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Chronobiological hypothalamic—pituitary—thyroid axis status and antidepressant outcome in major depression☆

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Thyrotropin (TSH);
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Summary

Background: We previously demonstrated that the difference between 2300 h and 0800 h TSH response to protirelin (TRH) tests on the same day (ΔΔTSH test) is an improved measure in detecting hypothalamic—pituitary—thyroid (HPT) axis dysregulation in depression. This chronobiological index (1) is reduced in about three quarters of major depressed inpatients, and (2) is normalized after successful antidepressant treatment. In the present study, we examined whether early changes in HPT axis activity during the first 2 weeks of antidepressant treatment could be associated with subsequent outcome.

Methods: The ΔΔTSH test was performed in 50 drug-free DSM-IV euthyroid major depressed inpatients and 50 hospitalized controls. After 2 weeks of antidepressant treatment the ΔΔTSH test was repeated in all inpatients. Antidepressant response was evaluated after 6 weeks of treatment.

Results: At baseline, ΔΔTSH values were significantly lower in patients compared to controls and 38 patients (76%) showed reduced ΔΔTSH values (i.e., <2.5 mU/L). After 2 weeks of antidepressant treatment, 20 patients showed ΔΔTSH normalization (among them 18 were subsequent remitters), while 18 patients did not normalize their ΔΔTSH (among them 15 were non-remitters) ($p < 0.00001$). Among the 12 patients who had normal ΔΔTSH values at baseline,

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8 out 9 who had still normal values after 2 weeks of treatment were remitters, while the 3 with worsening HPT axis function (i.e., reduced ΔΔTSH value after 2 weeks of treatment) were non-remitters ($p < 0.02$). A logistic regression analysis revealed that ΔΔTSH levels after 2 weeks of treatment could predict the probability of remission (odds ratio [OR] = 2.11, 95% confidence interval [CI] = 1.31—3.41).
Conclusions: Our results suggest that after 2 weeks of antidepressant treatment: (1) chronobiological restoration of the HPT axis activity precedes clinical remission, and (2) alteration of the HPT axis is associated with treatment resistance.

1. Introduction

Alterations of the hypothalamic—pituitary—thyroid (HPT) axis are one of the most common findings in major depressive episodes (Nemeroff and Evans, 1989). It has been consistently found that circadian thyrotropin (TSH) secretion is lower in depressed patients than in control subjects, especially in the evening and at night (Souetre et al., 1986; Bartalena et al., 1990; Jackson, 1998; Peteranderl et al., 2002; Mokrani et al., 2006). Moreover, the TSH response to morning injection of protirelin (thyrotropin-releasing hormone [TRH]) is blunted in 25—30% of depressed patients (for reviews, see Loosen and Prange, 1982; Jackson, 1998). Owing to the circadian activity of the thyrotrophs, which is maximal between 2300 h and 0100 h, pituitary TSH secretion is more sensitive to TRH stimulation in the evening (at 2300 h) than in the morning (at 0800 h) both in control subjects and depressed patients (Duval et al., 1990). We have previously demonstrated that the difference between 2300 h and 0800 h TSH response to TRH tests (ΔΔTSH) is an even more sensitive measure in detecting HPT axis dysregulation: this chronobiological index, correlated with circadian TSH variables (i.e., mesor and amplitude), is reduced in about three quarters of major depressed inpatients (Duval et al., 1990, 1994, 1996, 1999).

After successful antidepressant treatment, the nyctohemeral profile of plasma TSH is restored (Souetre et al., 1986). Concomitantly, the ΔΔTSH test is normalized irrespective from the primary pharmacological mode of action of the antidepressant drugs (Duval et al., 1996). Indeed, ΔΔTSH normalization after 4 weeks of treatment with amitriptyline, fluoxetine, venlafaxine, toloxatone, or tianeptine occurs only in remitted patients (Duval et al., 1996, 2002). Thus, it appears that the ΔΔTSH test status might be used as a state-related marker of clinical change in hospitalized depressed patients.

It is generally admitted that approximately 50% of depressive patients have not achieved complete remission of the symptoms after two trials of treatment in monotherapy, while two thirds have remitted after the establishment of four therapeutic strategies (Rush, 2007). This suggests that most patients need several sequential treatment steps to achieve remission. In this respect, it might be helpful to identify biomarkers of treatment response at the earliest possible time, especially in hospitalized depressed patients with severe symptoms, to avoid leaving patients under an inefficient medication. Some studies suggest that several classes of physiologic biomarkers, at baseline or early in the course of treatment, may be useful for predicting response (Ising and Holsboer, 2008; Leuchter et al., 2009; Dunlop and Mayberg, 2014). Recently, we found in a sample of 30 depressed inpatients, that normal ΔΔTSH values (i.e., >2.5 mU/L) after 2 weeks of antidepressant treatment could predict remission (Duval et al., 2013).

In this present study, conducted in a population of 50 hospitalized depressed patients, our primary aim was to evaluate whether early change of the ΔΔTSH test status after 2 weeks of antidepressant treatment, using different classes of drugs, was associated with subsequent clinical outcome.

