTs performed, data favors treating younger, higher TSH values (>10)
Treatment of TSH between 5 and 10?
Depends...

R16. Treatment should be considered particularly if they have symptoms suggestive of hypothyroidism, positive TPO antibodies or evidence of atherosclerotic cardiovascular disease, heart failure or have associated risk factors for these diseases.

Grade B, BEL 1; evidence not fully generalizable to stated recommendation and there are no prospective, interventional studies.

Treatment of TSH levels > 10 is recommended

R15. Patients whose serum TSH levels exceed 10 mIU/L are at increased risk for heart failure and cardiovascular mortality, and should be considered for treatment with L-thyroxine.

Grade B, BEL 1; not generalizable and meta-analysis does not include prospective interventional studies.

- Hypothyroid patients treated with normalized TSH are still more likely to feel poorly (Saravan Clinical Endo 2002; Boeving Thyroid 2011)

No Clinical Evidence that Adjusting TSH from (2.0 - 4.8)--> (0.3-1.99)-->(<0.3) Produces Benefit


<table>
<thead>
<tr>
<th>TABLE 3. Clinical parameters (descriptive mean ± SEM) analyzed by treatment (T₄ dosage) and by serum TSH at the end of treatment periods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T₄ dosage</strong></td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
</tr>
<tr>
<td>Ankle jerk relaxation time (msec)</td>
</tr>
<tr>
<td>Zulewski score</td>
</tr>
</tbody>
</table>

*Post hoc testing using the Scheffe procedure showed that middle and high doses were significantly different from low dose (P < 0.01).
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Initiating therapy in overt hypothyroidism

- Recommendation 22.7.1: When initiating therapy in young healthy adults with overt hypothyroidism, beginning treatment with *full* replacement doses should be considered. Grade B, BEL 2

- Recommendation 22.7.2: When initiating therapy in patients older than 50-60 years old with overt hypothyroidism, without evidence of coronary heart disease, an L-thyroxine dose of 50 mcg daily should be considered. Grade D, BEL 4

Clinical Practice Guidelines for Hypothyroidism in Adults: AACE and ATA 2012
Initiating treatment in subclinical hypothyroidism

- Recommendation 22.8: In patients with subclinical hypothyroidism initial L-thyroxine dosing is generally lower than what is required in the treatment of overt hypothyroidism.

- A daily dose of 25 to 75 mcg should be considered, depending on degree of TSH elevation. Further adjustments should be guided by clinical response and follow up laboratory determinations including TSH values. Grade B, BEL 2
Question 3.12 How should hypothyroidism be treated and monitored?

R23. L-thyroxine should be taken with water consistently 30 to 60 minutes before breakfast or at bedtime 4 hours after the last meal. It should be stored properly per product insert and not taken with substances or medications that interfere with its absorption.

Grade B, BEL 2.
Hyperthyroidism

Clinical signs and symptoms of overt disease

- Palpitations
- Exercise intolerance
- DOE
- Systolic HTN
- Hyperdynamic precordium
- Angina
- Atrial fibrillation/sinus tachycardia
- LVH
- Edema
- CHF
Subclinical hyperthyroidism

- Defined as subnormal TSH with normal Ft3/Ft4
- Can be caused by Graves’ disease or thyroiditis
- Most common cause is a multinodular goiter, but Graves’ disease and uninodular goiter is possible
- Deserve and uptake and scan as first test depending on severity
- Ultrasound is scan suggests nodular disease
Cumulative Incidence of Atrial Fibrillation among Subjects 60 Years of Age or Older, According to Serum Thyrotropin Values at Base Line.

