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BRIEF REPORT

Serum thyroid-stimulating-hormone concentration as an index of severity of major depression

Ivan Berlin[1], Christine Payan[1], Emmanuelle Corruble[2] and Alain J. Puech[3]

[1] *Department of Pharmacology, Hôpital Pitié-Salpêtrière, Paris, France*
[2] *Department of Psychiatry, Hôpital Paul Brousse, Villejuif, France*
[3] *Sanofi, Gentilly, France*

Abstract

Alterations in thyroid axis are common in depression and subclinical hypothyroidism may predispose to recurrent depressive episodes and resistance to antidepressants. The same normal reference ranges are used in both depressive and non-psychiatric patients to detect hypothyroidism. We hypothesized that in depressive patients, serum TSH (thyrotropin) elevation within the normal reference range ($\geqslant$ upper 25th percentile) may be related to patients ' characteristics reflecting the severity of the depressive illness.

We analysed, in a cross-sectional study, the relationship between serum TSH and serum-free thyroxine (T4) concentrations and different demographic and psychiatric characteristics in 94 depressive in-patients with DSM-III-R criteria for major depression.

The frequency of subclinical hypothyroidism (normal serum T4, higher than normal serum TSH) was 5.3%. In univariate analyses patients who had serum TSH concentrations $\geqslant$ upper 25th percentile of the normal range were more likely to have recurrent depression, longer disease duration, higher number of episodes of major depression, higher number of previous suicide attempts and higher body mass index than those patients who had serum TSH concentrations $<$ upper 25th percentile of the normal range (age-adjusted $p < 0.05$). Stepwise logistic regression analysis showed that serum TSH $\geqslant$ upper 25th percentile of the normal range was positively associated with recurrent depression ($p = 0.0001$), presence of somatic disease condition ($p = 0.04$), marital status ($p = 0.06$) and number of suicide attempt ($p = 0.1$). On the other hand, significantly higher serum TSH concentrations were observed in patients with recurrent depression, melancholia and associated somatic disease conditions. Correspondence analysis showed that serum TSH in the higher 25th percentile of the normal reference range projected together with the presence of melancholia, psychiatric and somatic disease conditions, severe major depressive episodes, recurrence of depressive episodes, prescription of at least two antidepressants or non-response to two antidepressants, and previous suicide attempts.

Our study suggests that serum TSH concentration in the upper 25th percentile of the normal reference range may be associated with characteristics of severe major depression. Further prospective studies are needed to establish whether serum TSH concentration in the upper 25th percentile of the normal reference range is a contributory causal factor or a consequence of the severity of major depression.

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Introduction

Depression may be a clinical symptom of primary hypothyroidism which is usually due to autoimmune disease or the destructive therapy of Graves' disease. Alterations in the thyroid axis are common in depression and several clinical symptoms are common to both depression and hypothyroidism (Nemeroff, 1989). Clinical hypothyroidism is rarely associated with depression (Ordas and Labbate, 1995) and the thyroid axis alterations are generally subtle in depressive patients. The absence of the normal nocturnal TSH surge which may result in a lower circadian thyroid hormone secretion (Jackson, 1996; Sullivan et al., 1997) may support the view that thyroid axis alterations are of central origin (Nemeroff, 1989). Subclinical hypothyroidism is characterized by serum concentrations of thyroxine (T4) within the reference range and a raised serum TSH concentration. This condition which increases with age is higher in women than men and has been found to be quite common in people older than 55 yr in community surveys (Bagchi et

Address for correspondence: Dr Ivan Berlin, Department of Pharmacology, Hôpital Pitié-Salpêtrière, 47 Bd de l'Hôpital, 75013 Paris, France.
Fax: 33 1 42 16 16 88
E-mail: ivan.berlin@psl.ap-hop-paris.fr

al., 1990; Parle et al., 1991; Sawin et al., 1985). Subclinical hypothyroidism has been observed in 3.5–13.6% of depressive patients (Gold et al., 1981; Joffe and Levitt, 1992; Sternbach et al., 1983). Further, exaggerated TSH responses to TRH (thyrotropin-releasing hormone) occurs more frequently in depressed patients with normal TSH concentrations, although in the upper half of the range considered normal (Kraus et al., 1997). Subclinical hypothyroidism may predispose to higher frequency of depressive episodes (Haggerty et al., 1993). Triiodothyronine and T4 have been proposed as adjuvant therapy in non-responders to antidepressants (Bauer et al., 1998; Hickie et al., 1996; Howland 1993; Jackson, 1996; Prange, 1996; Sullivan et al., 1997), although the efficacy of such treatments remains controversial.

