

# Evidence Based Medicine Leads to Mediation of Symptoms of Mimics of Hypothyroidism

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Evidence Based Medicine is a modern, scientific alternative to the eminence based medicine. Currently, eminence based medicine is ignoring the mimics of hypothyroidism. Consequently, those patients are seemingly doomed to a life of chronic suffering with the symptoms of hypothyroidism, constant exhaustion, hypo-metabolism, hyper-cholesterolemia, deformity by myxedema, droopy eye lids, weight gain, etc. Furthermore, these patients are doomed to a life shorted by their greater susceptibility to life's great killers, diabetes and heart disease.

Evidence Based Medicine (EBM)<sup>(1,2)</sup> is the conscience, explicit, and judicious use of best evidence in making decisions about the healthcare of patients. EBM "is the process of systematically finding, appraising, and using contemporaneous research findings as the basis for clinical decisions." It may be segmented into four potentially iterative efforts<sup>(1)</sup>

1. Formulate a clear clinical question from a patient's problem,
2. Search the literature for relevant clinical articles,
3. Evaluate (critically appraise) the evidence for its validity and usefulness, and
4. Implement useful findings in clinical practice.<sup>(1)</sup>

The clinical practices upon the mimics of hypothyroidism have exemplified the following point: "For decades people have been aware of the gaps between research evidence and clinical practice, and the consequences in terms of expensive, ineffective, or even harmful decision making."<sup>(1)</sup> Indeed, the clinical practice upon these mimics has been limited to declaring them "functional somatoform disorders"<sup>(3, 4)</sup> and their symptoms "nonspecific."<sup>(5, 6)</sup> These diagnoses have several problems. They are suspect, since millions<sup>(7-9)</sup> are not likely to be delusional. These diagnostics are illogical,<sup>(10)</sup> and pending the investigation "on the state of medical science"<sup>(11)</sup> below, are also incorrect.

## First - Formulate

First, we must "formulate a clear clinical question from a patient's problem." Marie, our hypothetical patient, has normal standard thyroid tests<sup>(12-19)</sup> with or without therapy with levothyroxine sodium. Unfortunately, Marie has continuing symptoms of hypothyroidism.

## Second - Search

Second, we must "search the literature for relevant clinical articles." Certainly, a continuing medical education course could be useful. A search finds one by Gossel<sup>(Table 1 of 20)</sup> and *Talking Points* on hypothyroidism by Garber.<sup>(21)</sup> From these we learn three things:

1. There is a resistance to the cellular reception of thyroid hormones, circa 1967.
2. Triiodothyronine (T3) is largely produced by peripheral conversion of thyroxine (T4), circa 1970.

Further searching finds this quotation that puts a substantial different view upon Marie's problem:

*"T<sub>4</sub> . . . is not the active ingredient. T<sub>3</sub> is the active ingredient, and it's the thing that accounts for the thyroid hormone action. As I've been reminded many times, there are no intracellular events that we know that can be described by T<sub>4</sub> at the level of the nucleus. Only T<sub>3</sub>. T<sub>4</sub> is not the active compound. Likewise, the site of action is in the nucleus. The site of action is not T<sub>4</sub> in the plasma."* – Dr. E. Chester Ridgway<sup>(22)</sup>

That statement is powerful. It puts a different light on Marie's problem. Perhaps, the lack of T3 is

producing the problem. But that is generally not mentioned in the guidelines for hypothyroidism<sup>(12-19)</sup> and dismissed elsewhere.<sup>(20, 21)</sup> On the other hand, Marie isn't getting better.

Further search reveals much more research on both peripheral hormone reception, for example,<sup>(23-28)</sup> and peripheral metabolism or conversion, for example.<sup>(29-39)</sup> Unfortunately, we also find some detractors of the use of triiodothyronine (T3),<sup>(5, 12-17, 40-43)</sup> as well as some studies that find T3 replacements useful.<sup>(44-48)</sup> It is no wonder that Anthony Toft and Geoffrey Beckett were puzzled.<sup>(49)</sup>

*"It is extraordinary that more than 100 years since the first description of the treatment of hypothyroidism and the current availability of refined diagnostic tests, debate is continuing about its diagnosis and management."*

### Third – Critically Appraise

As suggested in the third step: we must evaluate and critically appraise the evidence for its validity and usefulness.

*Wilson's Syndrome*,<sup>(5)</sup> a position paper by the American Thyroid Association (ATA), claims that no triiodothyronine (T3) containing therapy is needed because the peripheral metabolism or conversion is "regulated." In other words, this peripheral process never fails. This is a substantial statement from allopaths, whose entire adult lives have concentrated on somatic failures. Considering the lack of supporting references in *Wilson's Syndrome*, its counter-intuitive nature, and existing contrary references,<sup>(29-39, 40-43)</sup> this is a substantially misleading statement.

