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Treatment of Refractory Depression with High-Dose Thyroxine

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In an open clinical trial we investigated whether addition of supraphysiological doses of thyroxine (T_4) to conventional antidepressant drugs has an antidepressant effect in therapy-resistant depressed patients. Seventeen severely ill, therapy-resistant, euthyroid patients with major depression (12 bipolar, five unipolar) were studied. The patients had been depressed for a mean of 11.5 ± 13.8 months, despite treatment with antidepressants and, in most cases, augmentation with lithium, carbamazepine, and neuroleptics. Thyroxine was added to their antidepressant medication, and the doses were increased to a mean of 482 ± 72 μg/day. The patients' scores on the Hamilton rating Scale for Depression (HRSD) declined from 26.6 ± 4.7 prior to the addition of T_4 to 11.6 ± 6.8 at the end of week 8. Eight patients fulfilled the criteria for full remission (a 50% reduction in HRSD score and a final score of ⩽9) within 8 weeks and two others fully remitted within 12 weeks. Seven patients did not remit. The 10 remitted patients were maintained on high-dose T_4 and followed up for a mean of 27.2 ± 22.0 months. Seven of these 10 remitted patients had an excellent outcome, two had milder and shorter episodes during T_4 augmentation treatment, and one failed to profit from T_4 treatment during the follow-up period. Side effects were surprisingly mild, and no complications were observed at all. In conclusion, augmentation of conventional antidepressants with high-dose T_4 proved to have excellent antidepressant effects in approximately 50% of severely therapy-resistant depressed patients.

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KEY WORDS: *High-dose thyroxine; Major depression; Therapy-resistant depression*

Major depression is generally viewed as a disorder with a relatively favorable prognosis. Nonetheless, in recent years several epidemiologic studies have unanimously reported that between about 5 and 15% of depressed patients become chronically ill, i.e., they fail to recover over a period of several years (Lee and Murray 1988; Scott 1988; Keller et al. 1992; Howland 1993; Picinelli and Wilkinson 1994; Thase and Rush 1995; Thase et al. 1995). All of these epidemiologic studies investigated the course of mood disorders in a more or less "naturalistic" design, i.e., the long-term therapy of the depressed patients was not standardized. The question therefore arises as to whether chronically depressed patients might profit from more rigid, standardized therapeutic strategies. Such strategies could include treatment with different classes of antidepressants in sufficiently high doses over not less than 6 weeks respectively, as well as several "augmentation strategies" such as the addition of lithium, triiodothyronine (T_3) or neuroleptics, and electroconvulsive therapy (Thase and Rush 1995; Thase et al. 1995). With respect to thyroid hormones, several older studies reported that the addition of low-dose (25–50 μg/day) triiodothyronine (T_3) induced an acceleration of the response to tricyclic anti-

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depressants (e.g., Prange et al. 1969). Later, the addition of T_3 to conventional antidepressants was found to be highly effective in treatment-resistant depressed patients in some studies (e.g., Goodwin et al. 1982; Joffe and Singer 1990; Joffe et al. 1993), but not all (e.g., Garbutt et al. 1986; Gitlin et al. 1987; Thase et al. 1989a; for a review, see Joffe et al. 1995). An interesting hypothesis on the mechanism of action of T_3 was put forward by Joffe et al. (1984, 1995), namely, that depression is a state of relative T_4 excess and that T_3 acts by lowering the serum concentrations and subsequently also the brain concentrations of T_4 via inhibition of thyroid-stimulating hormone (TSH) secretion.

On the other hand, thyroxine (T_4) itself has now been reported to be effective in the prophylaxis of previously therapy-resistant, rapid-cycling bipolar disorders (Stancer and Persad 1982; Leibow 1983; Bauer and Whybrow 1986, 1990; Hurowitz and Liebowitz 1993). Our own group recently reported that treatment with supraphysiological doses of T_4 stabilized previously completely treatment-resistant, severely ill nonrapid cycling bipolar patients (Baumgartner et al. 1994a). In some of these patients prophylaxis with high-dose T_4 was initiated during a depressed episode. We gained the impression that in these patients the depressive episode subsided much faster than previously. These observations prompted us to conduct an open clinical trial in which we investigated the effects of high-dose T_4 augmentation in depressed patients who had failed to respond to conventional pharmacotherapy.

PATIENTS AND METHODS

As the administration of high doses of T_4 must still be regarded as an experimental therapeutic strategy, we thus intentionally accepted for this study only the most severely ill and treatment-resistant depressed patients who sought treatment at the in-or outpatient facilities of the psychiatric clinic between 1990 and 1995. The patients were not included in the trial unless several other available therapeutic and/or prophylactic treatments had already proved ineffective, either during the present episode or previously, and the idea of high-dose T_4 treatment thus presented itself as a kind of "last resort" treatment. The patients included in the study were therefore most likely to be more strongly resistant to treatment and had a more serious course of depressive illness than the patients usually included in "augmentation studies," who have as a rule failed to respond to only one previous trial of one antidepressant (Thase and Rush 1995; Thase et al. 1995).