2. Methods and material

2.1. Subjects

Fifty DSM-IV (American Psychiatric Association, 1994) major depressed inpatients without psychotic features (Table 1) completed at least 6 weeks of antidepressant treatment. Patients were recruited from the inpatient units of the Pole 8/9, Psychiatric Hospital of Rouffach (France). Patients were evaluated by means of at least two unstructured clinical interviews conducted by an experienced research psychiatrist (F.G., C.A., or A.E.) and a structured interview (Schedule for Affective Disorders and Schizophrenia—Lifetime Version (Spitzer and Endicott, 1975))—conducted by a separate psychiatrist (X.P., or I.B.). The final diagnoses were made by consensus of two psychiatrists blind to endocrine results. Severity of depression was measured with the 17-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960); inclusion in the study required a baseline HAM-D of 16 or greater (mean ± SD, 28.5 ± 4.2). In this present study, 20 patients were added to the initial sample of 30 patients described elsewhere (Duval et al., 2013).

All patients had a history of recurrent major depression without psychotic features (onset of depressive disorder at age 33.5 ± 11.2 years), and none had a history of a full hypomanic, manic, or mixed episode; 45 patients were treated with antidepressants at the time of hospital admission. Fifteen patients met DSM-IV criteria for melancholic subtype. Thirty patients had a history of suicide attempt (mean ± SD, 2.2 ± 1.4 lifetime suicide attempts); among them 18 were recent suicide attempters (the suicidal act occurred during the current depressive episode and had triggered their psychiatric hospitalization). Before testing, patients had been free of all drugs for a minimum of 7 days; this washout was supervised in hospital.

Table 1 Demographic and biological data on normal controls and patients at baseline and after 2 weeks of antidepresssant treatment.

	Control subjects ($n=50$)	Depressed patients ($n=50$)		Controls vs. MDD		MDD BL vs.
		Baseline	**Week 2**	Baseline	Week 2	Week 2
Age, y[a]	40.1 ± 8.3	43.7 ± 12.4		...		
Gender, M/F	20/30	17/33		...		
0800 h-TSH_B, mU/L	1.25 ± 0.52	1.18 ± 0.60	1.14 ± 0.56	...	...	...
2300 h-TSH_B, mU/L	1.21 ± 0.63	0.84 ± 0.37**	0.98 ± 0.50*			
0800 h-ΔTSH, mU/L	7.70 ± 3.65	6.88 ± 3.70	7.33 ± 4.11	...	...	...
2300 h-ΔTSH, mU/L	11.62 ± 3.80***	8.34 ± 4.02**	10.12 ± 4.80***	<0.0003	...	...
ΔΔTSH, mU/L	3.89 ± 1.45	1.46 ± 2.17	2.71 ± 2.39	<0.00001	<0.003	<0.002
0800 h-FT4B, pmol/L	11.8 ± 2.8	11.1 ± 2.4	10.3 ± 2.0	...	...	...
2300 h-FT4B, pmol/L	12.2 ± 2.7	11.9 ± 2.7 ***	10.8 ± 2.1**	...	...	...
0800 h-FT3B, pmol/L	5.1 ± 0.8	5.0 ± 0.8	4.9 ± 1.0	...	...	...
2300 h-FT3B, pmol/L	5.2 ± 0.9	5.1 ± 0.9	5.0 ± 1.2	...	...	...
Maximum post DST cortisol, nmol/L	43 ± 37	65 ± 80	52 ± 63	...	...	...
DST nonsuppression (%)	1 (2%)	10 (20%)	6 (12%)	<0.01	...	...

[a] Values are mean ± SD. Comparisons between controls and depressed patients (at baseline and at week 2) were tested with Mann—Whitney two-tailed test *U* test with Bonferroni's adjustment for 3 pairwise comparisons (quantitative variables) or by Fisher's Exact Test (qualitative variables). Within-subject differences were evaluated with the Wilcoxon two-tailed signed-rank test *T* test; *$p<0.05$, **$p<0.0001$, ***$p<0.00001$ for the difference between 2300 h and 0800 h values. MDD indicates major depressive disorder; BL, baseline (Day 0); TSH B, basal thyrotropin concentration; ΔTSH, peak concentration minus basal thyrotropin concentration; ΔΔTSH, 2300 h -ΔTSH minus 0800 h-ΔTSH; FT4B, basal free thyroxine concentration; FT3B, basal free triiodothyronine concentration; DST, dexamethasone suppression test. DST nonsuppression, cortisol level in excess of 140 nmol/l in anyone of the three samples (0800 h, 1600 h, and 2300 h) (Carroll et al., 1981).

To evaluate the degree of dysregulation of the HPT axis in patients, we selected data of 50 hospitalized normal volunteers from our database (Table 1). At screening, control subjects were given an interview including a psychiatric history, the SADS-LV and the Research Diagnostic Criteria—Family History (Endicott et al., 1978). All were free of concomitant psychiatric and medical illness. None had a personal or family history of major psychiatric illness. All were without current medication use. Control subjects were hospitalized 3 days before testing and remained hospitalized throughout the testing period (2 days).

