Reviewer’s report

Title: Time for a Reassessment of the Treatment of Hypothyroidism

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Reviewer: James V Hennessey

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BEND-D-18-00171R1

Time for a reassessment of the treatment of hypothyroidism is a very sophisticated, articulate review of several excerpts from the literature which support and oppose the findings of the authors previously published research and opinions. It is clear that the authors consider current evidence based guidelines to be applied restrictively by the clinical community. Based upon previous pieces by the authors, their investigations support the use of combined LT4/LT3 and thyroid hormone extracts for the treatment of hypothyroidism. As the current guidelines do not recommend combination therapy, the authors make the case for utilizing their approach in the clinical setting. The paper flows nicely, is very articulate and provides unique and advanced techniques of analyzing data which provide a platform to interpret their previous research supporting the use of combination therapy in individual patients.

Specific comments:
Page 4 Line 36
    Thyroid hormone extract products are "standardized" by adjusting the LT4 and LT3 content after HPLC measurement indicates that the batch in process is not within USP specifications. As these products are now pharmaceutically modified, some have stated that they are no longer "natural".


Page 5 Line 9 Perhaps the not only is hypothyroidism frequently diagnosed but often "over diagnosed" [mis-diagnosed] especially when subjects present with non-specific symptoms and their thyroid function test results are misinterpreted like single minimally "elevated" TSH, using non age adjusted expected ranges for TSH or FT3 especially in the setting of non-thyroidal illness.

Line 32 Perhaps much of the problem is assuming that subclinical hypothyroidism (SCHypo) actually IS associated with the non-specific symptoms commonly attributed to hypothyroidism. Or is it the opposite, that the symptoms that lead to the ordering of TFTs (see also Bould H et al. 2012 Family Practice 29:163-167) are not causally related to the minimal variances in TFTs which may be discovered in the search for organic disease. See also (Cathebras PJ et al. 1992 J Gen Intern Med; 7(3):276-86, Stadje R et al. 2016 BMC Family Practice 17:147, Carle A et al. Am J Med 2016;129(10):1082-92, Blum MR et al. 2016 Neuroendocrinolgy 103:291-299). Obviously, the utility
of the diagnosis of SCHypo and initiation of treatment for symptom relief has recently been called into question, especially in the elderly as the non-specific symptoms experienced by so many are very common (See also Carle A et al. Am J Med 2016;129(10):1082-92). Unfortunately, some in the holistic community diagnose hypothyroidism without biochemical confirmation solely based on symptoms and initiate thyroid hormone of various varieties. Recently, it has been shown that in older individuals that TSH and FT4 levels do not correlate with measures of QOL, mood or cognition using age adjusted normal ranges derived from the NHANES data base (Samuels MH et al. 2017 Thyroid 26(9):1185-94). This finding indicates that symptoms do not correlate with age adjusted TSH [values as high as 9 mIU/ml. Additionally, if SCHypo symptoms were actually clinically relevant and responsive to thyroid hormone replacement, the studies by Jorde/Parle and Stott would have demonstrated some symptomatic change when thyroid hormones were provided (Jorde R et al. 2006 JCEM 91:145-53, Stott DJ et al. 2017 NEJM 376:2534-2544). All three of these studies defined the presence of SCHypo just based on TSH greater than a locally determined upper normal. None of these cutoffs exceeded the age adjusted cutoffs used by Samuels. Symptoms were minimal to age expected in their non-specificity, thyroid hormone replacement induced no change in their clinical state. This lack of therapeutic efficacy is likely due to the absence of hypothyroidism as the administration of thyroid hormone replacement has no beneficial effect in those who are euthyroid (Pollock MA et al. 2001 BMJ; 323 (Oct):891-895). So, if the primary care community over diagnoses hypothyroidism, we should not be surprised as specialists when we are referred patients in whom there are residual (non-thyroid dependent?) symptoms once thyroid hormone "normalizes" TSH.

Page 6 Line 6 I agree with the authors that before the era of TSH the severity of hypothyroidism diagnosed with the techniques of the day was far more severe, the symptoms far more clearly caused by hypothyroidism and the results of thyroid hormone intervention (extract or LT4) for more likely to relieve symptoms as this was the end point which was available. I offer the alternative explanation outlined above to nuance that with only marginal TSH elevations perhaps these subjects are not sufficiently hypothyroid (maybe not at all) to respond so dramatically to thyroid hormone replacement.