Formally, all patients were required to meet the DSM-III-R (American Psychiatric Association 1987) criteria for major depression or bipolar disorder, depressed. Consensus diagnoses were made at a conference of two independent raters, using information from a diagnostic interview and from previous psychiatric case notes, which were available in all cases (see below). For inclusion in the study the patient had to be considered therapy resistant, according to the following criteria (standardized criteria for nonremission according to Nierenberg and Amsterdam 1990):

- Nonremission after administration of at least two chemically different antidepressant medications, each administered in standardized doses for a period of at least 6 weeks: tricyclics and tetracyclics >150 mg/day, selective serotonin reuptake inhibitors (SSRI) >20 mg/day; MAO-inhibitor tranylcypromine >30 mg/day). Nonremission was defined as a failure to achieve a reduction of at least 50% on the 21-item version of the Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960) or a final HRSD score of ⩾15.
- Nonremission on the basis of an analysis of the case history: 13 of the 17 patients who were finally included had been hospitalized at the psychiatric clinic during previous episodes, most of them several times (see Table 1). Case notes giving detailed information on their response or nonresponse to antidepressant therapies during previous episodes were therefore available. For the remaining four patients, this information was obtained from other medical centers or outpatient facilities. Almost all of the patients had indeed been resistant to several different antidepressant treatments in previous episodes. We decided that in these cases when previous nonremission to one or more antidepressants was already evident from the records, one 6-week trial with a sufficiently high dose of a standard antidepressant would be sufficient to consider the patient to be treatment resistant during the present episode also. Five patients for whom nonremission to both tricyclics and lithium had already been established in previous episodes were thus considered to be treatment resistant after only one 6-week trial with one antidepressant (patients nos. 2, 3, 5, 6, and 10; see Table 1).

The patients were also required to fulfil the following additional criteria:

- no history or concomitant abuse of alcohol or addictive drugs, including benzodiazepines
- no serious somatic illnesses or diseases considered to be a contraindication for high-dose T_4 treatment, such as severe cardiac insufficiency, a history of myocardial infarction, cardiac arrhythmias, or a history of thyroid adenoma or hyperthyroidism.

Four patients who were already receiving T_4 in physiological doses due to lithium-induced subclinical hypothyroidism and whose laboratory values showed them to be euthyroid, were accepted for the study.

Twenty-one patients fulfilling the above criteria

were considered for inclusion in the study. Four of them then had to be excluded owing to benzodiazepine and amphetamine abuse ($n = 1$), severe cardiac arrhythmias ($n = 1$) and a recent history of autonomic adenoma ($n = 2$). Thus, a total of 17 patients was finally accepted for the study.

The following clinical and laboratory investigations were performed for all patients: routine laboratory

Table 1. Demographic and Clinical Data of 17 Patients with Refractory Depression before Thyroxine Treatment

Pat. No.	Sex/ Age(Y)	DSM-III-R Diagnosis	Total No. of Episodes	Average No. Episodes/ Year	Length of Episode before T_4-Treatment (month)	Medication during Episode before T_4 Treatment		
						Name	Dose (mg/day)	Duration (month)
1	F/39	Bipolar disorder, depressed, with psychotic features	4	1	31	Amitriptyline	225	3
						Maprotiline	250	2
						Paroxetine	20	1
						Nortriptyline	200	1.5
						Perazine[a]	600	>12
						Clozapine[a]	700	6
						Lithium[a]	36 mmol	>12
						ECT	17×	
2	F/51	Bipolar disorder, depressed, severe	20	1.6	4	Fluoxetine	100	2.5
						Carbamazepine[a]	800	2.5
						Thioridazine[a]	300	2.5
3	F/44	Bipolar disorder, depressed, moderate	10	2.5	3	Fluoxetine	80	1.5
4	F/55	Major depression, recurrent, severe	1	_	50	Doxepine[b]	75	10
		Panic disorder, without agoraphobia				Clomipramine	250	1.5
						Dibenzepine	1200	4
						Nortriptyline	300	1
						Fluoxetine	80	1
						Clozapine	250	4
						Fluspirilene	0.3 IM	4
						Thioridazine	50	10
						Carbamazepine[a]	1500	2.5
						Lithium[a]	24 mmol	0.5
5	F/57	Bipolar disorder, depressed, with psychotic features	30	1.2	2	Amitriptyline	225	2
						Lithium[a]	18 mmol	2
6	F/42	Bipolar disorder, depressed	10	1.9	2	Tranylcypromine	30	2
						Lithium[a]	30 mmol	2
						Carbamazepine[a]	600	2
						Thyroxine[a]	150	2
						Perazine[a]	100	2
7	M/41	Bipolar disorder, depressed, severe	3	1.5	5	Doxepine	150	1.5
						Amitriptyline	150	2
						Imipramine	500	2
						Lithium[a]	36 mmol	2
8	F/46	Major depression, recurrent, severe	2	0.5	12	Doxepine[b]	300	10
						Nortriptyline	200	2
						Carbamazepine[a]	600	>12
						Lithium[a]	24 mmol	6
						Perazin[a]	300	6
						Thyroxine[a]	200	>12
9	F/59	Bipolar disorder, depressed, with psychotic features	10	0.4	13	Trimipramine[b]	175	6
						Trazodone	250	1
						Fluoxetine	100	4
						Imipramine	200	1.5
						Thioridazine[a]	600	8
						Carbamazepine[a]	1000	>12
						ECT	17	
10	F/43	Bipolar disorder, depressed, with psychotic features	30	1.2	2.5	Doxepine	225	2.5
						Lithium[a]	24 mmol	2.5
						Perazine[a]	400	2.5