The protocol was approved by the local ethical committee, and all participants gave written informed consent after complete description of the study. Routine blood tests and physical examination excluded subjects with medical illnesses. All patients and controls had basal thyroid hormone values (free thyroxine [FT4], free triiodothyronine [FT3], and TSH) within the normal range. All subjects were within the healthy weight category (i.e. body mass index between 18.3 and 24.7). Subjects with a history of thyroid or other endocrine diseases; alcoholism or drug abuse; previous treatment with lithium salts, carbamazepine, long-acting neuroleptics, monoamine oxidase inhibitors or electroconvulsive therapy within 1 year of testing; women taking oral contraceptives were excluded. All subjects had been on a caffeine-restricted diet for at least 3 days before testing and their environment was synchronized, with diurnal activity from 0800 h to 2300 h and nocturnal rest (sleep).

2.2. Procedures

We measured TSH, FT4, and FT3 levels before and after TRH given at 0800 h and 2300 h, on the same day. The first TRH stimulation test was carried out at 0800 h. Subjects were in bed, nonsmoking and kept fasting from 1900 h the previous day. An indwelling cannula was inserted at 0700 h into a forearm vein and kept open with an isotonic saline infusion. Two hundred micrograms of protirelin (TRH Ferring®, Ferring Pharmaceuticals, Kiel, Germany) was injected intravenously over 2 min at 0800 h. Blood was drawn for assay of serum TSH, FT4, and FT3 −15, 0, 15, 30 and 60 min after TRH injection. The challenge was repeated at 2300 h on the same day using the same procedure. Subjects were awake before and during the evening sampling and were kept without food from 1800 h.

A dexamethasone suppression test (DST) was started at midnight, with oral ingestion of 1 mg of dexamethasone (Dectancyl, Laboratoires Roussel, Paris, France), and blood samples were collected for cortisol assay at 0800 h, 1600 h, and 2300 h the following day (Carroll et al., 1981).

After 2 weeks of inpatient antidepressant treatment the same neuroendocrine tests were repeated in all patients.

2.3. Assays

Blood samples were immediately centrifuged at 3000 rpm and 4 °C; serum samples were then stored at −20 °C until assay. All hormone concentrations were determined by immunoassay techniques based on enhanced luminescence.

Average intra-assay and inter-assay coefficients of variation were respectively: TSH: 3.4—4.8%, sensitivity <0.01 mU/L (Access Hypersensitive hTSH Assay, Beckman Coulter, Inc., Fullerton, CA, USA); FT4: 2.8—5.1%, sensitivity <3.2 pmol/L (Access Free T4 Assay, same supplier); FT3: 4.7—4.8%, sensitivity <1.4 pmol/L (Access Free T3 Assay, same supplier). Cortisol: 5.1—6.8%, sensitivity <11 nmol/L (Access Cortisol Assay, same supplier).

2.4. Antidepressant treatment

To optimize antidepressant treatment response, medication was chosen on a clinical basis (i.e. history of the disorder, side-effect profiles, previous treatment response and side-effects [available for 45 patients], patient preferences) (Bauer et al., 2013). The choice of treatment was not an object of this study. After the medication-free period, antidepressants were given under supervision on the ward, at doses known to be effective (Bauer et al., 2013). At the time of the second ΔΔTSH test, all inpatients received antidepressant medication: 24 cases with venlafaxine extended release (VFX, a serotonin [5-HT]-norepinephrine reuptake inhibitor; mean ± SD dose, 178.1 ± 35.4 mg/d, range 150—225 mg/d); 15 cases with tianeptine (TIAN, a 5-HT reuptake enhancer; TIAN was begun at 37.5 mg/d then raised to 75 mg/d after 1 week); 5 cases with escitalopram (ESCI, a specific 5-HT reuptake inhibitor [SSRI]; mean dose: 16.0 ± 5.5 mg/d, range 10—20 mg/d); 6 cases with agomelatine (AGO, a melatonergic analog drug acting as MT1/MT2 receptor agonist and 5-HT2C receptor antagonist; 25 mg/d). Changes in dose were made if necessary after 2 weeks according to clinical response and tolerability.

Reevaluation of the adequacy of the medication dose was performed when subjects failed to show (1) an early improvement [HAMD decrease <20% at week 2])—except for patients treated with TIAN (since 75 mg/d is the maximum dose recommended)—, and/or (2) a positive response after 4 weeks of treatment [50% decrease in HAMD]. On day 42, mean doses of antidepressant drugs were: VFX, 307.8 ± 72.5 mg/d (range 150—375 mg/d); ESCI, 25.0 ± 10.0 mg/d (range 15—40 mg/d); AGO, 41.7 ± 12.9 mg/d (range 25—50 mg/d); TIAN, 75 mg/d.

Psychotropic drugs other than the study medication were, if possible, avoided. Alimemazine (maximum dose: 30 mg/d orally) was allowed in case of severe sleep disturbance. Patients were hospitalized for a minimum of 4 weeks; 5 patients able to be discharged from hospital before reaching week 6 were followed as outpatients until the end of the study, the other patients remained hospitalized throughout the study (6 weeks).

2.5. Clinical response

All patients were assessed weekly with the HAM-D by raters blind to neuroendocrine results and the medication used. After six weeks of treatment, we followed Frank et al. (1991) in defining response in terms of absolute rather than relative HAM-D scores. Remitters were defined as having a final HAM-D score less than 8. Throughout the study, patients were not aware of the neuroendocrine results.

