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High-Dose Levothyroxine for Bipolar Disorder; the Potential Role of Thyroid Function and Genetic Tests. Report from Twenty Cases.

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ABSTRACT

Rationale: *Rapid Cycling Bipolar Disorder (RCBPD) is a malignant course of bipolar disorder (BPD). The condition is associated with several co-morbidities and is difficult to treat. Supra- physiologic doses of levothyroxine (average 482 µg/day) (High-Dose Levothyroxine, HDL) have proven effective for treatment resistant BPD. It is unclear exactly how HDL benefits patients with BPD.*

Objectives: *In this paper, we present the retrospective analysis of clinical notes of 20 patients in remission from RCBPD for at least six months, who received HDL (150-1000 µg; median 472 µg/day). We examine the role of Thyroid function tests (TFTs) and genetic testing. We aim to demonstrate the utility of these tests for patient selection and response prediction for HDL.*

Findings: *All patients recovered with minimal side effects with no treatment discontinuations.*

One patient required a dose reduction because of palpitations and sweating. Seventeen patients had concomitant Repetitive Transcranial Magnetic Stimulation (rTMS). Ten patients (50%) required one psychotropic in the acute phase, two patients (10%) required two and eight patients (40%) required only HDL. Following remission, 11 patients (55%) were on HDL only. The average pre-treatment ratio of free T4 (thyroxine, fT4): free T3 (tri-iodothyronine, fT3) was 4:1, with fT4 increasing post-treatment to 5:1 while fT3 remained largely normal. Nineteen patients had single nucleotide polymorphism (SNPs) of DIO1, DIO_2, or both. One subject requiring 400 µg had a SNP in the SLCO1C1 thyroid carrier. A high fT4:fT3 noted as early as day 10 during treatment supports a role for DIO polymorphisms.

Conclusions: *This preliminary report demonstrates the usefulness of a high fT4/fT3 ratio in the second week as a predictive test for patient selection and response prediction for HDL. Recently we have developed a treatment protocol combining HDL and rTMS.*

Keywords
Levothyroxine, Bipolar disorder, Thyroid test, Genetic test.

Introduction
Rapid Cycling Bipolar Disorder (RCBPD) is a malignant course of bipolar disorder (BPD), affecting 25-43% of individuals with BPD and defined as four or more episodes (or changes of polarity) of (hypo)/mania and depression within 12 months [1]. Mixed episodes are characterized by manic and depressive symptoms, simultaneously or in short order [2]. The condition is often linked to alcohol use, increased inability to work, increased number of suicide attempts, and is regarded as treatment resistant with a

lower response to pharmacological treatments [3-5]. Controlled studies of pharmacologic intervention for RCBPD are sparse; with most being open label or post hoc analyses [6]. The National Institute for Health and Care Excellence (NICE) guidelines state that mixed affective states should be treated as mania and one should be cognizant to depression developing [7]. Yet, RCBPD remains difficult to treat without a "formal first-choice agent or combination" made more critical given that one in three patients remit, regardless of treatments [8,9]. Additionally, patients may require a combination of three or more mood-stabilizing medications, which carry a toxicity risk, and may increase the risk of complications and associated non-compliance [4,8,9].

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive, brain stimulation therapy with growing evidence for its use in bipolar depression [10]. Treatment-emergent affective switches are an issue when managing bipolar depression [4]. A meta-analysis of randomized controlled studies using rTMS in acute bipolar depression indicated low rates of treatment-emergent affective switches [10]. The Maudsley Prescribing Guidelines advise clinicians to consider adjunctive rTMS, but indicate no preference for one strategy [2]. This is contrary to the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Guidelines from the United States, which recommend electroconvulsive therapy (ECT) instead of rTMS based on existing evidence. ECT however has a higher side-effect profile than rTMS [11,12].