Several evidences confirm the association of thyroid axis deficiency with depression, and routine screening for thyroid axis alterations has been advised (Szabadi, 1991). However, only a few studies evaluated the association of clinical characteristics with thyroid status (Kraus et al., 1998; Sullivan et al., 1997). Furthermore, to establish subclinical hypothyroidism in depressive patients, the reference ranges used are based on observations in non-psychiatric, endocrinological patients with hypothyroidism. It may, however, be hypothesized that more subtle alterations in the thyroid axis may be related to clinical characteristics in depressive patients and that even small elevations in serum TSH levels, usually considered to be within the normal range, may have clinical consequences.

Materials and methods

Subjects

A total of 151 patients meeting DSM-III-R (American Psychiatric Association, 1987) criteria for major depression as their primary diagnosis and necessitating hospitalization were screened in seven hospitals of the Assistance Publique-Hôpitaux de Paris. Among these patients 97 had serum TSH and serum-free T4 determined within 8 d of commencing hospitalization; three patients were excluded from the analyses because they were treated with T4 at the time of serum TSH and T4 determinations. Patients were classified for diagnostic criteria by the MINI International Psychiatric Interview (Lecrubier et al., 1997). Patients with bipolar disorder, pregnancy, and older than 75 yr were not included in the study. Investigators classified patients as responders or non-responders when they were discharged from hospital. Patients were considered as non-responders if they did not respond to one antidepressant and required at least two different types of antidepressant in succession, at doses generally accepted as sufficiently high to elicit a therapeutic response. The mean age of the 94 patients included in data analysis was 44 ± 13 yr; 66 (70%) were women, 49 (52%) were married, 64 (68%) had recurrent depression and 60 (64%) patients presented melancholia according to DSM-III-R criteria for major depressive episode melancholic type. The mean duration of major depressive disorder was 7.6 ± 8.5 yr (median 3.7 yr) and that of the current episode 8.3 ± 8.6 months (median 4 months). Twenty (21%) patients were receiving neuroleptics, 62 (66%) benzodiazepines, 8 (8.5%) anxiolytics other than benzodiazepines, and 1 patient was on lithium and another on carbamazepine (2%). Fifty (53%) patients had associated somatic disease conditions. The most frequent somatic illnesses were: hypertension (13 patients) endocrinological disease, mainly diabetes mellitus (7 patients), allergic manifestations (8 patients), and rheumatologic disease conditions (6 patients). None of the patients were treated by drugs known to modify thyroid function and all were free of iode-containing radiopaque agents. Informed written consent was obtained from each patient and the study was approved by the Ethics Committee of the Cochin Hospital, Paris.

TSH and T4 assays

Serum TSH concentration was measured by third generation chemiluminescent assay (Spencer et al., 1990) and serum T4 by BeriLux FT4 solid phase antigen luminescent technique (Behringwerke AG, Marburg, Germany).

Statistical analyses

Serum TSH and serum-free T4 concentrations were determined in seven different centres. There was no difference between the centres for either serum TSH or serum-free T4 concentrations. As normal ranges of each laboratory were somewhat different, TSH data were transformed as percentages of the respective normal ranges of each laboratory. Further, because TSH and T4 data were not normally distributed [especially TSH data which were negatively (left) skewed] data were normalized by logarithmic transformation. Statistical analyses were thus performed on log-transformed data. Normal laboratory ranges for serum TSH (and serum-free T4) are determined to exclude overt hypo- or hyperthyroidism. We hypothesized that in psychiatric conditions more subtle thyroid axis changes may play a role, and dichotomized this population of patients with major depression into two categories: (i) patients who had serum TSH concentrations $<$ upper 25th percentile and (ii) those who had serum TSH concentrations $\geqslant$ upper 25th percentile of the reference range.

Although for age no significant difference occurred, age was included in each statistical analyses as covariate. ANCOVA was used for between-group comparisons of

continuous variables. Frequencies were compared by the Mantel–Haenszel χ^2 test. Stepwise forward logistic regression analysis was used to identify variables associated with serum TSH status. Correspondence analysis was used to identify aggregates of different variables. Statistical analyses were performed by statistical software BMDP (release 7, 1992, Los Angeles, CA). All tests were two-tailed. Differences were considered significant if $p < 0.05$.

Results

Among the 94 patients with major depression only five had serum TSH concentrations higher than the normal reference range and only one had a serum TSH concentration twice as high as the upper limit of the reference range. None of the patients had serum-free T4 concentrations beyond the limits of the reference range. Thus, the frequency of subclinical hypothyroidism in this sample was 5.3%.

Table 1 shows the effect of the normal range of serum TSH concentration $\geqslant$ upper 25th percentile when compared with that $<$ upper 25th percentile. Patients who had serum TSH concentrations $\geqslant$ upper 25th percentile of the normal range, or higher, were more likely to have recurrent depression, longer disease duration, higher number of previous suicide attempts, higher number of episodes of major depression, and higher body mass index. Variables having a p value lower than 0.1 were included in a stepwise age-adjusted logistic re-

Table 1. Relationship between serum TSH concentration [upper 25th percentile of the normal range (or higher $n = 5$)] and demographic and selected psychiatric characteristics of patients hospitalized for major depression [n (%) or mean $\pm$ S.D.]