Increased risk of developing atrial fibrillation in patients with subclinical hyperthyroidism
Atrial Fibrillation

- Clear association with hyperthyroidism
- 2-20% of thyrotoxic patients will have this in some series
- One series found an afib prevalence in 2.3% of controls and in 13.8% of hyperthyroid patients
- TSH suppression of less than 0.1 with normal Ft3 and Ft4 seems to carry the same risk as overt, frank hyperthyroidism
- Treatment is beta blockade, anti thyroid drugs, and permanent therapy with RAI or surgery as indicated
Other Adverse Outcomes

- Progression to hyperthyroidism
- Hip fractures
- CHD mortality
- Hip and non spine fracture
Subclinical Hyperthyroidism: Initial Evaluation

- Helpful to break into Grades
  - Grade I: TSH 0.1-0.39 miU/l (or whatever low normal is in your lab)
  - Grade II: TSH less than 0.1 miU/l
- Check other thyroid function tests (Free T4 and Free T3)
- Consider non-thyroidal illness, pituitary insufficiency, exposure to iodine and steroids
- If normal, retest in 2-3 months
Subclinical Hyperthyroidism: Ongoing Follow up

- Grade 1 can be observed
- Grade two:
  - Uptake and scan
  - Ultrasound if uptake and scan suggest a nodule or multiple nodules
  - Consider THRab or TSI to evaluate for Graves’ disease
Subclinical Hyperthyroidism: Treatment, Over Age 65

- Due to well established risks of afib, should be treated just as frank, outright hyperthyroidism in most patients
- Grade 2 and over 65, treat
- Grade 1, consider treatment
- Bone density scan and ECG/Doppler/Echo are appropriate in selected patients
- Whether it causes osteoporosis has not been answered definitively
- Surgery, RAI, Medications all options
Subclinical Hyperthyroidism, Younger Patients

- Treat if Grade 2 and symptomatic
- Treat if a clearly defined cause (Graves’ or nodules)
- OK to follow Grade 2 if completely asymptomatic, may get a remission
- Grade 1, observe if no clear cause, no symptoms, normal scans
You check thyroid function tests at the request of an asymptomatic 40 year old patient. Her TSH comes back at 0.22 mIU/L (normal 0.35-4.5). You then perform a T3 and T4 and they are normal.

- A. She has subclinical hyperthyroidism. Repeat the level in 2-3 months
- B. She has subclinical hyperthyroidism and should have a radioactive iodine ablation
- C. She has subclinical hyperthyroidism. There is not enough evidence to state whether these labs are associated with any clinical risks or not.
- D. She needs an MRI of the pituitary gland.
Thyroid Hormone Replacement

- The still-symptomatic patient with normal thyroid tests is a conundrum
- Very time-consuming
- Guidelines have been unhelpful and a bit dogmatic
- May patients are interested in T3 replacement
- Verdict is IN on the internet: DO IT!
- Helps to have a systematic approach
T4 to T3 conversion

Peripheral Conversion of Thyroxine to Triiodothyronine

Conversion is by the enzyme iodinase which is specific for the 5 or 5' position

Tetraiodothyronine (T₄, Thyroxine)

3,5,3' Triiodothyronine (T₃) Active
33% (25 mcg) 5 mcg directly from Thyroid

Deamination, Decarboxylation, Conjugation glucuronide sulphate

Diatiodothyronine (Reverse T₃) Inactive
46% (35 mcg)

3,3',5' Triiodothyronine (Reverse T₃) Inactive < 5 mcg from Thyroid
Fig. 2. The distribution of 12 monthly measurements of total T₄ in 15 healthy men (□) and in one individual, number 11 (■). The distribution in one individual is about half the width of the distribution in the group.
Primary Hypothyroidism

Figure 3. Mean Prethyroidectomy $T_3$ and $T_3$ at Time Point 4 for Patients With Benign Thyroid Disease or Thyroid Cancer

- **Benign Thyroid Disease**
  - (n = 33)

- **Thyroid Cancer**
  - (n = 17)

$T_3$ indicates triiodothyronine. Mean prethyroidectomy $T_3$ (mean of time points 1 and 2) and $T_3$ at time point 4 (postthyroidectomy) measured by immunoassay are plotted on a single line. Each line is an individual patient. Filled circles and vertical lines indicate mean (SD), respectively. To convert $T_3$ to nmol/L, multiply by 0.0154.

JAMA 2008. Triiodothyronine levels in athyreotic individuals during levothyroxine therapy
Has a Role in the Treatment of Hypothyroidism Been Demonstrated with T3?

