The Chimera of Circular Insanity and the labours of Thyreoidea

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COMMENTARY:

What is already known on the topic:

In full rage, mania or ‘maenomenos’ is alluded to by Homer to have the ferocity of a lion. However, modern day bipolar illness is perhaps more similar to the mythological Chimera: a composite of three differing beasts; described by Falret in 1854 as: “the manic state, the melancholic state, and a more or less prolonged lucid interval”.

The thyroid gland, named from the Greek *thyroidea*, means shield like; owing to its shape and perhaps also to its modulation of key physiological function of the human body including mood. Thus, like an epic hero’s labours against a gargantuan challenge, Walshaw et al(1) put rapid cycling bipolar illness to the test of adjuvant thyroid hormone therapy.

THYROID AND AFFECTIVE DISORDERS

Initially linked to depressive disorders(2), recent evidence shows more relevance of the hypothalamic-pituitary-thyroid (HPT) axis to the clinical course of bipolar affective states(2, 3). This relationship may involve neurotransmitter-like mechanisms (due to structural similarities of thyroid hormone to dopamine and norepinephrine); the thyroid gland exhibiting properties of GABA transport and degradation mechanisms; the concentration of T3 in nuclei of central noradrenergic systems, and the distribution of thyroid receptors in the limbic system. These might account for the putative neuromodulatory and mood regulating role of the HPT axis. PET scans of hypothyroid patients on thyroid replacement have shown restoration of blood flow and glucose metabolism in key cognition and affect regulating areas of the brain, particularly the limbic, subcortical and frontal regions(2). Studies have also demonstrated cortical perfusion asymmetry(2) in patients with thyroiditis leading to a hypothesis linking cortical hypoperfusion, thyroid autoimmunity and bipolar affective disorder(2). Recent evidence of monozygotic/ dizygotic positivity for thyroid antibody titres has engendered the theory that HPT dysfunction might be an endophenotype for bipolar affective disorder accounting for the genetic vulnerability for development of bipolar affective disorder(3).

RAPID CYCLING: DEFINITIONS AND CHALLENGES

Rapid cycling bipolar disorder (RCBD), was defined by Dunner and Fieve (1974) as a course specifier of four or more mood episodes (or polar switches) in one year. RCBD has been described in literature as malignant(3), refractory(1) and treatment resistant(1) and is estimated to affect up to 20% of patients with bipolar affective disorder. The dysfunction of the HPT axis in RCBD has been found in numerous studies; Gyulain et al(3) examined the whether HPT hypofunction was responsible for rapid cycling by giving the participants in a case-control study a short-term lithium challenge. After treatment with lithium, serum concentrations of thyroxine significantly decreased, whereas basal thyrotropin (TSH) and DeltaTSH(max) significantly increased in both patients and control subjects(3). However, the neurophysiological underpinnings of this remain unclear.
The effects of lithium on the thyroid are well documented(3) and further complicate the association of the HPT axis with bipolar illness. Lithium may evoke an exaggerated TSH response to TRH or exacerbate pre-existing autoimmune response in thyroid illness(3); mechanisms which in themselves may be implicated in mood cycling and mood instability. Hence, there is a highly complex scenario in bipolar illness treated with lithium.

Methods of the study:

In the study thirty-two treatment-resistant, rapid cycling patients who had failed a trial of lithium were randomized into three treatment arms: L-T4, T3, or placebo. They were followed for ≥4 months with weekly clinical and endocrine assessments(1). Dunner and Fieve criteria were used to diagnose rapid cycling in addition to DSM III-R and /or Research Diagnostic criteria(1). HDRS was ≥15 for depression and YMRS was ≥7 for mania. The assessment included physical examinations and weekly TFTs. For LT4 group the dosage was adjusted until the FT4 index was between 4.5 to 7.5 and/or TSH suppression reached. Follow up was for at least one complete mood cycle: mania/ depression/ mixed state to euthymia/remission(1).

What does this paper add?

This randomized placebo-controlled trial examined the relationship between adjunct treatments of supraphysiologic thyroxine in refractory mixed affective states of Bipolar disorder. The analysis was divided into between-group (i.e., LT4, placebo and T3) and within group for affective states (i.e. pre and post treatment comparison on affective states).