Thyroid function has long been associated with behavioral disturbances [13-15]. A higher prevalence of thyroid dysfunction is likely in RCBPD and other refractory forms of BPD [13]. Thyroid dysfunction is associated with poor treatment response, particularly in bipolar depression and mixed states [16]. Findings suggest hypothyroidism may increase the risk of rapid cycling in BPD, regardless of aetiology [17,18].

Supra-physiologic doses of levothyroxine (average 482 µg/day) have proven effective for treatment-resistant BPD [19]. In two open label studies with a follow-up period of two and four years respectively, treatment-resistant patients improved following supra-physiological doses with minimal side effects [20,21]. In a randomized, double blind, placebo-controlled study of HDL in BPD. Patients with BPD received levothyroxine (300 µg once daily) as adjunctive therapy. The primary measure was reduction of mean change in Hamilton Rating Scale for Depression. None developed side effects needing a change in treatment [22].

Osteoporosis remains a concern for long-term HDL use despite reassuring data on the contrary [23] with only sporadic cases reported of women with mood disorders having reduced bone mineral density (BMD) on HDL [24]. The most malignant manifestation of thyrotoxicosis is thyroid storm, which is thought to develop when a precipitating factor(s) such as surgery, medication, or myocardial infarction is present [25].

It is unclear exactly how HDL benefits patients with BPD. However, there is precedence for the influence of genetics in BPD - heritability is estimated at 60-80% [26]. Genetic factors influence circulating thyroid hormone (TH) levels [27]. TH status is associated with cognitive function and emotional well-being [28]. The genes encoding the iodothyronine deiodinases alter the balance of TH levels [29]. In particular, deiodinase types 1 and 2 (DIO_1 and DIO_2) convert thyroxine (T4) to 3,5,3′-triiodothyronine (T3) [29]. All T4 and 20% of T3 come from the thyroid gland [29]. DIO_1 generates the majority of circulating T3 while DIO_2 produces intracellular T3 [30]. The effects of TH are mediated by T3 in target tissues, thus T4 acts as a pro-hormone. DIO_1 and DIO_2 gene polymorphisms have been shown to have significant effects on the T4:T3 ratio [31]. DIO_3 promptly inactivates HDL in the peripheral tissues, which leads to increased levels of Reverse T3 (rT3) [30]. rT3 further inhibits T3 production by inhibiting DIO_1 and DIO_2 [30].

HDL may improve RCBPD symptoms, by potentially increasing local production of T3 in the brain. Intracellular T3 concentrations vary significantly in different tissues partly due to the actions of DIO enzymes. Unlike in peripheral tissues, DIO_2 ubiquitinatin is less pronounced so DIO_2 tends to remain "active". T3 production in the hypothalmo-pituitary glands is therefore, preserved relative to the peripheral circulation [32].

Additionally, DIO_2 becomes inactivated after converting T4 to T3. Thus, in peripheral tissues, higher T4 concentrations mean a greater need for DIO_2 to inactivate this pro hormone by converting to T3. This then leads to reduced levels of active DIO_2 and ultimately T3. So, higher levels of T4, mean greater reduction in DIO2 activity, which prevents excessive production of harmful T3 [33,34].

Therefore, it could be argued that deiodinase (DIO) single nucleotide polymorphisms (SNPs) may affect neuropsychological parameters because DIO activity is important for local T3 availability in the brain.

A Chinese case-control study showed that patients with a heterozygote polymorphism of the DIO_2 gene (CT allele) had a 1.6-fold increased risk of BPD and a 3.75-fold increased risk if they had a homozygous variant (CC allele) compared to controls [35]. Thr92Ala is one of the most commonly studied DIO_2 polymorphism. Mice with selective inactivation of DIO_2 in the astrocytes (astrocyte DIO_2 knockout mice), showed substantial reduction in DIO_2 messenger ribonucleic acid (mRNA), reduced DIO_2 activity (but normal DIO_3 activity) in the cerebral cortex and hippocampus, and they exhibited anxiety/depression-type behavior with reduced hippocampal expression of markers that are associated with depression in animal models [36].

