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Research paper

Long-term treatment with supraphysiologic doses of levothyroxine in treatment-refractory mood disorders – A prospective study of cardiovascular tolerability

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ABSTRACT

Background: To investigate long-term effects of adjunctive prophylactic treatment with supraphysiologic doses of levothyroxine (L-T4) on cardiovascular tolerability in 23 patients with treatment-refractory mood disorders.
Methods: Starting point for a comprehensive cardiovascular assessment in patients was the indication for long-term maintenance treatment with L-T4 (mean dose 463 mcg/day). Prospective longitudinal assessment of the cardiovascular risk profile included in addition to a physical examination and blood pressure measurement, several technical investigations: resting electrocardiogram, transthoracic echocardiogram, cardiac stress test, and holter electrocardiogram. Statistical analysis was performed by linear mixed effects models (LMM) for evaluation of longitudinal changes in various heart measures.
Results: During the mean observational period of 20.4 months none of the heart measures reached statistical significance in change over time. None of the assessed cardiac parameters of each single patient was in a range predictive for cardiac dysfunction.
Limitations: Small sample size, no technical cardiac investigations prior to L-T4 initiation, no patient control group with mood disorders who did not receive L-T4.
Conclusions: Results of this study indicated no increased risk for cardiovascular disorders during treatment with supraphysiologic L-T4 doses in patients with refractory mood disorders.

1. Introduction

The field of pharmacotherapy for severe mood disorders has developed towards polypharmacy, which has become the rule rather than the exception in bipolar and unipolar disorders. Despite a magnitude of options for combination therapy in acute and long-term treatment, a significant group of patients (estimates range from 10 to 30%) remains unstable and develop a course of treatment-refractoriness (Bauer et al., 2002b, 2014; Diazgranados et al., 2010).

Supraphysiologic doses of levothyroxine (L-T4) has offered promise in several open and controlled studies, including rapid cycling, prophylaxis-resistant bipolar patients and for patients with refractory unipolar or bipolar depression (Bauer and Whybrow, 1990; Bauer et al., 1998, 2002b; Bauer et al. 2005). Adjunctive treatment with supraphysiologic doses of L-T4 has also demonstrated efficacy in reducing depressive symptoms in a recent double-blind, placebo-controlled trial (Stamm et al., 2014; Bauer et al., 2016). Augmentation with high doses (average dose 90.4 mcg) of triiodothyronine (T3) in treatment-resistant patients with bipolar II disorder and bipolar disorder NOS showed beneficial effects in a large retrospective chart sample (Kelly and

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Lieberman, 2009).

Despite its efficacy and effectiveness, a broader acceptance of the treatment with supraphysiologic doses of L-T4 has been limited by the sparse number of long-term studies investigating its tolerability and potential somatic side effects. Additionally erroneously classifying patients receiving treatment with supraphysiologic doses of L-T4 as "hyperthyroid" or even "thyreotoxicated" limited the prescription by psychiatrists (Kelly, 2015). Concerning more specific side effects, Kelly (2015) pointed out to two major concerns that prevent wide acceptance of high doses of L-T4 for the treatment of mood disorders: treatment with high doses of L-T4 might be a risk factor for developing osteoporosis, and secondly, it increases cardiovascular risks (Kelly, 2015).

With regard to general side effects acute studies with treatment up to 8 weeks have demonstrated good tolerability of treatment with supraphysiological L-T4 (Bauer et al., 1998; Bauer et al., 2005; Stamm et al., 2014; Bauer et al., 2016). Additionally, treatment with supraphysiological doses of L-T4 did not cause significant effects on sleep architecture by means of polysomnography in healthy subjects over 8 weeks (Kraemer et al., 2011). Cross-sectional studies investigated clinical tolerance assessed with the clinician-rated Thyroid Symptom List (Bauer et al., 2002a) and a self-rated complaint list. Rating 24 patients with refractory mood disorders (Bauer et al., 2001) receiving a mean dose 368 mcg/d for a mean of 54 months indicated an overall favorable side effect profile with only slightly elevated general physical and mental symptoms. In line with cross-sectional studies in pre- and postmenopausal women with mood disorders (Gyulai et al., 2001; Gyulai et al., 1997), Bauer et al. (2004) and Ricken et al. (2012) found no evidence for significant bone loss or reduced bone mineral density during long-term treatment with supraphysiologic doses of L-T4.

A recent review systematically investigating cardiovascular tolerability of treatment with supraphysiologic doses of L-T4 in patients suffering from mood disorders criticized that there are no direct studies assessing the cardiovascular risk of this treatment. Identifying both differences and overlaps of high dose treatment with thyroxine and hyperthyroidism the author concluded from retrospective data that the cardiovascular risks of treatment with supraphysiologic doses of LT4 appeared to be low (Kelly et al., 2016).