2.6. Statistical analysis

Baseline TSH (TSHB), FT4 (FT4B), and FT3 (FT3B) values were defined as the mean of the two samples before TRH injection (*t*−15 and *t*0). ΔTSH was defined as the maximum increment above the baseline value after TRH injection. The highest post-DST serum cortisol value in any blood sample obtained at 0800 h, 1600 h, and 2300 h on day 2 was used to evaluate the cortisol response to DST.

Despite logarithmic or other transformations, the distribution of some data remained non-normal (Kolmogorov—Smirnov one-sample test for goodness-of-fit) and it was necessary to use non-parametric statistical methods. Between-group differences (at baseline and during treatment) were tested for significance with the Kruskal—Wallis one-way analysis of variance by ranks (*H*-test); and, where the overall effect was significant, by Mann—Whitney two-tailed test (*U*-test), followed by Bonferroni's post hoc test. Within-subject differences were evaluated with the Wilcoxon two-tailed signed-rank test (*T* test). Correlations between quantitative variables were estimated using the Spearman rank coefficient (ρ). Categorical data were analyzed with the Fisher exact test. Logistic regression was used to estimate the probability of remission/non-remission based on ΔΔTSH values after two weeks of treatment. Results were considered significant when $p \leq 0.05$.

3. Results

3.1. Comparison between controls and medication-free patients

As shown in Table 1, controls and depressed patients were comparable for age and sex. Compared to controls, untreated patients demonstrated significantly lower 2300 h-ΔTSH and ΔΔTSH values. Defining reduced ΔΔTSH as a response below 2.5 mU/L (Duval et al., 1996), we observed that 38 patients showed abnormal response (i.e., sensitivity, 76%; specificity, 97%).

Unlike controls, patients exhibited decreased TSHB and increased FT4B values at 2300 h compared to 0800 h values. In the whole sample, in the control group, and in the depressed group the effects of age and gender were not significant for the thyroid function tests (TSHB, ΔTSH, ΔΔTSH, FT4B, and FT3B).

3.2. Evolution of ΔΔTSH values after 2 weeks of antidepressant treatment

Compared with baseline, ΔΔTSH values were higher at week 2, but remained lower than in controls (Table 1). Changes in ΔΔTSH values were strongly correlated with changes in 2300 h-ΔTSH values ($\rho = 0.74$; $n = 50$; $p < 0.00001$). Moreover, there was a negative relationship between changes in 2300 h-ΔTSH and 2300 h-FT4B values ($\rho = -0.39$; $n = 50$; $p = 0.005$).

Although 29 patients (58%) showed normal ΔΔTSH values at week 2 (i.e., ≥2.5 mU/L), 21 patients (42%) still exhibited reduced values. Among the 38 patients with a reduced ΔΔTSH value at baseline, 20 showed normalization of the

Table 2 Demographic, endocrine data, and clinical outcome of patients classified according to the evolution of ΔΔTSH status after 2 weeks of antidepressant treatment.

ΔΔTSH status at baseline ΔΔTSH status at week 2	Reduced Normal ($n = 20$)	Reduced Reduced ($n = 18$)	Normal Normal ($n = 9$)	Normal Reduced ($n = 3$)	p^a
Age, y (mean ± SD)	44.0 ± 13.3	43.0 ± 11.9	45.2 ± 12.5	41.3 ± 14.22/1	...
Gender, M/F	5/15	8/10	2/7	2/1	...
Age at onset, y	31.4 ± 12.2	32.6 ± 12.4	33.4 ± 13.1	32.9 ± 13.8	...
Melancholic subtype	6	6	2	3	...
VFX/TIAN/ESCI/AGO	9/5/4/2	11/4/1/2	3/4/0/2	1/2/0/0	...
Remitters ($n = 29$)/non-remitters ($n = 21$)	18/2	3/15	8/1	0/3	<0.00001
Duration of hospitalization, weeks	7.1 ± 3.1	16.3 ± 11.2	9.3 ± 5.9	14.3 ± 5.7	0.006
HAM-D Scores, baseline	30.2 ± 3.4	28.1 ± 3.8	28.9 ± 3.2	28.5 ± 5.5	...
HAM-D Scores, week 2	15.0 ± 6.6**	20.7 ± 6.7**	16.8 ± 8.1**	19.7 ± 4.7	...
HAM-D Scores, week 6	6.9 ± 5.0**	14.1 ± 7.6**	6.4 ± 6.5**	14.0 ± 4.0	0.002

[a] p values of Kruskal—Wallis rank sum test. ΔΔTSH indicates the difference between 2300 h and 0800 h TSH response to TRH tests (ΔTSH). Threshold for a reduced ΔΔTSH value < 2.5 mU/L. HAM-D indicates Hamilton Rating Scale for Depression. VFX, venlafaxine; TIAN, tianeptine; ESCI, escitalopram; AGO, agomelatine. **$p < 0.001$ by Wilcoxon 2-tailed signed rank T-test for the difference between values before and after 2 weeks or 6 weeks of antidepressant.

test, while 18 did not normalize. Among the 12 patients with an initial normal ΔΔTSH value, 9 remained normal, and 3 exhibited reduced ΔΔTSH values, indicating a worsening of their HPT status. The evolution of ΔΔTSH status after 2 weeks of treatment was independent of demographic and clinical features at baseline, and of the medication used (Table 2).