(*continued*)

screening, including red cell count (RBC) and white cell count (WBC), aspartate aminotransferase (GOT), alanine aminotransferase (GPT), creatinine and erythrocyte sedimentation rate (ESR), as well as serum concentrations of TSH and thyroid hormones (T_4, T_3, fT_4). In addition a thoracic X-ray, a 24-h echocardiogram (ECG) recording, blood pressure measurement three times a day, and a thorough physical examination by an experienced endocrinologist (K.-J. G.) were performed. Patients with a history of or suspected thyroid disorder also underwent thyroid sonography and scintigraphy.

Detailed demographic data, diagnoses, and information on the previous clinical courses of all 17 patients are provided in Table 1. Sixteen of the patients were female and one male, and the mean age of the whole group was 50.1 ± 8.1 years (range: 39–70 years). Thirteen of the patients were receiving treatment as inpatients and four as outpatients. Five patients had unipolar depression and 12 bipolar disorder. Four patients had psychotic features and one an additional diagnosis of panic disorder (patient no. 4, Table 1).

After complete description of the study to the subjects, written informed consent was obtained. The trial protocol had been approved by the Ethics Committee of the Klinikum Rudolf-Virchow of the Free University of Berlin.

Study Design

All patients included in the study were given T_4 in addition to the antidepressive medication they had been receiving during the preceding weeks. The T_4 was administered in a single dose each morning. The starting

Table 1. (*continued*)

Pat. No.	Sex/ Age(Y)	DSM-III-R Diagnosis	Total No. of Episodes	Average No. Episodes/ Year	Length of Episode before T_4-Treatment (month)	Medication during Episode before T_4 Treatment		
						Name	Dose (mg/day)	Duration (month)
11	F/46	Major depression, recurrent, with psychotic features	15	0.9	7	Imipramine	300	6
						Nortriptyline	200	1.5
						Lithium[a]	30 mmol	6
						Carbamazepine[a]	900	6
						Haloperiodol[a]	13	2
						Perazine[a]	450	2
12	F/53	Bipolar disorder, depressed	3	0.5	34	Maprotiline[b]	150	>12
						Clomipramine	225	2
						Lithium[a]	18 mmol	2
						Perazine[a]	500	>12
13	F/46	Bipolar disorder, depressed, severe	12	1.9	3	Amitriptyline	300	1.5
						Imipramine	300	1.5
						Carbamazepine[a]	600	3
						Thyroxine	150 μg	
14	F/70	Bipolar disorder, depressed, severe	~70	~1.9	5	Amitriptyline	200	1.5
						Fluoxetine	80	2
						Paroxetine	60	1.5
						Perazine[a]	100	5
						Thyroxine	100 μg	
15	F/48	Major depression, recurrent, severe	13	0.7	5	Lofepramine	280	1.5
						Fluoxetine	80	1.5
						Imipramine[b]	400	2
						Lithium[a]	24 mmol	5
						Carbamazepine[a]	900	5
						Clozapine[a]	300	5
16	F/63	Bipolar disorder, depressed, severe	~30	1.9	13	Amitriptyline	200	2
						Doxepine	300	3
						Clomipramine	150	2
						Moclobemid		3
						Paroxetine	80	3
						Carbamazepine[a]	900	13
						Flupentixol[a]	3	4
17	F/49	Major depression, recurrent, severe	8	0.5	4	Fluoxetine	60	2
						Lofepramine	350	2
						Carbamazepine[a]	450	4
∑ ± SD			15.9 ± 17.0	1.1 ± 0.6	11.5 ± 13.8			

[a] Lithium, carbamazepine, thyroxine and neuroleptics were given concomitantly with an antidepressant medication.
[b] These treatments were performed outside the facilities of the Psychiatric Department of the Free University.

dose was 50 μg T_4/day, and the dosage was increased by 50 μg/day every 3 days, i.e., 100 μg/day on day 4, 150 μg on day 7, etc. until a dose of 500 μg/day was reached, usually on day 35. This dosage was then maintained until day 56, i.e., the end of the 8-week treatment period.