	Serum TSH $<$ upper 25th percentile ($n = 70$)	Serum TSH $\geqslant$ upper 25th percentile ($n = 24$)	p value‡
Age (yr)	43 $\pm$ 13	47 $\pm$ 12	0.2
Sex (females)	47 (67)	19 (79)	0.27
Body mass index (kg/m^2)	23 $\pm$ 4.4	26 $\pm$ 6.4	0.03
Marital status (married)	32 (46)	17 (71)	0.07
Disease duration (yr)	6 $\pm$ 8	11 $\pm$ 10	0.04
Present episode duration $\geqslant$ 3 months	36 (51)	14 (58)	0.68
Recurrent depression	40 (58)	23 (96)	0.002
Number of previous episodes of major depression			0.0003
None	28 (40)	1 (4)	
1	22 (31)	11 (46)	
2	2 (3)	6 (25)	
$\geqslant$ 3	18 (26)	6 (25)	
Melancholia present*	42 (60)	18 (75)	0.37
Severity†	52 (74)	17 (71)	0.9
Previous suicide attempt(s)	25 (36)	14 (57)	0.12
Number of previous suicide attempt(s)	0.76 $\pm$ 1.2	1.68 $\pm$ 2.3	0.009
Other psychiatric diagnoses present	38 (55)	14 (58)	1
Somatic disease condition associated	33 (47)	17 (71)	0.09

* According to DSM-III-R criteria for major depressive episode melancholic type.
† Number of patients with DSM-III-R severity, grade 3 (severe, without psychotic features) + 4 (with psychotic features).
‡ Age-adjusted.

