

Concerns regarding Quality of Currently Marketed Levothyroxine Products

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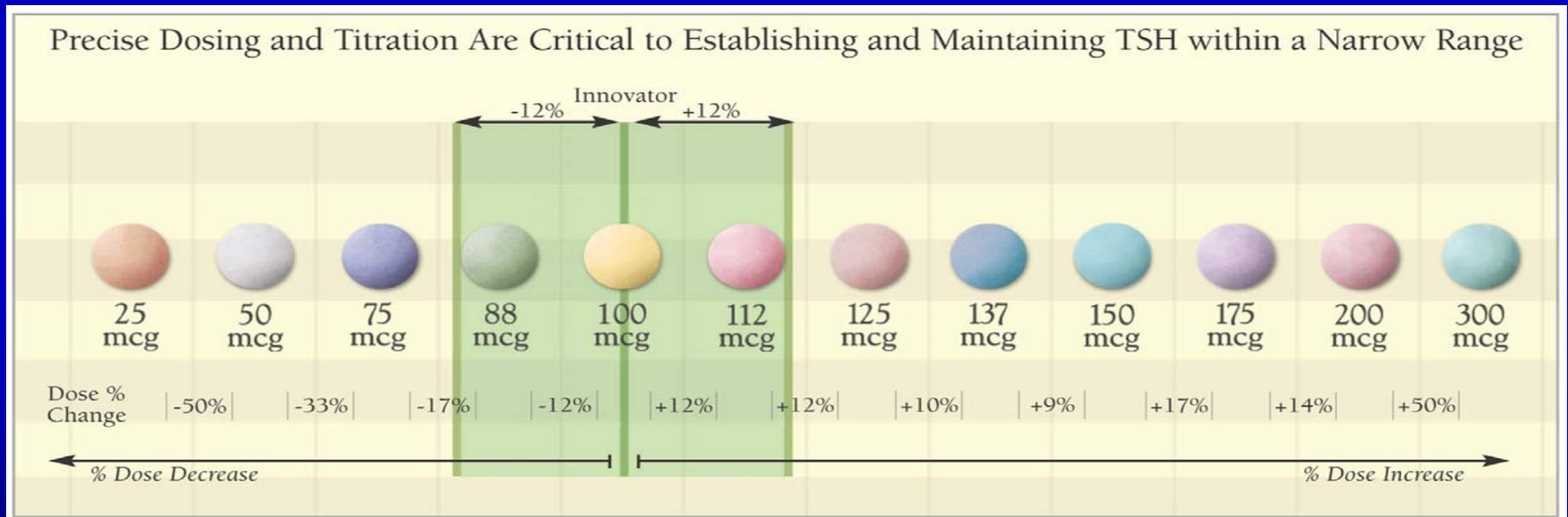
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Narrow Therapeutic Range (NTR) Drugs

- **Levothyroxine** sodium is a compound with a narrow therapeutic range with small differences between therapeutic and toxic doses
 - Requires careful dose titration, monitoring
- In this regard, L-T4 is like other NTI drugs:
 - Warfarin
 - Digoxin
 - Phenytoin
 1. FDA Industry Guidance: BA/BE Studies for Orally Administered Drug Products. October, 2000.
 2. FDA Guidance: Levo.Sodium Tablets—*In Vivo* Pharmacokinetic and BA Studies. December, 2000.

FDA Bioequivalence Standards Should Distinguish a 12.5% Dose Difference

Current FDA recommendations to determine bioequivalence may not be sufficiently sensitive to detect small differences



- Small differences in dosage have significant clinical impact, both on safety and efficacy

Potential Medical Consequences of Differences in Quality or Bioequivalence

Caused by Levothyroxine Substitution

Imprecise Thyroxine Dosing Results in Subclinical Thyroid Disease

- Subclinical **Hyper**thyroidism
 - Normal T4, T3
 - TSH < 0.3 mU/L

- Subclinical **Hypo**thyroidism
 - Normal T4, T3
 - TSH 5 – 10 mU/L

Imprecise Thyroxine Dosing Vulnerable Populations

- **Patients with (or at risk of) cardiac disease**
 - **Hypercholesterolemia**
 - **Coronary ischemia**
 - **Myocardial infarction**
 - **Arrhythmias; atrial fibrillation**
 - **Death**

Imprecise Thyroxine Dosing Vulnerable Populations

- **Patients with (or at risk of) osteoporosis**
 - **Fractures**
- **Elderly patients**
 - **Symptoms; cardiac events**
- **Pregnant women**
 - **Miscarriage; fetal death**
 - **Child's IQ**

Imprecise Thyroxine Dosing Vulnerable Populations

- **Thyroid cancer patients**
 - **Inadequate TSH suppression**
 - **Progression of tumor; metastases**
- **Children**
 - **Growth**
 - **Developmental abnormalities**

TSH as a Pharmacodynamic Marker

Why do We Need It?

- TSH is the most sensitive measure of Thyroid Hormone Action
- **Normal Thyroid Hormone Levels are not accurate measures of Normal Thyroid Hormone Action**
- Blood T4 levels are not the 'active ingredient' at the 'site of action'.
- The Toxicities of Excessive or Deficient Thyroid Hormone Levels are defined by TSH Levels, not by Thyroid Hormone Levels

Switching: Impact on Physicians

- Often not informed of switch
- More office visits by patients
- Need to justify reimbursement for additional TSH testing
- Patients presenting with ill-defined symptoms & not aware of switch
- More calls to and from pharmacists

Switching: Impact on Patients

- Potentially symptomatic until retitrated
 - **“Doctor, I don’t feel right”**
- Inconvenience and time for office visits
- Cost of extra TSH testing
- Cost impact of complications
- Increased risk for adverse effects of
 - **under- dosage**
 - **over - dosage**

FDA Guidance (2000)

- Drug substitution may lead to:
 - “Suboptimal response and hypothyroidism”
 - “Toxic manifestation of hyperthyroidism such as cardiac pain, palpitation, or cardiac arrhythmia...”
 - “In patients with coronary heart disease, even a small increase in the dose of levothyroxine sodium may be hazardous.”

Conclusions - 1

- L-T₄ is a narrow therapeutic index drug
- Physicians carefully titrate L-T₄ dosage
- Small dosage changes alter TSH, the parameter measured by physicians.
- LT₄ products differing by as little as 10% place patients at risk over- or under-treatment.
- Switching T₄ in patients on stable dose causes
 - increased chance of adverse outcomes
 - increased physician, pharmacist workload without economic benefit

Conclusions - 2

- We need better methods to determine equivalence and quality of NTI drugs like T4 to minimize impact of switching
- Current FDA bioequivalence standards are not sufficiently sensitive to detect small differences
- The FDA erred in allowing pharma to delete warning for dosage retitration after switching
- Current policy frustrates physicians, is unnecessarily expensive & wastes resources, and does not serve the health needs of the public.