Table 3 displays the thyroid function tests before and after 2 weeks of treatment, according to the evolution of ΔΔTSH status distributed into 4 groups. Interestingly, in patients who showed ΔΔTSH normalization, we observed, from baseline to week 2, increment in 2300 h-ΔTSH values, and decrements in 2300 h-FT4B and post-DST cortisol values. In this group, increments in ΔΔTSH and 2300 h-ΔTSH values were correlated ($\rho = 0.80$; $n = 20$; $p < 0.00001$), but were unrelated to post-DST cortisol values.

3.3. Clinical outcome

All patients completed the 6 weeks of therapy. At week 6, 29 patients (58%) were classified as remitters, and 21 (42%) as non-remitters. The clinical efficacy of antidepressants, despite different mechanisms of action, was comparable. Confirming previous reports (Kraemer et al., 2006; Rush et al., 2008), no baseline demographic and clinical features (age, sex, illness-related variables, history of suicidal behavior, HAM-D scores at inclusion) appeared to be associated with subsequent antidepressant response.

3.4. Evolution of ΔΔTSH status after 2 weeks of treatment and clinical outcome

Among the 20 patients who normalized their ΔΔTSH after 2 weeks of treatment (Fig. 1), 18 were remitters after 6 weeks of treatment, while only 2 were non-remitters. Fifteen patients among the 18 who did not normalize their ΔΔTSH were non-remitters. Thus, normalization of the ΔΔTSH test at week 2 was significantly associated with subsequent remission ($p < 0.00001$ by Fisher exact test). Moreover, the mean duration of hospitalization (see Table 2) was about 9 weeks longer in patients with a lack of normalization of HPT axis function ($p < 0.005$ by U test corrected with Bonferroni's adjustment for 4 pairwise comparisons).

Among the 12 patients who had normal ΔΔTSH values at baseline, 8 out 9 who had still normal values after 2 weeks of treatment were remitters, while the 3 with worsening HPT axis function (i.e. ΔΔTSH value <2.5 mU/L) were non-remitters. Thus, patients who still showed a normal ΔΔTSH test after 2 weeks of treatment were more likely remitters ($p < 0.02$ by Fisher exact test).

3.5. Possible therapeutic applications of the ΔΔTSH test

To explore possible applications in the therapeutic field, we related the ΔΔTSH status at baseline and at week 2—-independently of its evolution from baseline—to clinical outcome. At baseline, ΔΔTSH status was not associated with subsequent treatment outcome: 21 out of 38 patients with a reduced ΔΔTSH value were remitters at week 6, while 4 out of 12 patients with a normal ΔΔTSH value were non-remitters ($p > 0.5$ by Fisher exact test).

After 2 weeks of treatment, almost 90% of patients (26/29) with normal ΔΔTSH values were remitters; conversely, 86% (18/21) of non-remitters exhibited reduced ΔΔTSH values ($p < 0.000001$ by Fisher exact test). Fig. 2 displays a model, provided by a simple logistic regression analysis, predicting the probability of remission for any value of ΔΔTSH after 2 weeks of treatment.

4. Discussion

The most striking finding from the present study is that patients who showed, after 2 weeks of antidepressant treatment, a normalization of a low ΔΔTSH value (at study inclusion) had higher chance to become almost

Table 3 Evolution of $\Delta\Delta$TSH satus after 2 weeks of antidepressant treatment and endocrine data.

ΔΔTSH status at baseline ΔΔTSH status at week 2	Reduced Normal (n = 20)	Reduced Reduced (n = 18)	Normal Normal (n = 9)	Normal Reduced (n = 3)	p[a]
0800 h-TSHB, mU/L					
Baseline	1.25 ± 0.56	1.06 ± 0.59	1.38 ± 0.75	0.85 ± 0.08	...
Week 2	1.14 ± 0.56	1.00 ± 0.50	1.49 ± 0.64	0.92 ± 0.41	...
2300 h-TSHB, mU/L					
Baseline	0.86 ± 0.44	0.72 ± 0.29	0.99 ± 0.31	1.01 ± 0.39	...
Week 2	1.07 ± 0.55	0.77 ± 0.39	1.26 ± 0.52	0.89 ± 0.37	...
0800 h-ΔTSH, mU/L					
Baseline	6.92 ± 3.29	6.22 ± 4.46	8.19 ± 3.07	6.54 ± 3.90	...
Week 2	6.71 ± 2.88	6.40 ± 4.67	9.45 ± 3.50	7.68 ± 6.78	...
2300 h-ΔTSH, mU/L					
Baseline	7.37 ± 2.90	6.89 ± 3.73	12.63 ± 3.93	10.73 ± 4.13	0.002
Week 2	10.36 ± 4.00**	7.19 ± 3.87	14.15 ± 3.71	9.35 ± 6.08	0.0005
ΔΔTSH, mU/L					
Baseline	0.45 ± 1.69	0.66 ± 1.45	4.35 ± 1.19	3.59 ± 0.98	<0.00001
Week 2	3.92 ± 1.74**	0.77 ± 1.50	4.72 ± 1.91	0.25 ± 0.25	<0.00001
0800 h-FT4B, pmol/L					
Baseline	11.4 ± 2.8	11.1 ± 2.6	10.9 ± 1.4	9.4 ± 0.9	...
Week 2	10.5 ± 2.2	10.5 ± 2.0	9.9 ± 1.7	9.4 ± 1.9	...
2300 h-FT4B, pmol/L					
Baseline	12.3 ± 3.1	11.9 ± 2.9	11.8 ± 1.6	9.6 ± 0.8	...
Week 2	11.0 ± 2.3*	11.1 ± 2.2	10.2 ± 1.5*	9.6 ± 1.3	...
0800 h-FT3B, pmol/L					
Baseline	4.9 ± 0.8	5.1 ± 1.0	5.2 ± 0.9	5.4 ± 0.6	...
Week 2	4.6 ± 1.1	4.8 ± 1.0	5.3 ± 0.7	5.8 ± 1.0	...
2300 h-FT3B, pmol/L					
Baseline	4.9 ± 1.0	5.1 ± 1.0	5.5 ± 0.7	5.6 ± 0.7	...
Week 2	4.8 ± 1.5	4.9 ± 1.1	5.3 ± 0.7	5.7 ± 0.6	...
Post-DST cortisol, nmol/L					
Baseline (N.S.)	92.4 ± 108.9 (6)	53.1 ± 55.8 (2)	33.7 ± 24.2 (1)	51.9 ± 50.8 (1)	...
Week 2 (N.S.)	63.9 ± 74.8* (4)	51.0 ± 66.7 (2)	33.0 ± 28.0 (0)	35.3 ± 9.6 (0)	...