Addressing this lack of evidence, we systematically monitored changes of cardiac markers prospectively during long-term treatment of mood disorders with supraphysiologic doses of L-T4. Since it is well known that hyperthyroidism causes cardiac arrhythmias, e.g. atrial fibrillation, as well as tachycardia, systolic hypertension and especially "high output cardiac failure" we looked for cardiac function based on these markers. In line with cardiologic diagnostic guidelines (ACC/AHA guidelines for the clinical application of echocardiography, 1990; ESC Working Group on Exercise Physiology, Physiopathology and Electrocardiography, 1993; Schlant et al., 1992) cardiovascular risk was inferred by repeated comprehensive assessment of echocardiography, cardiac fitness by ergometry and 24-h holter ECG.

2. Patients and methods

2.1. Design and subjects

This cohort study was designed to prospectively investigate effectiveness and tolerability of add-on supraphysiologic L-T4 doses in patients with unstable mood disorders who had not responded to various standard prophylactic therapies. It was intended to perform annual comprehensive cardiac assessments in the patients under routine treatment conditions. After the procedures were thoroughly explained, written informed consent was obtained from each study participant at the time of enrollment.

Patients were recruited from a maintenance treatment study of adjunctive treatment with supraphysiologic doses of L-T4 in patients with prophylaxis resistant affective disorders described elsewhere (Bauer et al., 2002b, 2004; Ricken et al., 2012). We included two additional patients who had received similar treatment with L-T4 and cardiac measurements. Since we conducted this study under routine treatment conditions, patients presented in different stages of their mood disorder ranging from remitted to moderate and severe episodes within bipolar disorder, recurrent depressive disorder or schizoaffective disorder (Table 1 for demographical, clinical and treatment characteristics of the study population).

Table 1
Demographic, clinical and treatment characteristics of 23 patients with treatment-refractory mood disorder and supraphysiologic L-T4 therapy.

Gender (male)	6 / 23	26%
Index diagnosis		
Bipolar disorder	15 / 23	65%
Major depressive disorder, recurrent	5 / 23	22%
Schizoaffektive disorder	3 / 23	13%
Severity of illness at baseline		
Remitted	6 / 23	26%
Moderate	3 / 23	13%
Severe	11 / 23	48%
Psychotic	3/ 23	13%
History of thyroid illness	5 / 23	22%
smoker	7 / 23	30%
Medication at baseline		
Lithium	14 / 23	61%
Anticonvulsants	18 / 23	78%
Antidepressants	17 / 23	74%
Neuroleptics	10 / 23	43%
Estradiol	3 / 23	13%
Other psychotropic medication	2 / 23	9%
	Mean	SD
Age at baseline	47.8	8.0
Age at initial manifestation	31.5	9.5
Years of illness	16.4	12.1
Number of episodes prior to L-T4	20.3	19.0
Treatment with L-T4		
Mean duration of L-T4 at first cardiologic observation (month)	16.4	16.1
Mean duration of L-T4 at last cardiologic observation (month)	36.2	23.7
Mean duration of cardiologic observation	20.4	13.7
fT4 serum level at baseline [ng/l]	10.2	3.3
fT3 serum level at baseline [ng/l]	1.1	0.3
TSH basal level at baseline [mlU/l]	1.5	1.2
Systolic blood pressure at baseline [mm HG]	125.2	13.5
diastolic blood pressure at baseline [mm HG]	78.8	8.9
Heart rate at baseline [bpm]	79.4	11
BMI at baseline [kg/m^2]	26.2	4.3
Alcohol consumption (drinks / week) at baseline	1.4	3.1
Average numbers of ergometries per patient	1.6	1.1
Average numbers of long-term ECGs per patient	1.9	1.0
Average numbers of echocardiographies per patient	1.6	0.8

Abbreviations: BMI, body mass index; fT3, free trijodothyronine; fT4, free thyroxine; TSH, thyroid stimulating hormone.

2.2. Maintenance treatment with L-T4

Patients received supraphysiologic doses of L-T4 in addition to the psychotropic medications they had received prior to study entry. Medications included lithium, anticonvulsants, antipsychotics and antidepressants according to clinical needs. L-T4 dosage was adjusted due to clinical needs and TSH was suppressed (TSH ≤ 0.1 ml U/l) during the entire observational period (except at two measurements, Table 1). Blood for examination of thyroid levels was routinely drawn in the morning before L-T4 intake.

2.3. Assessment of cardiovascular risk profile

The cardiovascular risk was assessed by a cardiologist (G.B.). The complete assessment included

a. case history with particular attention to dyspnoe, palpitations, edema, less exercise capacity, or other discomfort.