Whether this regime was adhered to as prescribed depended on the following criteria:

- Clinical improvement: when improvement had been clinically evident over a 3-day period, no further increases in the dose of T_4 were made.
- Side effects: when side effects that were most likely attributable to the T_4 medication occurred, the dose was not further increased. Side effects considered to be relevant were tachycardia of over 100 BPM, dyspnea on exercise or restlessness, but not slight tremor or sweating.
- Serum levels of TSH and thyroid hormones: blood samples were drawn for serum every third day, i.e., on the day before the dose of T_4 was raised. The results of the hormone determinations were usually available within 3 days and could thus be taken into account when considering the next-but-one increase in the T_4 dosage. We raised the dosage of T_4 until the TSH concentrations were completely suppressed and the serum level of T_4 of each respective patient was approximately double the value determined before institution of T_4 treatment.

Throughout the 8-week study, heart rate and blood pressure were monitored daily and an ECG was performed twice weekly. For patients receiving lithium and/or carbamazepine the serum levels of these drugs were determined weekly to ensure that the serum concentrations were within the range considered to be effective (≥0.6 nmol/L for lithium and ≥5 mg/L for carbamazepine).

Ratings on the 21-item Hamilton Rating Scale for Depression (HRSD) were performed on the day before institution of T_4 treatment and thereafter every second week, until the end of week 8, always by the same rater (M.B.).

At the end of the 8-week trial the efficacy of high-dose T_4 augmentation was defined as follows.

- nonremission was defined as a failure to attain a reduction of at least 50% on the HRSD and the consensus between physician and patient that a change in treatment plan (e.g., a trial of electroconvulsive therapy) was necessary;
- partial remission was defined as a reduction of ≥50% in the HRSD score, but a final score of ≥10;
- response was defined as a reduction of ≥50% in the HRSD score and a final score of ≤9, resulting in an almost symptom-free condition requiring no further changes in therapy.

At the end of week 8 the patient, the treating physician, and the investigator met to discuss whether in the respective case T_4 medication should be maintained or withdrawn.

The clinical courses of each of the patients who continued to receive high-dose T_4 were regularly monitored, and ratings on the HRSD were performed every second week in the inpatients. All outpatients and discharged inpatients who continued to receive T_4 were treated on an outpatient basis by one of the authors. During outpatient treatment the patients underwent regular checks on serum concentrations of thyroid hormones, ECG, and HRSD ratings at least once a month. Patients who continued to receive high-dose T_4 as outpatients for more than 6 months underwent serum hormone measurements and ECG recordings every 3 months and computer tomographic measurements of bone density (osteodensitometry) once a year.

For the patients taking T_4 who were followed up, "remission," "recovery," and "relapse" were defined according to criteria recently suggested (Thase and Rush 1995; Thase et al. 1995; Frank et al. 1991). Remission was defined as attainment of a virtually asymptomatic status, equivalent to HRSD score of ≤7 for at least 2 weeks. Recovery was defined as remission for ≥6 consecutive months. Relapse was defined as a return of symptoms meeting the full criteria for an episode of major depression during the period of remission, whereas recurrence referred to the occurrence of a new episode of major depression during recovery.

The determinations of thyroid hormones (T_4, fT_4, T_3) and TSH were performed by an endocrine research laboratory, all in duplicate with the following commercially available kits: the IRMA kit for TSH, RIA kits for T_4 and T_3 and the Dyno-Test for fT_4, all from Henning, Berlin. Details on the sensitivities of the kits used and the interassay coefficients of variation determined by our laboratory have been published previously (Baumgartner et al. 1988, 1990). Normal ranges for serum concentrations of thyroid hormones and TSH had been determined previously by the same methods in 60 age- and sex-matched healthy subjects. The resulting ranges were as follows: total thyroxine (T_4) 45–125 μg/L, free thyroxine (fT_4) 7–19 ng/L, triiodothyronine (T_3) 0.8–1.6 μg/L and TSH 0.4–3.5 mU/L.

RESULTS

The 17 patients who entered and completed the study had had a mean of 15.9 ± 17.0 (1–70) episodes of mood disorder. The mean length of the episode before T_4 treatment was 11.5 ± 13.8 (2–50) months (see Table 1). Their mean HRSD score before T_4 treatment was 26.6 ± 4.7 (range: 20–37). On day 56, the mean HRSD rating had fallen to 11.6 ± 6.8 (range: 1–22).