[a] p values of Kruskal—Wallis rank sum test. TSHB, basal thyrotropin (TSH) concentration; ΔTSH, peak concentration minus basal TSH concentration; ΔΔTSH, 2300 h-ΔTSH minus 0800 h-ΔTSH; FT4B, basal free thyroxine; FT3B, basal free triiodothyronine; and DST, dexamethasone suppression test (N.S., number of patients with DST nonsuppression). Threshold for a reduced ΔΔTSH value < 2.5 mU/L. *p < 0.05; **p < 0.001 by Wilcoxon 2-tailed signed rank T-test for the difference between values before and after 2 weeks of treatment.

asymptomatic after 6 weeks of treatment compared to patients whose ΔΔTSH values remained reduced. The current study also confirms our preliminary report, which showed that normal ΔΔTSH values after 2 weeks of antidepressant treatment are associated with subsequent remission of depression (Duval et al., 2013). Thus, our data suggest that (1) chronobiological restoration of the HPT axis activity precedes clinical remission, and (2) alteration of the HPT axis after 2 weeks of treatment would be predictive of poor outcome.

4.1. Significance of a reduced ΔΔTSH value

We have previously discussed that the different indexes of HPT axis function are interrelated and that the TRH stimulation test is a more powerful clinical tool in psychiatric patients that a simple measurement of basal TSH (Duval et al., 1994). As evidenced by low ΔΔTSH values, a high proportion of patients in our study (76%) exhibit a chronobiological dysregulation of the HPT system at baseline.

From a pathophysiological viewpoint, the ΔΔTSH test takes into account 4 interdependent components of the HPT axis:

1) The ΔΔTSH test is correlated with the nyctohemeral profile of TSH secretion (Duval et al., 1990; Mokrani et al., 2006), which is flattened in depression (Souetre et al., 1986; Bartalena et al., 1990; Peteranderl et al., 2002).
2) Owing to circadian changes in the sensitivity of target biosystems (i.e., chronesthesy), TRH stimulation at 2300 h produces greater ΔTSH differences between drug free depressed inpatients and control subjects than stimulation at 0800 h. Decreased ΔΔTSH values, which are strongly correlated with 2300 h-ΔTSH values (Duval et al., 1990, 1994), may reflect a hyposensitivity of pituitary TRH receptors of the pituitary thyrotrophs possibly because of prolonged increased central TRH secretion (Loosen and Prange, 1982; Jackson, 1998).
3) The ΔΔTSH test takes into account the dynamic characteristics of the negative feedback of thyroid hormones