In this paper, we describe a cohort of twenty patients with the diagnosis of RCBPD who were treated with HDL and rTMS, had regular monitoring of thyroid function and were then retrospectively tested for genetic variations of thyroid enzymes to explore their association with treatment outcome and experience of side effects.

Methods

The methods described constitute a protocol used at The London Psychiatry Centre, UK. We conducted an evaluation of 20 consecutive individuals in remission from RCBPD for whom we had at least six months follow-up post-treatment. Patients' treatment start date was between 2008 and 2017. TFTs were routinely undertaken from the beginning whilst genetic testing was conducted in 2018 routinely at the centre, and these 20 patients were the first. All patients provided written, informed consent and fulfilled the International Classification of Diseases (ICD)-10 for BPD. Twelve patients had dual-energy x-ray absorptiometry (DEXA) scans to measure BMD.

Pre-treatment electrocardiograms (ECGs) and other routine baseline observations were performed. ECGs were checked weekly - patients with abnormal ECG were referred to a cardiologist before receiving levothryoxine.

Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Sheehan Disability scales, and mood charts, were used alongside reports from patients and their relatives to judge remission (i.e. symptom free).

Blood samples were taken to assess thyroid function (thyroid stimulating hormone [TSH], fT4, fT3, and ferritin) pre-treatment, at 150 µg (day 4-5 of 150 µg dose) and at every dose increase thereafter and then every three months during remission to prognosticate long-term safety of their treatment regimen (Roche electro chemiluminescence analyzer). Reverse T3 was measured using liquid chromatography-tandem mass spectrometry (Quest Diagnostics, UK). Subsequently, and after acquiring patient consent, we assessed DIO_1 and DIO_2 status and whether patients were homozygous, heterozygous or showed no variance. These genetic data were coupled with pre- and post-treatment endocrine data. Testing started from 2018, so patients treated before this date were tested retrospectively after reaching remission.

Patients' clinical notes were examined, and genetic and thyroid function test (TFT) data assessed for any correlation between patients' genetic status, overall treatment response, and incidence of adverse effects.

Levothyroxine dosing, started at 50 µg and was adjusted in 50 µg increments every four to seven days up to 150 µg and then increased further every seven days until remission.

Results

Patient's baseline characteristics

The average patient age was 32.4 (range: 15-61) years and 17 (85%) were female (Table 1). Seventeen (85%) patients had daily rTMS, using a right-sided DLPFC 1 Hz stimulation protocol (Magventure TMS, Reading, UK). The mean number of sessions was 32, median was 30 and range was 16-65 (Table 1). One of these patients received HDL followed by rTMS one year later following side effects on levothyroxine 600 µg. One patient received HDL three months after receiving ECT (rTMS was not available in the UK at that time) and two patients received HDL without rTMS (Table 1).

Table 1: Baseline Patient Characteristics.

Patient number	Sex	Age, years	Levo dose, µg		rTMS	No of rTMS sessions	DEI01	DEI02	Pre-fT4, pmol/L	Pre-fT3, pmol/L	Pre-fT4:fT3
			Initial	Last/ latest							
1	F	34	450	600	Yes	40	Homo	Homo	25.9	4.6	5.63:1
2	F	36	600	175	Yes	45	No var	Hetero	13.7	1.9	7.06:1
3	F	17	150	150	Yes	19	Hetero	Hetero	15.4	5.3	2.91:1
4	F	27	500	500	Yes	25	No var	Hetero	14.5	4.7	3.09:1
5	F	39	300	300	Yes	25	No var	Homo	13.2	4.6	2.87:1
6	F	23	400	500	Yes	32	No var	Hetero	22.9	6.1	3.75:1
7	F	43	750	800	Yes	40	Hetero	Hetero	12.3	3.6	3.42:1
8	F	17	800	1000	Yes	21	Hetero	No var	16.3	3.9	4.18:1
9	F	44	200	200	Yes	23	Hetero	Hetero	14.1	3.3	4.27:1
10	F	15	550	650	Yes	53	Homo	No var	15.2	4.9	3.10:1
11	F	20	500	500	Yes	17	Homo	No var	16.1	5.2	3.10:1
12	F	21	400	400	Yes	34	No var	No var	17.4	3.4	5.12:1
13	F	31	600	200	Yes	20	Hetero	No var	13.4	3.8	3.53:1
14	F	61	350	350	No	N/A	Homo	No var	2.8	5.2	4.19:1
15	M	21	500	500	Yes	16	Hetero	Homo	13.5	7.2	1.88:1
16	F	57	550	600	Yes	41	Homo	No var	58.2	10.4	5.60:1
17	M	22	600	600	Yes	30	Hetero	No var	11.8	4.9	2.41:1
18	M	51	400	400	No	N/A	Hetero	Hetero	17.5	4.9	3.57:1
19	F	49	250	250	No - ECT	N/A	Homo	No var	21.9	4.4	4.98:1
20	F	44	400	750	Yes	65	No var	Hetero	20.5	3.9	5.26:1