Lines 16-19 Not sure what the authors are expressing here. Either needs a reference or a bit more transparency.

Lines 29-43 I disagree here as I believe that data derived from observational studies were utilized to observe that clinical outcomes were not improved by excessive TSH suppression and therefore, given the prevailing thought that suppressed TSH levels were indeed associated with both atrial fibrillation and bone loss/fracture, it would be safer to back off on the degree that TSH needed to be suppressed from both perspectives. No one is denying that TSH can stimulate thyroid cancer growth, however is does not appear that an undetectable TSH is necessary in the vast majority of thyroid cancer patients.

Lines 43-49 I believe that the reference cited has been superseded by more recent clinical data. (See also Carhill AA et al 2015 JCEM 100(9):3270-3279).

Page 7 Lines 19-26 Patients complaining of symptoms when they know they are on LT4 and are aware that the doses of LT4 have been reduced is NOT an accurate (objective) assessment of the need for more or less thyroid hormone. (See also Walsh JP et al. 2006 JCE&M 91(7):2624-30, Samuels MH et al. 2018 JCEM 103(5):1997-2008).

Lines 39-42 To interpret such data there would need to be a be a blinded, controlled experience for the patients as the mere knowledge that they are hypothyroid, are on thyroid hormone and have chronic disease(s) generates symptoms independent of the thyroid function test results. See also (Quinque EM et al. Health and QOL 2013. 11:68, Wouters H et al. ENDO2018 OR34-1, 20 Mach 2018, Massolt ET et al. Clin Endo 2016; 85(5):781-788). This statement should be put into context.

Line 49-50 The reference cited here has nothing to do with thyroid cancer treatment, is a
relatively short-term study (only 6-month data) on treating Hashimoto's thyroiditis, concluding that there may be a component of the symptoms that are attributable to the Hashimoto's independent of the hypothyroidism. In addition of the n= 63 Completers TSH was still elevated in 24/63 (38%). The authors should find a more appropriate reference.

Line 56 An excellent reference has also recently appeared which supports the drama of patent self-reporting. These reports are problematic as there seems to be no control on who the respondents are and if robots are producing a portion of the reports. This most recent survey supports that the patients are upset over LT4 treatment a bit more than they are over LT4/LT3 and thyroid hormone extract as a large proportion report that other treatments must be found. The patients also seem to be upset with the the physicians who prescribe these therapies. (Se also Peterson et al. Thyroid 2018 28(6):707-721).

Page 8 Line 29 It should be made clear that the Winther study was done in an open label manner, all patients were aware of their diagnosis, all knew they were on LT4 and all had Hashimoto's thyroiditis which the authors seem to believe may be an independent factor to be considered when assessing patient symptoms on LT4. Again, it needs to be emphasized that upwards of 38% of the subjects in this study were still hypothyroid as assessed by elevated TSH at the time of the QOL assessments. So this study can not be directly translated into clinical practice as none of us would assume that symptoms should be attributed to hypothyroidism treatment failure if the TSH were still elevated and sufficient time had not passed to allow for tissue T3 equilibrium to occur.

Line 56 FT3 seems to have been repeated here.

Page 9 Line 26 I do not think most clinicians (primary readership) are familiar with the paradox. This paragraph is above the level of clinician understanding. If the point is that each individual is unique, how are we to assess each individual with the tools we currently have. Symptoms don't help, FT3 is not associated with symptoms in numerous studies, TSH being slightly elevated, high normal or low normal all seem to have the same outcomes. Is a clinician to do?

Page 10 Line 9 Other well done studies reach the conclusion that there is no convincing relationship between Symptoms and individual TFTs. (Massolt ET et al. Clin Endo 2016; 85(5):781-788, Wouters HJ et al. 2017 Thyroid 27(2):147-155, Samuels MH et al. 2018 JCEM 103(5):1997-2008). The authors are asked to acknowledge these data.

Line 19 There are 4 metanalyses all looking at the same, but not completely overlapping studies which also comes to this conclusion. Perhaps for completeness the authors would consider including all of these reviews.

Line 26 Might acknowledge that the end of study preference info is subjective and when in placebo-controlled trials, patients tend to prefer the study period which they perceive they were on the highest dose of LT4(Samuels MH et al. 2018 JCEM 103(5):1997-2008). In the Hoang study of course only 48% preferred the thyroid hormone extract phase while the majority (52%) either liked LT4 better or could not tell a difference.