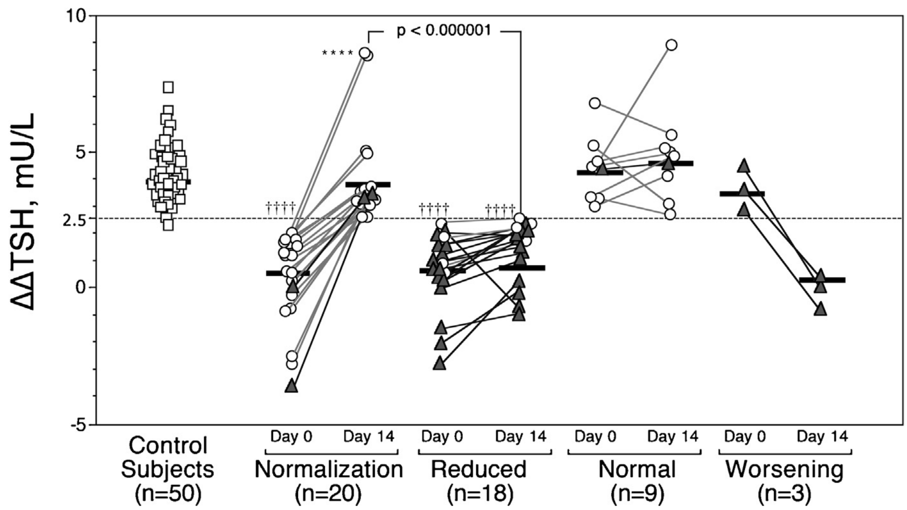

Figure 1 Evolution before and after 2 weeks of antidepressant treatment of the difference between 2300 h and 0800 h maximum increments in thyrotropin (ΔΔTSH) according to 4 patterns: ''normalization'', ''reduced'', ''normal'', ''worsening''. Threshold for a reduced ΔΔTSH value < 2.5 mU/L. Circles represent subsequent remitters; triangles represent non-remitters (after 6 weeks of treatment). Comparisons by *U* test with Bonferroni's adjustment (for 5 pairwise comparisons), $^{††††}p < 0.00001$ vs. controls. Within-subject differences (between day 0 and day 14): $^{****}p < 0.00001$, by *T* test.

on TSH secretion, since the morning TRH test stimulates secretion of thyroid hormones that may increase the negative feedback in the evening (Duval et al., 1994). This could explain why, despite the expected circadian increase in TSH levels in the evening, basal TSH values do not change between 0800 h and 2300 h in control subjects. In depressed patients, basal TSH values are lower at 2300 h than at 0800 h and FT4 values are slightly but significantly higher at 2300 h (Table 1), suggesting a strengthening of negative feedback by thyroid hormones at the pituitary level.

4) Given that TRH stimulates preformed TSH (Piette and Beck, 1976), the evening TSH blunting in patients could also be related to a decrease in TSH resynthesis in the thyrotrophs during the day after the morning challenge.

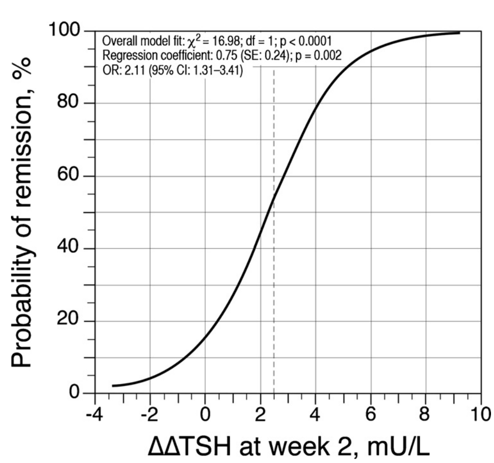

Figure 2 Predicted probability of remission/non-remission (at week 6) based on ΔΔTSH values after 2 weeks of treatment using logistic regression prediction curve. Logistic regression produces the regression coefficient (and standard error [SE] of estimate, and significance level) and odds ratio (OR, with 95% confidence interval [CI]) associated with each ΔΔTSH value.

This disturbance could involve a hyposensitivity of the TRH receptors (secondary to TRH hypersecretion) and/or an increased negative feedback of thyroid hormones, both leading to understimulation of TSH synthesis. On the other hand—especially in recent suicide attempters (Duval et al., 2010)—, a decreased central TRH activity could also lead to such understimulation. Indeed, in a postmortem study Alkemade et al. (2003) have found low TRH mRNA levels within the paraventricular nucleus suggesting a decreased hypothalamic TRH drive in some depressed patients.

In agreement with several reports (Loosen and Prange, 1982; Duval et al., 1990, 2010), but not all (Jackson, 1998; Alkemade et al., 2005), it seems unlikely that abnormal TRH drive could be secondary to hyperactivity of the hypothalamic—pituitary—adrenal (HPA) axis, since, in our study, post-DST serum cortisol concentration and DST non-suppression do not differ across the patients when classified according to their ΔΔTSH status.

4.2. ΔΔTSH patterns and clinical outcome

During antidepressant treatment, we observed 4 patterns of ΔΔTSH changes over time (Fig. 1): one group of patients ($n = 20$, 40%) showed a reduced ΔΔTSH value at baseline and a normalization within 2 weeks of treatment (''normalization pattern''); another group of patients ($n = 18$, 36%) showed abnormal ΔΔTSH values whenever they were tested (''reduced pattern''); a third group ($n = 9$, 18%) showed normal ΔΔTSH values both at baseline and during treatment (''normal pattern''); the fourth group ($n = 3$, 6%) showed normal ΔΔTSH values at baseline which became reduced after 2 weeks of treatment (''worsening pattern''). These four groups of patients did not differ in demographic characteristics, diagnostic subtypes, illness-related variables, history of suicidal behavior, severity of depression at study inclusion, or medication during the trial.

From a clinical point of view, remission after 6 weeks of antidepressant treatment was significantly associated with both ''normalization'' and ''normal'' ΔΔTSH patterns, while non-remission was associated with both ''reduced'' and ''worsening'' patterns. One may note that our results were obtained in a sample of selected nonpsychotic severely depressed inpatients requiring adequate antidepressant treatment and more vigorous medication dosing than in current practice. Thus, the remission rate observed in our study (58%) is substantially higher than that usually cited in the literature (in the range of 30—45% [Carvalho et al., 2007]). However, this rate is in accordance with some previous reports showing that two-thirds of patients treated with second-generation of antidepressants ultimately achieved remission (Quitkin et al., 2005).