DEI: deiodinases; ECT: electroconvulsive therapyf: female; fT3: free T3 (tri-iodothryonine); fT4: free T4 (thyroxine); hetero: heterogenous; homo: homogenous; Levo: levothyroxine; m: male; N/A: not applicable; rTMS; repetitive transcranial magnetic stimulation var: variation.

Treatment outcomes

Follow-up period was for a maximum of 12 years (Table 2). Patients 1, 11 and 14 were discharged but contact was re-established at the time of the evaluation and were confirmed to have remained well.

The longest period of remission was 12 years; the shortest was four months following relapse after an initial 36-month remission. Mean remission period was 46.6 (median: 33; mode: 29; range: 16-145) months. None of the patients discontinued HDL. All patients had normal cardiac function while receiving HDL (normal ECGs and no cardiac symptoms).

The mean daily dose of HDL was 471.25 µg, the median and mode were 500 (150-1000) µg was needed to achieve remission. Mean duration of remission in the 12 non-relapsers (60%) was 57.4, median 45.5 (range: 26-145) months.

Eight patients (40%) relapsed, of which six (75%) recovered with an increase in HDL dose plus rTMS, and one disengaged; one remains in treatment, bringing the total in full remission to 90%. Mean duration to relapse in this group was 31.5 (median 26.5; range 16-65) months. Following recovery after relapse the mean duration of remission was 12.33 (range: 4-21) months.

To achieve remission, 12 patients (60%) required additional medication: 11 (55%) required a neuroleptic in the acute phase, of which two (10%) required a neuroleptic plus mood stabilizer; and one (5%) an antidepressant namely Tianeptine (Table 2).

For maintenance, 11 (55%) patients were on HDL only, 9 (45%) needed additional medication: six were taking one neuroleptic, two were taking a neuroleptic plus a mood stabilizer, and one was taking an antidepressant, namely Tianeptine.

Six patients had additional rTMS/HDL increase and one had a neuroleptic with no rTMS, six of which took alcohol or caffeine against advice, or had post-traumatic stress disorder (PTSD), all of which can trigger relapse in BPD. Patient 6 did not reach remission after relapse and disengaged, and was lost to follow-up (Table 2).

Thyroid function

Pre-treatment: average fT4 was 17.0 (12-22) pmol/L, average fT3 was 4.5 (3.1-6.8), and average fT4:fT3 was 4:1 (Table 1). Post-treatment: average fT4 increased to 59.7 pmol/L, average fT3 increased to 5.3 pmol/L and average fT4:fT3 increased to 5:1 (Table 2).

Pre-treatment TFTs were normal but at 150 µg, fT4:fT3 was high, with elevated fT4 and normal fT3 levels; TSH levels had decreased. This is the predictive test we advocate and should be used at doses of 150 µg, by day 10 of initiation of treatment.

Table 2: Post-treatment Assessment Outcomes.