- Endpoints are subjective in most trials
- Trials have been relatively short
- Studies to date mixed...and meta-analyses generally negative, but not completely
- Combination therapy still not yet completely understood in the setting of patient preferences
Box 2
Recommended Evaluation for Patients Who Have Persistent Symptoms Despite Normalization of Serum Thyrotropin Concentrations While on Levothyroxine Therapy

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<tr>
<th>Evaluation</th>
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<td>Complete history and physical examination</td>
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<td>General laboratory evaluation</td>
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<tr>
<td>Comprehensive metabolic panel</td>
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<tr>
<td>Complete blood cell count</td>
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<tr>
<td>Erythrocyte sedimentation rate</td>
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<tr>
<td>Celiac disease testing</td>
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<tr>
<td>Sleep apnea screening or testing</td>
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<tr>
<td>Endocrine laboratory evaluation</td>
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<tr>
<td>25-Hydroxyvitamin D</td>
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<tr>
<td>Thyroid antibodies</td>
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<tr>
<td>Serum cortisol</td>
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<tr>
<td>Consider a cosyntropin stimulation test</td>
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<tr>
<td>Study</td>
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<td>-----------------------------</td>
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<tr>
<td>Bunevicius (32,33)</td>
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<td>Walsh (34)</td>
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<td>Apellhof (39)</td>
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<tr>
<td>Escobar-Morreale (40)</td>
</tr>
<tr>
<td>Rodriguez (41)</td>
</tr>
<tr>
<td>Regalbuto (42)</td>
</tr>
<tr>
<td>Slawik (43)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

<sup>a</sup> Patient preference for the combined levothyroxine and liothyronine treatment. NA indicates the patients were not asked about their preference.
L-T4 is the Preferred Treatment

- **R22.1** Patients with hypothyroidism should be treated with L-thyroxine monotherapy Grade A, BEL1.

- **R22.2** Evidence does not support using L-T4 and L-T3 combinations to treat hypothyroidism. Grade B, BEL1.

- Not considered Grade A because unresolved issues raised by studies reporting some patients prefer and some patient subgroups may benefit from L-T4 and L-T3 combination.

Some Patients May not Convert T4 to T3 Well:

There are subtypes of the deiodinase gene (present in 16% of a recent study population) and associated with:
- Worse baseline GHQ scores in patients on LT4
- Enhanced response to combination T(4)/T(3) therapy, but did not affect serum thyroid hormone levels

Panicker, 2009 JCEM
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Recommended Management Options for Patients Who Have Persistent Symptoms Despite Normalization of Serum Thyrotropin Levels With Levothyroxine Therapy</strong></td>
</tr>
</tbody>
</table>

- Well-balanced diet: adequate amounts of fruits, vegetables and high value protein
- Regular exercise: 30 to 45 minutes daily, 6 days/week; combination of aerobic and resistance work
- Good sleep habits: go to bed at the same time 5 to 6 nights each week; sleep 7 to 8 hours per night
- Stress reduction: relaxation, biofeedback, entertainment, meditation, yoga, counseling
- Depression management: biofeedback, counseling, medications
- Medical illness management: appropriately treat existing medical illness, comanage with primary care physician
- Optimize levothyroxine therapy: maintain serum thyrotropin in 0.5-2.0 mIU/L range
- Change to another levothyroxine brand: be knowledgeable about medication fillers and colors
- Consider combination levothyroxine and liothyronine therapy
Question

- A 36 year old female comes to the office. She has Hashimoto’s thyroiditis, diagnosed as a teenager. Her TSH was 35 mIU/ml at diagnosis. She is currently on generic levothyroxine and her TSH is 1.1 mIU/ml. She feels very tired all the time and is napping frequently. She has done a great deal of research on her thyroid condition and requests armour thyroid. You should:
  - A. Prescribe armour immediately
  - B. Question her closely about possible sleep apnea
  - C. Tell her there is no role for armour thyroid in the treatment of hypothyroidism
  - D. Suggest cytomel instead (T3 or triiodothyronine)
T4/T3: My Personal Approach

- Rarely do I suggest it
- I don’t battle about it
- I have tried to be more open-minded about it
- Levels do tend to be less reliable
- Higher risk of TSH suppression, an adverse event
- Risks of this discussed, afib specifically
- It often helps answer a question
  - Anecdotally 30% like it
  - 50% can’t tell a difference
  - 30% dislike it