Bipolar spectrum disorders treatment with a new protocol of High Dose Levothyroxine (HDT) and rTMS and thyroid genetic mutations: a cohort evaluation

Dr Andy Zamar 1, Dr Christos Kouimtsidis 2, Dr Abbi Lulsegged 3, Dr Robin Roberts 4, Prof Daniel Stahl 5.

1 Consultant Psychiatrist, The London Psychiatry Centre, London
2 Consultant Psychiatrist, The London Psychiatry Centre, London
3 Consultant Endocrinologist Health121 Ltd, London
4 Consultant Cardiologist Aupres Medical, London
5 Professor Daniel Stahl, Professor of Statistics KCL, London

Introduction

- Bipolar spectrum disorder (BPS) encompasses bipolar 1 (BP1), 2(BP2) and subthreshold bipolar disorder SBP including Rapid Cycling Bipolar Disorder (RCBPD). Rapid Cycling bipolar disorder (RCBPD) is defined as 4 or more episodes of hypomania/ depression or 4 clear switches of polarity in a 12-month period.
- It is highly prevalent (2.4%) of the general population and more disabling than all forms of cancer and neurological diseases (1)
- BPS have an estimated mortality rate of 56% with 38% dying of cardiovascular disease 10 years before the general population and 18% through accidents or suicide (2)
- Despite being as prevalent as diabetes, failure of diagnosis of bipolar disorders is very high (60-85%), with an delay of 13 years. (3)
- It is generally less responsive to treatment with standard treatments with mood stabilizers and antipsychotics being ineffective and drug combinations are often needed. As a rule with 80% requiring an average 3.8 drugs (4).

Methods

- We report a cohort of 66 patients with BPS
- The cohort was evaluated during a follow up appointment for a period of 4 months of clinic attendees.
- Remission was measured using the Sheehan Disability Scale (SDS), a quality-of-life scale used by WHO to measure burden of disease measuring impairment of work/ study, family, and social life from 0-10.
- All patients had ECG and cardiac review
- All were severely symptomatic and resistant to treatment at the outset.
- We report the use of a stand-alone protocol or add on to bipolar 1 (BP1) using repetitive Transcranial Magnetic Stimulation (rTMS) for neuroplasticity and supraphysiological doses of Levothyroxine.

Results

- 39 (58.5%) were female and 27 (41.5%) were male. Average age 38.62yrs.
- 53 had SBP, 7 had BP2 and 6 had BP1
- Genetics were tested in 63 subjects (96.92%) of those 62 (98.41%) showed mutations in DiO1, DiO2 or SLCO1C1, thyroid activating enzymes and intra cerebral transporter protein carrier.
- 57 (86.2%) were treated with rTMS and 1 with ECT for neuroplasticity.
- 38 (58.56%) took only Levothyroxine, with only 16 (24.2%) requiring an antipsychotic and 5 (7.6%) a mood stabilizer, 17 (25.7%) needing anxiolytics for comorbid anxiety alongside Levothyroxine or additional drugs and 13 (19.7%) requiring a sleeping pill. As a rule, BP1 required lithium and an antipsychotic.
- Discontinuation rate was 0%. Only 1 patient had side effects, of feeling hot and palpitations and this subsided when dose was reduced .
- The average number of drugs across all 66 patients including anxiolytics and sleeping pills was 1.7 drugs.
- Dose of levothyroxine range was 50 mcG-1000 mcg with the average dose at 416 mcg.
- Pre-treatment level was 7.32 with post remission SDS was 1.29, (-6.03- 95% CI 5.39-6.75) with 22/65 scoring 0. The effect size of the change is d= 2.94, a very large effect size.
- 63 patients were in full remission with no residual symptoms and 3 never reached remission, 1 not attempting rTMS, 1 for non-compliance with HDT and 1 had no funding to continue with rTMS. Mean remission was 2.34 years.
- 6 patients relapsed, with 1 for no precipitant or reason, 3 for non-compliance with monthly maintenance rTMS or Levothyroxine, 2 who improved on low dosage of Levothyroxine, relapsed then recovered on higher doses.
- Blood tests showed a high FT4/FT3 ratio with a equal rise in T3 and reverse T3 (rT3)
- Cardiac status was normal and there were with no signs of hyperthyroidism. No other patient showed side effects due to Levothyroxine .

Discussion

- BPS was shown to be associated with mitochondrial dysfunction (5)
- Thyroid hormones induce mitochondriogenesis as well as stimulating mitochondrial activity. (6)
- RTMS, increases rCBF and oxygen consumption in the ipsilateral stimulated area by 33% (7).
- We postulate that this represents the first treatment protocol aimed at addressing possible mitochondrial dysfunction in BPS.
- HDT is in the prescribing guidelines for BPS but despite a network analysis showing rTMS to be effective in bipolar depression, it has yet to find a place in the guidelines except for 1 UK guideline for 11 years but withdrew it in its most recent edition this year.
- However, the absence of hyperthyroidism despite large, unconventional doses remains unclear.
- This novel report shows a strong association with SNP of DIO2/DIO1, SLCO1C1 and RCBPD.
- We speculate that BPS is a form of cerebral hypothyroidism, and that HDT helps to overcome the deficit while robust inactivating deiodinases in the periphery protect from systemic thyrotoxicosis.
- This is evidenced by findings of normal clinical examination (euthyroid) and elevated rT3.
- rTMS exercises its well established neuroplastic effect, helping to achieve and maintain remission as an adjunct to HDT through delivering more oxygen and glucose to the mitochondria, whilst HDT induces mitochondrial repair and action .

Conclusion

- Rapid cycling bipolar disorders are conditions with very high mortality and morbidity rates.
- Our data highlights an association between polymorphisms of the DIO2 gene and bipolar disorder and previous studies have highlighted the safety and effectiveness of adjunctive HDT in achieving remission.
- This novel approach with HDT/rTMS is well tolerated and appears to be effective in inducing long term remission in resistant RCBPD

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Declaration Of Interest: The London Psychiatry Centre has pending patents for the treatment protocol in Europe and the US, with Dr Zamar being the inventor.