*Wilson's Syndrome*, [5] also claims that continuing symptoms are "nonspecific" in view of Barsky. [6] However, the Barsky subjects may have had hypothyroidism because they were not screened against hypothyroidism. Thus, the ATA wishes to separate continuing symptoms from hypothyroidism with data tainted by hypothyroidism. This is a logical faux pas. Further, "nonspecific symptoms" are also discredited by *Hypothyroidism Presenting with Musculoskeletal Symptoms*.<sup>(50)</sup>

*Wilson's Syndrome*,<sup>(5)</sup> continued with this errant logic in depreciating an indicator of hypothyroidism found by a pioneer, Dr. Broda Barnes,<sup>(51)</sup> the low basal temperature. The citation<sup>(52)</sup> is of a study that also did not screen out subjects with hypothyroidism. Another logical faux pas.

The papers<sup>(40-43)</sup> which demonstrate that triiodothyronine (T3) is not effective or useful, support the established thyroxine-only therapy. These papers suffer for several reasons:

1. Many studies were done with subjects who had primary hypothyroidism or had thyroidectomies. The subjects showed little if any benefit with the addition of triiodothyronine (T<sub>3</sub>) to their therapy in lieu of some of the thyroxine (T<sub>4</sub>). There were no subjects identified as suffering from deficient peripheral metabolism or deficient hormone reception. Consequently, these results proved nothing for patients suffering from these deficiencies.<sup>(10)</sup>
2. The low occurrence rate of subjects that have post-thyroid or exo-endocrine deficiencies permitted the authors to round off the low rate of improvement and conclude "no improvement."<sup>(10)</sup>
3. Anecdotally, the triiodothyronine doses were quite low, usually about 5 micrograms per day. This dose in a patient that actually suffers from post-thyroid deficiencies did not produce sustained noticeable benefits. Indeed, that dose is less than 5% to 10% of the usual replacement dose of 50 mcg to 100 mcg daily. In fact, 5 micrograms is the recommended starting dose for more sensitive patients, infants and the elderly. [53]

The papers<sup>(44-48)</sup> are more positive about the use of a T3 containing hormone replacement. But what

about selecting an approach? A further search turns up two papers, by Baisier, Hertoghe and Eeckhaut,<sup>(54)</sup> and Brady.<sup>(55)</sup>

#### Fourth – Implement

The Baisier paper is important because these physicians examined patients with continuing symptoms of hypothyroidism, i.e., the failures of established endocrinology, for their symptoms and for the T3 in their 24-hour urine sample. They produced a clinical algorithm for evaluating symptoms that correlated with further evaluation. Then, for a more objective measurement, the T3 in the 24-hour urine sample correlated quite well with symptoms.<sup>(54)</sup> In a follow-up study, they found 40 of the 89 volunteers and treated them with desiccated thyroid with success.<sup>(54)</sup>

The Brady paper has a diagnostic aid in Table 2. Brady claims that Euthyroid Sick Syndrome and deficiencies in peripheral metabolism or peripheral hormone reception can be differentially diagnosed with the following conditions<sup>(55)</sup>

T4	Normal or Low	Free T4 index	Normal or Low
Free T4	Normal or Low		
T3	Normal or Low	T3 resin uptake	Normal or Low
rT3	High		
TSH	Variable,		
TRH	Normal or low		

This set of conditions, particularly a high rT3 in the presence of other hypothyroidism indicators and assays, suggests that the peripheral metabolism or peripheral hormone reception is deficient. Since the dominant hormone in that realm is triiodothyronine (T3), one of the approved several T3 replacements<sup>(56)</sup> is a logical consideration.

#### Cautions

Of course, with the administration of any drug, due care must be taken. The manufacturer's approved usage recommendations must be considered and followed. Further, for patients requiring a T3 replacement, there probably is not a valid equivalency between a levothyroxine sodium (T4) therapy and a T3-containing therapy because the efficiency of the peripheral metabolism of T4 to T3 probably is not normal.

#### Conclusion

Evidence Based Medicine (EBM) can, if given a chance, produce a solution to quite unsatisfactory results of extensive hypothyroidism diagnostics and therapy attempts. It can because there are physical reasons for the continuing symptoms. The information about these causes and treatments of these symptoms exists.

#### Endnotes

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<b>Replacement Manufacturer</b>	<b>Replacement Name</b>	<b>Approval / Acceptance</b>
Forest Laboratories, Inc. 909 Third Avenue, 23 <sup>rd</sup> Floor New York, NY 10022	Armour™	Desiccated thyroid was Manufactured prior to 1937
	Thyrolar™	NDA 16-807
King Pharmaceuticals, Inc. 501 Fifth Street Bristol, TN 37620	CytomeI™	NDA 10-379
Western Research Laboratories 2404 West 12 <sup>th</sup> Street, Suite 4 Tempe, AZ 85281	Westhroid™ Nature-throid™	Desiccated thyroid was Manufactured prior to 1937