According to our criteria, eight patients fully remit-

Table 2. Efficacy of High-Dose Thyroxine Treatment in Therapy-Resistant Patients

Pat. No.	Medication during T_4 Treatment (mg/day)		HRSD-Score before T_4 Treatment (day 0)	HRSD-Score after 8 Weeks of T_4 Treatment (day 56)	Final Dose of T_4 (μg/day)	Side Effects	Response	Follow-Up on T_4-Medication (months)	Outcome
1	Nortriptyline Lithium	300 36 mmol	26	3	300	At 500 μg/day: tremor, sweating, oedema, increase of pulse rate (up to 130 beats/min) at 300 μg/day: mild sweating	Responder week 6	21	Excellent, no more depressive and manic episodes
2	Fluoxetine Carbamazepine Thioridazine	100 800 300	23	1	500	—	Responder week 8	12	Good, one mild depressive episode
3	Fluoxetine	80	24	12	500	Sweating	Partialresponder	T_4 withdrawn after 4 months, hypomanic 4 months after study end	
4	Nortriptyline Thioridazine	300 50	37	9	500	Increase of pulse rate (up to 100 beats/min)	Responder week 6	18	Excellent, no more depressive episodes, no panic attacks
5	Amitriptyline Haloperidol	225 5	34	3	300	Sweating	Responder week 7	30	Good, depressive episodes compared to former milder, shorter and without psychotic features, no more hospitalisation
6	Tranylcypromine Lithium Carbamazepine	20 36 mmol 600	26	9	400	Sweating	Responder week 5	18	Excellent, no more depressive episodes
7	Imipramine Lithium	400 36 mmol	21	day 56: 17 day 70: 10 day 100: 7	600	Tremor, sweating	Nonresponder responder week 10	14	Excellent, no more depressive and manic episodes
8	Doxepine Lithium Carbamazepine Perazine	300 30 mmol 600 200	26	day 56: 13 day 84: 7	600	Tremor, sweating, increase of pulse rate (up to 120 beats/min)	Partialresponder (day 56), responder week 12	5	Full recovery during 4 months follow up
9	Imipramine Thioridazine	150 300	32	22	500	Sweating	Nonresponder	6	Response after addition of lithium; good outcome with lithium (18 mM and thyroxine (200 μg/d)
10	Doxepine Lithium Perazine	225 24 mmol 500	22	12	500	—	Nonresponder	T_4 withdrawn	

(*continued*)

Table 2. (*continued*)

Pat. No.	Medication during T_4 Treatment (mg/day)		HRSD-Score before T_4 Treatment (day 0)	HRSD-Score after 8 Weeks of T_4 Treatment (day 56)	Final Dose of T_4 (μg/day)	Side Effects	Response	Follow-Up on T_4-Medication (months)	Outcome
11	Nortriptyline Perazine Haloperidol	200 175 7	28	5	500	Feeling of heat, flush	Responder week 7	27	Poor, 5 depressive episodes
12	Clomipramine Lithium	225 18 mmol	20	13	500	Tremor, sweating	Nonresponder	T_4 withdrawn, still depressed 9 months after study end; no response to ECT, tranylcypromine, paroxetine	
13	Imipramine Carbamazepine	300 600	26	8	500	—	Responder	81	Excellent full recovery, no relapse
14	Paroxetine Perazine	60 100	25	22	500	—	Nonresponder	T_4-dose increased to 700 μg/day, withdrawn after 3 months. Patient later responded to ECT	
15	Imipramine Carbamazepine Clozapine	500 900 300	22	20	500	—	Nonresponder	T_4-dose increased to 800 μg/day, withdrawn after 3 months. Patient remitted spontaneously	
16	Paroxetine Carbamazepine Flupentixol	80 900 3	32	21	500	—	Nonresponder	T_4-dose increased to 800 μg/day, withdrawn after 2,5 month. Patient responded to ECT	
17	Lofepramine Carbamazepine	350 450	28	7	500	—	Responder	46	Excellent, full recovery, no relapse
$\Sigma \pm$ SD			26.6 ± 4.7	11.6 ± 6.8	482 ± 72			27.2 ± 22.0 (n = 10)	

ted, two partially remitted, and seven did not remit (Table 2). In the remitted patients, the onset of remission did not occur before the period between weeks 5 and 8. In all eight remitted patients, conventional prophylactic medication such as lithium and/or carbamazepine had previously proved to be ineffective in preventing further episodes. All of the patients therefore agreed that high-dose T_4 treatment should be maintained as a trial of its prophylactic efficacy. At the time of writing, all eight remitted patients are still receiving high-dose T_4, thus their mean total treatment period to date is 27.2 ± 22.0 months (range: 5–81 months). Five of the patients recovered fully, i.e., they had no further depressive episodes. Two further patients (nos. 2 and 5, Table 2) had a positive outcome in the sense that their episodes of depression were much milder and shorter than previously and no longer require hospitalization. The 8th remitted patient (no. 11) had a poor outcome, experiencing five more depressive episodes during the 27-month follow-up period, necessitating hospitalization three times. The two partially remitted continued to take T_4 beyond day 56, in the hope that full remission could be achieved. One of these patients (no. 3) had a hypomanic episode 4 months later, during which she discontinued T_4 medication. Patient no. 8 responded fully on day 84 and recovered without any further recurrence.

In five of the seven nonremitted patients, no clear side effects had been observed up to day 56. The dosage of T_4 was therefore gradually increased to between 600 and 1,000 μg/day. Four of these patients had side effects, mainly dyspnea on exercise, restlessness, and tachycardia, but no favorable effect on the depressive symptomatology. T_4 was therefore withdrawn in these cases. The 5th patient (no. 7) responded to a combination of 600 μg T_4 and 400 mg imipramine on day 100. He continued with this medication, fully recovered, and had no recurrence during the 14-month follow-up period.