Line 42 Agree with the authors that patients with thyroid cancer seem to have symptoms and m the presence of symptoms has a negative impact on their quality of life. This is a far cry from demonstrating that these symptoms are caused by some deficiency in thyroid hormone replacement therapy (which the Hedman et al. did not do. Again the work of Massolt ET et al. Clin Endo 2016; 85(5):781-788 concludes that co-morbidities are a better explanation of symptoms in these patients than an TFT. The authors should reflect an acknowledgment of these contradictory studies.

Line 52 This may also be explained by the observation that patients tend to prefer doses of LT4 that they perceive to be higher (Samuels MH et al. 2018 JCEM 103(5):1997-2008).
I do think that TSH is a prognostic tool in predicting bone loss (Uzzan B, et al. J Clin Endocrinol Metab. 1996;81:4278-4289), fracture (Bauer DC, et al. Ann Intern Med. 2001;134:561-568, Flynn RW et al. 2010 JCEM 95:186-193, Blum MR et al. 2015 JAMA 313:2055-2065) and Afib (Sawin CT, et al. N Engl J Med. 1994;331:1249-1252, Cappola, AR et al 2006 JAMA 295(9):1033-41, Flynn RW et al. 2010 JCEM 95:186-193). The fact that the degree of TSH suppression found in thyrotoxicosis is higher that that observed when the TSH is in the expected range is understandable to me. A higher degree of elevated circulating thyroid hormones sufficient to suppress TSH should have more impact on bone and cardiac outcomes than when the TSH is normal. In the Chaker study indeed FT4 (for the most part in the expected range) levels appear to predict the onset of Afib while TSH levels in the expected range do not. As the authors know, T3 or FT3 levels were not analyzed in this cohort and this study is focused on the 98% of subjects dependent on endogenous thyroid hormone production. The LT4 component in this study is quite small, but when the 720 LT4 users were analyzed separately, the 12 Afib events analyzed did not show a statistically significant risk (where the FT4 levels would be expected to be the highest observed). 720 subjects at risk is not trivial, if the FT4 levels generated by LT4 ingestion were a clear risk, I would have thought that a clinician might observe this from time to time. Statistical significance (not in this trial) does not always equate to clinical significance. The authors assertion here may be misconstrued by the reader and should be put in proper context.

Line 53 I would say the opposite, combination therapies fail "the superiority test". Combination therapy is far more expensive less convenient (TID dosing closest to physiology with current preparations) and potentially supraphysiologic post absorption T3 levels when ingested in commonly used LT3 doses. So if it is not superior (n of 1 trials aside) why recommend this to patients when a safe, inexpensive, non-inferior product is available?

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Line 9 I believe thyroid hormone production and physiology is different in rats.

Line 22 In the US this would exclude thyroid hormone extracts as they are not FDA approved and have been removed from the list of approved drugs eligible for Medicare reimbursement under Part D of Medicare. Please make this clear in the conclusion.

Line 32 I agree, seek alternative explanations for the complaints before anchoring in on the thyroid as the cause of all complaints in those with well documented hypothyroidism.

Line 53 It is unclear what is meant by the term "unresolved hypothyroidism" when the symptoms are so non-specific and the differential so broad. Again anchoring on hypothyroidism as the root of all symptoms may be a dis-service to the patient.

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Line 1 I agree, the trend is prescribe more LT4 (labeling the patient as hypothyroid whether hypothyroidism has caused their symptoms or not), decreasing the TSH threshold generating a LT4 prescription thus likely over diagnosing "hypothyroidism as a cause of symptoms".

Line 29 I agree, the medical profession seems to be taking a short cut, not listening to the patient, not considering the differential diagnosis of the complaints and giving out LT4 for the non-specific symptoms associated with a diagnosis of hypothyroidism as "hypothyroidism is easy to treat" and to move the patient along in busy primary care practices. I am not surprised when many "non-thyroid" symptoms persist. I do not equate this to a failure of LT4 to resolve the symptoms but rather a failure of LT4 to improve the QOL in euthyroid individuals as Dr. Pollack taught us many years ago.

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Line 36 Is this a research report (new data?) or a review/opinion piece?

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No
Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

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