The between group analysis showed that LT4 group spent greater time in a euthymic state and less time in a mixed state as compared to placebo; with both values reaching significance. There was also a trend in LT4 group compared to T3 group of spending less time in depressed state however this did not reach significance (p= 0.121)(1).

Within group analysis showed LT4 group spent significantly less time depressed or in a mixed state and greater time in euthymic state post treatment compared to pre-treatment (p= 0.022, 0.031 and 0.22 respectively). LT4 group spent less time in a manic state however this did not approach significance. The T3 group showed a similar trend however did this not approach significance(1).

Limitations:

- The small sample size of 34 when the study was originally powered for 60 thus not allowing for the ANOVA to be used for data analysis;
- The Markov chain matrices in the paper are based on the assumption that transition from any affective state to the other is possible. The original Kraeplenian theory describes the mixed state being the transitory state from mania/hypomania to depression and vice-versa(5); i.e., a patient developing mania after depression would transition through mixed state instead of independent transition from mania to depression without experiencing the mixed state. So far there is only limited evidence(4) dispelling this.
- The Markov chain matrices allowing for independent transition also run into another problem since the paper mentions using all three criteria (Dunner-Fieve, DSM III and RDC) to make a diagnosis of RCBD for inclusion. This makes it confusing since a matrix designed using the Dunner-Fieve model would allow for independent transition between states; however, both DSM and RC would need to have euthymia remission prior to transition. These subtle
differences in the three criteria are fleshed out in more detail by Maj et al (1999) in their paper looking at different definitions of RCBD
- These original transition matrices are then used in the study to calculate the long run fraction of time the participants would spend in each affective state under the three treatment arms. We query if the results would have appeared different under a different transition matrix: one affective state and/or the diagnostic definition of rapid cycling?
- The duration of lithium treatment for the patients was not mentioned which might have an impact on the efficacy of LT4 due to time-dependant antithyroid HPT dysfunction;
- Inclusion criteria includes failure to respond to lithium which would have benefited from a standard definition for consistency.

What next in Research?

A few further avenues of research might be pursued next.

- The Autoimmune thyroid:

  There is growing evidence of thyroid antibodies being implicated in affective cycling. Thyroid levels (TSH, T3, FT4) need to be studied in conjunction with thyroid antibodies for a more holistic picture of how thyroid affects mood symptoms. All patients in this study were euthyroid. However there is evidence of asymptomatic peripherally euthyroid patients having mild sub-threshold autoimmune thyroiditis. Which might account for the euthyroid patients in LT4 group responding to adjuvant thyroid in this study.

- Replication and Larger trials:

  The findings from this study should be replicated in larger trials. Studying adjunctive therapy of thyroxine with other mood-stabilizing medication utilising Bayesian inferences for efficacy would be another area for future research.

- Euthyroid cut-offs and lithium:

  Another question raised is if we need different/ more sensitive euthyroid cut-offs for patients on lithium therapy? It would be interesting to see if patients on lithium with their TSH/FT4 at a certain point show response to supraphysiological thyroxine or if there is no association between baseline level and response.

- YMRS and HSRD:

  It would be interesting to see if there are items on the YMRS and HSRD during the rapid cycling that respond particularly well to the addition of thyroxine. This might point to the neurophysiological underpinnings as discussed earlier and help deciding on management in a patient personalised way considering specific symptoms in the presentation

- Thyroxine as a mood-stabilizing adjunctive agent:

  Another interesting question that arises would be to investigate if thyroxine could prove to be an adjunct to other (traditional) mood-stabilizing medications which are not anti-thyroidal in nature like lithium. This would further understanding of supra-physiological thyroxine and mood stabilizing properties would be of value.
Do these results change your practices and why?

These data open a new research approach for understanding of refractory rapid cycling states and bipolar affective disorder in general. However, in current clinical practice the scope of including supraphysiologic doses of thyroxine in the euthyroid state remains limited. Clinicians will remain cautious of prescribing thyroxine treatment for any state except for depression due to the potential for iatrogenic hyperthyroidism and its putative association/similarity with manic features.

However, if the findings of this study are adequately replicated it would seem possible for thyroxine to be considered as an adjunct to mood stabilizing medications in treatment guidelines and clinical practice in the future.

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Competing interests

None

References