In conclusion, nine of the patients in this study had an excellent ($n = 7$) or good ($n = 2$) long-term outcome on T_4, whereas eight failed to benefit from high-dose T_4 treatment. The T_4 treatment did not provoke a manic episode in any patient. Of the five unipolar patients, three (nos. 4, 11, and 17) responded favorably to T_4, whereas the other two did not (no. 15) or only partially (no. 8). Of the 12 bipolar patients, five (nos. 1, 2, 5, 6, and 13) responded to T_4, whereas seven did not (nos. 7, 9, 10, 12, 14, 16) or only partially (no. 3).

The side effects that occurred during the 8-week study period are listed in Table 2. Seven patients had no side effects at all. The others noted mild side effects such as tremor, sweating, flushing, and a slight increase in heart rate. Reduction of the dosage of T_4 became necessary in only one patient (no. 1) during the 8-week trial, namely from 500 to 300 μg/day, owing to an increase in heart rate of up to 130 BPM. Later, this patient remained well on 300 μg T_4/day throughout the 21-month follow-up period. The mean heart rate of all patients before T_4 treatment (day 0) was 81.3 ± 16.9 BPM (range: 57–108 BPM). On day 56 the mean heart rate had risen to 91.4 ± 11.4 BPM (range 81–120 BPM). The mean systolic blood pressure prior to T_4 treatment was 118 ± 11 mm Hg and the mean diastolic pressure 77 ± 7 mm Hg. This value was virtually unchanged on day 56 (113 ± 11 mm Hg systolic pressure and 70 ± 7 mm Hg diastolic pressure).

The mean weight of all patients before the institution of T_4 treatment was 72.7 ± 17.9 kg (range: 49–107 kg). On day 56 the mean weight was 72.3 ± 19 kg (range: 49–109 kg). No "undesired" weight loss occurred in any patient. However, two young women, one of whom was receiving lithium and the other carbamazepine and both of whom had been chronically and greatly overweight before T_4 treatment, did reach their ideal weight during the follow-up period without further difficulty. As already noted above, an increase in the T_4 dosage above 700 μg/day in four nonremitted patients led to dyspnea, restlessness, and tachycardia in all cases.

In the seven patients who continued to take T_4 and were followed up for more than 1 year, osteodensitometry and ECGs were done at least twice: once when the decision was made to continue with the T_4 treatment as prophylaxis and again 1 year later. Although this number is still too small for reliable statistical analysis, our preliminary evaluation of the results shows clearly that neither bone density nor heart size or function showed above average deterioration. No serious illnesses such as cardiac infarction or autoimmune disease occurred during follow-up in any of the patients receiving T_4.

Serum concentrations of thyroid hormones and TSH before and after treatment with thyroxine are shown in Table 3. Before the start of T_4 treatment only one patient (no. 7) had a slightly elevated baseline concentration of TSH (5.5 mU/L, Table 3), indicating a possible subclinical hypothyroidism. Values for total T_4, free T_4, and total T_3 in all patients were well within the normal range before T_4 institution, showing that the patient sample was euthyroid, that is, as based on their laboratory values, at least. In 16 of the 17 patients the serum levels of T_4 had at least doubled by the end of week 8. This also applied to the serum levels of fT_4 of all 17 patients. Rises in the concentrations of T_3 were generally lower, the values increasing by more than 100% in only seven patients. No significant differences were noted between the changes in any hormone in the remitted patients over the 8-week period and those in the nonremitted patients, calculated by the Mann-Whitney U test. The mean T_4–T_3 ratios before and after T_4 treatment were 72.4 and 93.8, respectively ($p < .05$, Wilcoxon's rank test). In remitted patients ($n = 8$) the mean T_4–T_3 ratio increased from 70.5 to 99.8 ($p < .05$), and in the nonremitted group ($n = 7$) from 70.1 to 89.7 ($p < .05$) after T_4 treatment. The differences between remitted and nonremitted patients were not statistically significant.

DISCUSSION

The patient sample included in this study comprised the most therapy-resistant patients seen at our psychiatric clinic during a 5-year period. It therefore seems remarkable that about 50% of them remitted to high-dose T_4 augmentation. It may be argued that our study was not double-blind, and we were therefore unable to control the rate of placebo response or spontaneous remission. However, a 50% placebo response seems rather unlikely in patients who had already been unsuccessfully treated with many different antidepressants, as well as combinations of antidepressants and lithium and/or neuroleptics. In their recent review, Thase and Rush (1995) and Thase et al. (1995) estimated the placebo response rate in therapy resistant depressed patients at between 0 and 10%. Several double-blind studies in which different "augmentation strategies" such as the addition of T_3 or lithium were tried with depressed patients who had failed to respond to a single antidepressant trial showed placebo response rates of between 19 and 25% (Thase et al. 1989a,b). Placebo remission rates in chronically depressed patients seem to be even lower, e.g., 12% as shown in the study by Kocsis et al. (1988).