The ''normalization ΔΔTSH pattern'' suggests a restoration of a normal chronobiological activity of the HPT axis by antidepressants within the first two weeks of treatment. However, the mechanisms by which antidepressants could induce this change are poorly understood. It has been hypothesized that antidepressants could influence the function of the biological clock molecular machinery (Benedetti, 2012); however, very little data is available on the effects of antidepressants on the biological clock. In rodents, it has been found that fluoxetine, when combined with L-tryptophan, induces phase advances of suprachiasmatic nucleus (SCN) (Sprouse et al., 2006), whereas other SSRIs can shorten circadian period in SCN (Nomura et al., 2008). In normal humans, agomelatine (a MT1/MT2 receptor agonist and 5-HT2C receptor antagonist) may induce a phase advance (Krauchi et al., 1997), but data in depression is lacking. It is worthy to note that melatonin could regulate diurnal changes in TSH production via MT1 receptors and/or the biological clock (Aizawa et al., 2007). Concerning the effects of antidepressants on TRH responsiveness, preclinical studies have yielded contradictory findings: unchanged (Atterwill et al., 1989; Kennedy et al., 1997) or decreased (Bennett et al., 1986) responsiveness has been reported—while repeated electroconvulsive shock enhanced the effects of CG 3509 (a TRH analog; Bennett et al., 1986). Interestingly, administration of various antidepressant compounds may lead to decreased thyroid hormone levels by reduction of synthesis and/or metabolism, or enhanced clearance (Atterwill et al., 1989; Kennedy et al., 1997; Eravci et al., 2000). In clinical studies, greater reductions in T4 or FT4 levels have been consistently found in antidepressant responders compared to non-responders (Joffe and Levitt, 1993; Rao et al., 1996; Gendall et al., 2003; Gambi et al., 2005). In our study, a significant decline in FT4 in the evening associated with a rise in 2300 h-ΔTSH is only observed in patients who normalized their ΔΔTSH test. This finding suggests that the decrease in the negative feedback exerted by thyroid hormones on TSH secretion at the pituitary level may contribute to the normalization of the evening TRH-TSH response. On the other hand, the decreased negative feedback may promote TSH resynthesis leading to adequate TSH reserves ensuring normal evening response.

The current conceptualization of antidepressant actions is that it is the downstream effects on protein synthesis and neuroplasticity that account for therapeutic efficacy, rather than the immediate effects on synaptic monoamine levels (Grady and Stahl, 2013). Stassen et al. (2007) postulated that antidepressant drugs might induce a ''natural resilience mechanism'' that controls recovery from depression. This mechanism might be triggered during the first two weeks of treatment by the action of antidepressants, via a restoration of the neuroplasticity that leads to neural adaptations. In this frame, the ΔΔTSH test normalization might reflect processes underlying the restoration of neuroplasticity.

Patients with a ''reduced pattern'' were mostly treatment non-responders. In these patients, no significant changes in HPT function were observed during the trial. Moreover, they remained hospitalized, in average, 9 more weeks—despite different readjustments in the therapeutic strategy—than those with a ''normalization pattern''. This finding suggests that early ΔΔTSH non-normalization is associated with a probable treatment resistance, although optimal strategy for treating antidepressant non-responders has yet to be identified (Papakostas, 2009; Coplan et al., 2014).

Patients with a ''normal pattern'' showed a favorable outcome. We have previously found that normal ΔΔTSH test is associated with blunted prolactin response to D-fenfluramine, a specific 5-HT releasing/uptake-inhibiting agent (Duval et al., 1999). This could mean that the 5-HT tone is decreased when the HPT axis activity is normal in depressed patients. It has been shown that different types of antidepressant treatment enhance 5-HT neurotransmission, although each treatment achieves this result via different mechanisms (Bourin et al., 2002; Blier, 2013). In this frame, it is conceivable that patients with a ''normal pattern'' would better respond to antidepressant compounds.

Given the scarcity of the ''worsening pattern'', it is difficult to draw at present any pathophysiological interpretation. However, all the patients of this group ($n = 3$) were non-remitters. This observation is consistent with the hypothesis that a chronobiological alteration of the HPT axis after 2 weeks of treatment would be predictive of poor outcome.

4.3. Limitations of the present study

Some shortcomings in our study require discussion. Firstly, our results obtained in severely depressed hospitalized patients (synchronized with their environment) do not appear at present transposable to outpatients. Secondly, although the raters were blind to the medication used as well as to the neuroendocrine results, antidepressant treatment was given in an open-label manner. In order to optimize the response to treatment we used several classes of compounds by taking into account primarily the specific side effects of each drug, and, when available, previous antidepressant response; most patients (90%) had already been treated with antidepressants—with inconsistent results—at the time of their admission to hospital. Thirdly, we did not use placebo as a comparative treatment. However, the aim of the study was not to demonstrate antidepressant efficacy of the compounds. Finally, although the primary findings appear to be statistically robust, they must be considered preliminary until replicated in a larger patient population.

In conclusion, our pilot study suggests that the ΔΔTSH test status after 2 weeks of antidepressant treatment is associated with subsequent clinical outcome, and thus could potentially provides an early therapeutic decision help in a clinical setting. Further studies in a wider population are needed to confirm the value of this chronobiological index in the therapeutic field.

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Conflict of interest

No conflict of interest is declared.

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