Patient number	Post-fT4, pmol/L	Post-fT3, pmol/L	Post- fT4:fT3	Mood stabiliser (Y/N)	Neuroleptic (Y/N)	In remission since, months	Time to relapse, months	Reason for relapse	Time period of feeling well since second round of rTMS, months
1	52.5	8.6	6.10:1	No	No	30	..	..	..
2	100.0	18.2	5.49:1	AD	No	26	..	..	..
3	31.2	7.9	3.95:1	No	No	35	..	..	..
4 N	50.5	11.2	4.51:1	No	Yes	31	..	..	..
5	34.8	9.6	3.63:1	No	Yes	56	..	..	..
6	37.1	8.4	4.42:1	No	No	..	16	Caffeine/ disengaged from treatment plan	..
7	85.6	15.8	5.42:1	No	Yes	..	38	High-dose caffeine use	4
8	59.8	9.2	6.41:1	No	Yes	..	41	PTSD (death)	9
9	33.2	5.1	6.51:1	No	Yes	89	..	..	..
10	33.4	7.0	4.77:1	No	No	..	20	Exams	18
11	100.0	14.8	6.76:1	No	No	..	24	No trigger	18
12 N	100.0	21.3	4.69:1	No	Yes	79	..	..	..
13	100.0	16.8	5.95:1	No	No	29	..	..	..
14	48.0	11.4	4.21:1	Yes	Yes	28	..	..	..
15 N	31.4	7.2	4.36:1	No	Yes	84	..	..	..
16	52.4	13.0	4.03:1	Yes	Yes	..	19	PTSD (death)	21
17	100.0	14.7	6.80:1	No	No	57			..
18	41.1	9.8	4.19:1	No	Yes	..	29	Alcohol/ Caffeine	In treatment
19	52.8	7.5	7.04:1	No	No	145	..	..	..
20	50.2	8.3	6.05:1	No	Yes	..	65	PTSD (work-related)	4

N: denotes those patients for which acute phase neuroleptic was discontinued in maintenance.
fT3: free T3 (tri-iodothryonine); fT4: free T4 (thyroxine); PTSD: post-traumatic stress disorder; rTMS; repetitive transcranial magnetic stimulation.

Reverse T3 levels were uniformly elevated except in patient 13 whose reverse T3 was at the upper limit of the normal range (Table 3). This is most likely because of the more modest dose of levothyroxine the patient was taking compared to the other patients.

Table 3: Reverse T3 for Each Patient Where the Lower Range is 10 ng/dL and higher is 24 ng/dL.

Patient number	rT3 (ng/dL)
1	99
2	35
3	..
4	66
5	30
6	87
7	70
8	..
9	63
10	72
11	134
12	121
13	24
14	47
15	93
16	87
17	..
18	..
19	77

rT3: reverse T3 (tri-iodothryonine).

Genetics

Fourteen patients (70%) had single nucleotide polymorphisms (SNPs) of DI01 (rs2235544), while 11 (55%) had SNPs of DI02 (rs12885300 and/or rs225014) (Table 1). One patient (5%) had an abnormal SLC0 1C1 (5%) carrier and has now been in remission for approximately seven years on 400 µg of levothyroxine.

Bone Mineral Density

Of the 12 patients who had DEXA scans, nine had normal BMD at the spine, and seven at the hips. In three patients, serial DEXA scans were available: one patient had significant improvements in BMD and the other two had significant reductions of 10% and 15%; the latter required dose reduction due to a possible association between dose and BMD decline. Consequently, their previously stable mood deteriorated.

Adverse effects

One patient required a dose reduction (750 to 600 µg) due to BMD anomalies, had side effects (palpitations/sweating), and was mildly thyrotoxic. Additional rTMS was administered in this patient to remission. A second patient was also administered rTMS (this patient had originally declined rTMS) and HDL was reduced from 600 to 200 µg with no side effects. This patient has now been in remission for almost two years after being ill for some 10 years.