All of the patients who had a favorable outcome to T_4 treatment had suffered from at least one episode in the year preceding the institution of T_4 augmentation. If the recovery seen in these patients had reflected a mere placebo response then relapses should have been expected with a high probability in a mean follow-up period of 27.2 ± 22.0 (5–81) months. Sackeim et al. (1990), for example, reported a relapse rate of 50% within 12 months after ECT treatment, the relapse rate being even higher in patients who had not responded adequately to antidepressant pharmacotherapy before ECT. The fact that all but one of the patients in whom T_4 had an antidepressant effect remained stable during follow-up therefore also militates against a placebo effect of T_4.

One might raise the question as to whether it is necessary to administer T_4 in supraphysiological doses or whether somewhat lower doses than those taken by our patients would have led to the same beneficial results. Especially in the first patients given high-dose T_4 (Baumgartner et al. 1994a) for prophylaxis and also in the follow-up periods of the patients who responded to T_4 augmentation we repeatedly noted that some mild depressive symptoms only subsided when T_4 was further increased, e.g., from 500 to 600 μg/day, and that after a reduction of only 100 μg/day mild depressive symptoms are often reported 1 or 2 weeks later. Our impression that only supraphysiological doses are of value is also shared by other groups (Stancer and Persad 1982; Leibow 1983; Bauer and Whybrow 1986, 1990; Hurowitz and Liebowitz 1993) and is consistent with the negative results published by Joffe and Singer

Table 3. Serum Levels of Thyroid Hormones[a] and Basal TSH[a] before and after 8 Weeks of High-Dose Thyroxine Treatment

	Before T_4 Treatment				High-Dose T_4 Treatment				
Pat. No.	T_4 (μg/L)	fT_4 (ng/L)	T_3 (μg/L)	Basal TSH (mU/L)	T_4 (μg/L)	fT_4 (ng/L)	T_3 (μg/L)	Basal TSH (mU/L)	Final T_4 Dose (μg/day)
1	89	8.8	1.8	0.5	153	28.1	2.2	0.01	300
2	59	4.9	1.7	0.8	129	29.6	1.6	0.04	500
3	126	14.3	1.2	1.2	172	44.0	2.1	0.01	500
4	80	13.5	1.2	2.5	188	38.7	2.7	0.01	500
5	102	10.7	0.9	0.3	198	27.5	1.0	0.2	300
6[b]	61	9.8	0.6	0.4	127	21.8	1.0	0.01	500
7	68	9.2	1.0	5.5	128	18.9	1.8	0.01	500
8[b]	86	8.5	1.2	3.5	121	19.4	1.4	0.03	600
9	52	6.8	0.8	0.6	166	66.6	1.9	0.01	500
10	62	7.7	0.9	2.7	113	12.4	1.7	0.02	500
11	77	5.9	1.2	2.8	175	19.5	2.6	0.01	500
12	66	5.3	1.2	1.7	187	23.0	1.8	0.9	500
13[b]	55	8.4	1.0	1.9	138	22.4	1.6	0.01	500
14[b]	86	12.3	0.8	1.5	217	29.3	1.9	0.03	500
15	75	10.4	1.0	2.0	180	18.5	1.9	0.01	500
16	57	9.3	1.1	1.5	136	25.5	1.5	0.02	500
17	48	7.5	0.6	1.3	141	22.0	1.4	0.01	500
Σ ± SD	73.5 ± 20.1	9.02 ± 2.67	1.07 ± 0.32	1.81 ± 1.32	157.0[c] ± 30.8	27.5[c] ± 12.6	1.77[c] ± 0.46	0.07[c] ± 0.21	482[c] ± 72.8

[a] For normal ranges see methods.
[b] Patients were already receiving physiological doses of thyroxine.
[c] $p < .01$ compared with the values before T_4 treatment.
T_4 = total thyroxine; fT_4 = free thyroxine; T_3 = triiodothyronine; TSH = thyroid-stimulating hormone (thyrotropine).

(1990), according to which augmentation with 150 μg T_4 remained ineffective in treatment-resistant depressed patients. Finally, the fact that four of our patients had already been receiving substitution therapy with physiological doses of T_4 and were still treatment-resistant also supports the above conclusion.

Our experience in treating our first patients with high-dose T_4 (Baumgartner et al. 1994a) as well as that reported by others (Bauer and Whybrow 1986; Hurowitz and Liebowitz 1993) suggests that T_4 may have a prophylactic and also an antidepressant effect only when given together with a standard antidepressant or prophylactic medication. The patients in the present study repeatedly reported the recurrence of mild depressive symptoms after attempts to slightly reduce their doses of antidepressant medication (which in some cases were extremely high), particularly during the follow-up period. In cases in which an increase the dosage of T_4 was not advisable because the serum levels of thyroid hormones were already high and/or because of side effects, the dosage of the antidepressant was raised and the prodromal symptoms subsided in all cases.

It is surprising how few side effects were observed, during both the 8-week augmentation period and the subsequent follow-up period. However, this is in line with previous observations made in rapid-cycling bipolar patients during high-dose T_4 treatment (Stancer and Persad 1982; Leibow 1983; Bauer and Whybrow 1986, 1990; Hurowitz and Liebowitz 1993). The results of our preliminary evaluation of the effects of long-term T_4 treatment on bone density are also consistent with the results obtained by Whybrow's group (Whybrow 1994; Gyulai et al. 1997), i.e., no abnormal increase in osteoporosis parameters. As serum T_4 and fT_4 were clearly in the hyperthyroid range in all of our patients toward the end of the augmentation period and during the follow-up phase, the question arises as to why these patients did not suffer from symptoms of Graves' disease. We are currently investigating the question as to whether depressed patients are less sensitive to thyroid hormones than patients with hypothyroidism of autoimmunologic origin.

The biochemical mechanisms underlying the antidepressive and prophylactic effects of T_4 are as yet unclear. It has been suggested that the beneficial effects of high-dose T_4 prophylaxis seen in patients with rapid-cycling bipolar disorder may be due to a correction of subclinical hypothyroidism, which is frequently seen in these patients (Bauer and Whybrow 1990). However, only one patient in our study showed laboratory values indicative of subclinical hypothyroidism; all the others were clearly euthyroid before T_4 augmentation was instituted. The effects of T_4 are therefore obviously not attributable to a correction of manifest or subclinical hypothyroidism.

Serum levels of T_4 are of paramount importance for the action of thyroid hormones in the brain insofar as hardly any of the physiologically active hormone T_3 is taken up from the circulation, but derived from intracellular deiodination of T_4 (Crantz et al. 1982). It therefore seems interesting that serum levels of T_4 have been shown to fall during electroconvulsive therapy, treatment with various antidepressants such as imipramine, desipramine, clomipramine, and maprotiline, treatment with carbamazepine and after cognitive psychotherapy and treatment with bright and dim light (Kirkegaard and Faber 1981; Roy-Byrne et al. 1984; Baumgartner et al. 1988; Joffe and Singer 1990; Baumgartner et al. 1996; Joffe et al. 1996). In the majority of all studies published to date, these reductions in serum concentrations of T_4 were significantly correlated to the degree of clinical response (Kirkegaard and Faber 1981; Roy-Byrne et al. 1984; Baumgartner et al. 1988; Joffe and Singer 1990; Baumgartner et al. 1996; Joffe et al. 1996). Furthermore, the importance of initially high serum levels of T_4 for the mechanisms of action of antidepressants is also underlined by the results of several studies that have shown that high serum concentrations of T_4 predict a favorable response to such different antidepressant therapies such as antidepressant drugs (Prange et al. 1969; Baumgartner et al. 1988), total sleep deprivation (Baumgartner et al. 1990), and partial sleep deprivation (Szuba et al. 1992).

A series of animal experiments has shown that the declines in serum concentrations of T_4 seen during antidepressant treatment are most likely due to enhanced degradation of T_4 to T_3, i.e., enhanced activity of the 5′II deiodinase isoenzyme in the CNS (Campos-Barros et al. 1994; Baumgartner et al. 1994b). As a result, the concentrations of T_3 rise in various regions of the rat CNS after subchronic administration of different antidepressant drugs such as desipramine and fluoxetine, as well as after sleep deprivation (Campos-Barros and Baumgartner 1994; Campos-Barros et al. 1993, 1995). An increase in the activity of 5′II deiodinase and/or an inhibition of the activity of the 5D-III isoenzyme have now also been reported after 14 days' administration of lithium and carbamazepine (Baumgartner et al. 1997).

In conclusion, very different antidepressant and prophylactic treatments seem to affect thyroid hormone metabolism in the CNS by enhancing the degradation of T_4 and increasing tissue concentrations of T_3. In other words, some antidepressants, and also lithium and carbamazepine, may "need" T_4 to unfold their specific actions. Therefore, the more T_4 is available to the brain, the more effective antidepressant therapies may be. This hypothesis would also explain the fact that—at least according to the clinical impression gained by both Bauer and Whybrow (1990) and ourselves, high-dose T_4 treatment is effective only when given together with a conventional antidepressant or prophylactic drug.

Studies investigating the as yet almost unknown

functions of T_3 in the adult CNS are needed for further clarification of the question as to whether an increase in T_3 function may be involved in the as yet unknown mechanisms of action of antidepressant drugs.

Finally, why both hypo- and hyperthyroidism should induce symptoms of depression and other disorders is one of the unsolved riddles of thyroid disorders (Hall et al. 1986). In this connection it is, however, noteworthy that in our study approximately 50–60% of the patients responded to T_4 augmentation, whereas the others failed to benefit at all. Moreover, the fact that some of the depressed patients also seemed to benefit from low-dose T_3 treatment (for a review, see Joffe et al. 1995)—which has exactly the opposite effect on thyroid hormone function in the CNS from T_4 treatment—needs explaining. Although this remains speculative at present, it may be that patients who do not respond to T_4 are already "functionally hyperthyroid" and may therefore profit from low-dose T_3 treatment, in line with the hypothesis put forward by Joffe (Joffe et al. 1995). It would therefore be interesting to investigate whether patients who fail to respond to high-dose T_4 improve during low-dose T_3 administration and vice versa.

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