Discussion

Following our protocol described here, all 20 patients receiving HDL and rTMS reached remission from RCBPD with minimal side effects. During maintenance, 12 (60%) were on monotherapy, six (30%) were on two drugs and two (10%) were on three drugs. A survey of outpatient bipolar patients showed that a third were taking four or more medications, most taking three or more drugs and less than one in five on monotherapy. We observed that these patients had a high fT4:fT3 ratio during treatment, indicating inefficient conversion of T4 to T3. Furthermore, we observed strong association between RCBPD and SNPs of DI01 and/or DI02 and the biochemical response correlated with the clinical response i.e. mood stabilization and minimal adverse effects.

This novel approach to treating bipolar spectrum disorders shows that those individuals who went into remission were more likely to have a high free T4 to free T3 ratio by day 10 and at 150 mcgs Levothyroxine and polymorphisms of the DIO_1 gene, or DIO_2 gene, or both. Thus, the high FT4/FT3 ratio, which correlated with the presence of these SNPs, helped to predict a safer treatment response in this small cohort of patients.

Based on these observations, we speculate that BPD is a form of cerebral hypothyroidism and HDL helps to overcome the deficit. Furthermore, robust inactivating deiodinases in peripheral tissues protect from systemic thyrotoxicosis.

We have also shown that the well-established neuroplastic effects of rTMS helped to achieve and maintain remission when used as an adjunct to HDL. Many physicians seem reluctant to prescribe HDL for RCBPD due to concerns relating to hyperthyroidism as patients' blood results are typically in the thyrotoxic range and patients are clinically euthyroid – or risks of cardiac bone mass issues, yet HDL is used frequently to treat thyroid cancer.

Using our protocol, patients received HDL and rTMS, and none discontinued treatment - only two patients needed dose reduction, which improved the clinical scenario. It is worth noting that the second patient with reduced BMD was older and female, therefore raising the possibility of other factors affecting BMD, such as menopause.

Our cohort of patients had very abnormal yet unique biochemistry, but showed markedly different clinical manifestations. Patients with thyroid storm are unwell, symptomatic and more likely to exhibit clinical signs commensurate with hyperthyroidism. By contrast, our patients showed substantial mood improvements without significant side effects.

We cannot discount the possibility of mild adverse effects from HDL given one of our patients reported palpitations and reduced BMD. Nevertheless, the benefit to risk ratio favoured levothyroxine (on a reduced dose) given the high mortality risk associated with RCBPD. There were no side effects on the reduced dose when rTMS was deployed. Possible explanations for the disconcordance between lack of thyroxicosis clinical features yet clear biochemical evidence of elevated TH and suppressed TSH include:

DIO_3 promptly inactivates HDL in the peripheral tissues which leads to increased levels of rT3. Concentrations of rT3 were

significantly elevated in our patients. rT3 further inhibits T3 production by inhibiting DIO_1 and DIO_2.

Conclusion

Our novel protocol enables previously treatment-resistant RCBPD patients with severe symptoms to receive long term HDL plus rTMS with minimal side effects and achieve remission. We observed that the patients who do well on HDL have a high fT4:fT3 ratio and a DIO_1 and/or DIO_2 mutation. The methodology we use is conducive to clinical practice and enables TH and genetic profiles to be assessed to help improve the effectiveness and tolerability of treatment. Further exploration is now required in a larger cohort of patients to also enable us to establish cause and effect in relation to the genetic profiles of these patients and the outcomes we observed, and if the high fT4/fT3 ratio correlates well with the genetics and the clinical picture we could advocate the use of the ratio instead of genetic testing where such testing is not available.

Conflicts of Interest

Andy Zamar is the founder and owner of The London Psychiatry Centre. He is the inventor of the protocol described in this article for which The London Psychiatry Centre has filed a patent application, which is pending. Robin Robers has no conflict of interest. Abbi Lulsegged is an employee of HEALTH121 Ltd and has no other conflict of interest. Alexander Bedu Addo is a medical student and has no conflict of interest to declare. Christos Kouimtsidis provides clinical sessions at the London Psychiatry Centre. He has no other conflict of Interest.

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