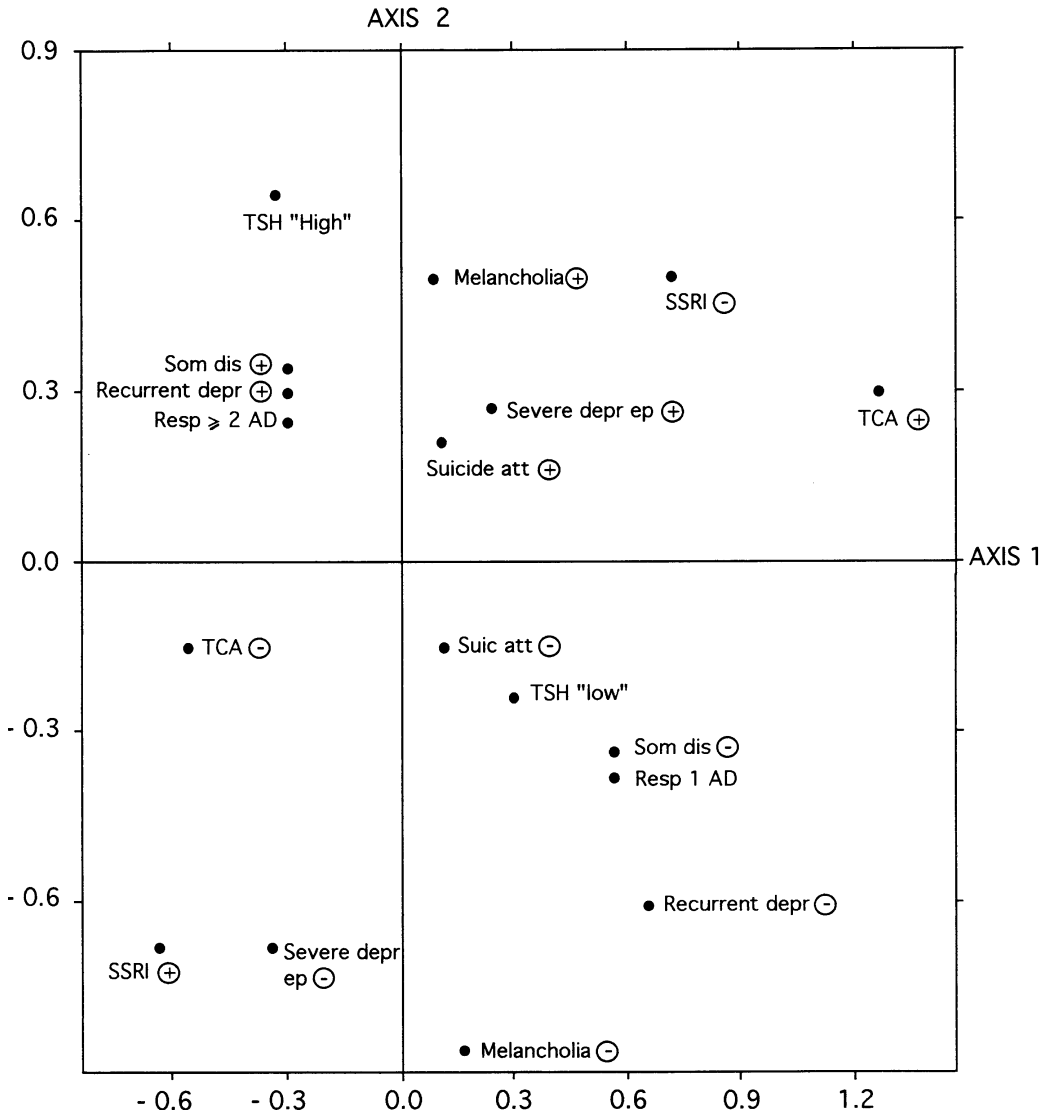

Figure 1. Correspondence analysis. Each variable is represented by two factor scores (factor 1 = axis 1, factor 2 = axis 2). The higher the absolute value of the factor score the higher the contribution of the variable to this factor. The distance of the coordinate scores between variables expresses the intensity of their relationship: the smaller the distance the stronger the relationship. Abbreviations: *TSH 'High'*, serum TSH concentration ⩾ upper 25th percentile of the normal range; *TSH 'Low'*, serum TSH concentration < upper 25th percentile of the normal range; *Recurrent depr* ⊕, recurrent depression present; *Recurrent depr* ⊖, recurrent depression absent; *Som dis* ⊕, somatic disease condition present; *Som dis* ⊖, somatic disease condition absent; *Resp ⩾ 2 AD*, response to ⩾ 2 antidepressants or non-response, *Resp 1 AD*, response to 1 antidepressant; *Melancholia* ⊕, melancholia present; *Melancholia* ⊖, melancholia absent; *Suicide att* ⊕, previous suicide attempt(s); *Suic att* ⊖, no previous suicide attempt; *Severe depr ep* ⊕, severe depressive episode (as defined by DSM-III-R) present; *Severe depr ep* ⊖, severe depressive episode absent; *SSRI* ⊖, no administration of serotoninergic antidepressant; *SSRI* ⊕, administration of serotoninergic antidepressant; *TCA* ⊕, administration of tricyclic antidepressant; *TCA* ⊖, no administration of tricyclic antidepressant.

gression analysis. Four variables remained in the final model with a model fit of 97%: recurrent depression ($p = 0.0001$), and presence of associated somatic disease condition ($p = 0.04$), marital status ($p = 0.06$) and number of previous suicide attempts ($p = 0.11$). Disease duration and body mass index did not enter in the final model. This model correctly classified 81% of the patients.

The relationship between variables can be further illustrated by correspondence analysis. Figure 1 gives projections of the variables on the first two axes and shows that serum TSH concentrations ⩾ upper 25th percentile of the normal reference range are projected on the upper side of and close to axis 2, along with the following variables: presence of melancholia, presence of

Table 2. Comparison of serum-free thyroxine (T4) and TSH concentrations according to some selected patients' characteristics (means of raw data ± S.D.)

	Serum-free T4 (pmol/l)	TSH (mU/l)
Recurrent depression		
Yes	13.4 ± 3	1.8 ± 1.2***
No	13.7 ± 2.6	0.9 ± 0.6
Melancholia present		
Yes	13.4 ± 2.9	1.7 ± 1.2*
No	13.6 ± 2.7	1.1 ± 0.7
Previous suicide attempt(s)		
Yes	13.1 ± 2.6	1.5 ± 0.9
No	13.8 ± 3	1.5 ± 1.2
Other psychiatric diagnoses		
Yes	13.1 ± 2.7*	1.6 ± 1.2*
No	14 ± 3	1.4 ± 1
Number of antidepressants used		
1	14.1 ± 2.7	1.3 ± 1
⩾ 2	13 ± 2.9	1.6 ± 1.2
Somatic disease condition associated		
Yes	13.5 ± 2.7	1.7 ± 1.3**
No	13.5 ± 3	1.2 ± 0.8

Statistical analysis was performed on log-transformed data.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$

somatic disease condition, recurrence of depressive episodes, prescription of at least two antidepressants, presence of severe major depressive episodes and a previous history of a suicide attempt.

When serum-free T4 and TSH levels were directly compared according to several characteristics of the depressive illness, a higher serum TSH concentration was observed in patients with recurrent depression, melancholia and associated psychiatric and somatic disease conditions. Patients with other associated psychiatric diagnoses also had a lower serum-free T4 concentration (Table 2). The presence of associated generalized anxiety disorder ($n = 29$) did not influence serum-free T4 (12.4 ± 2.6 vs. 13.9 ± 2.9 pmol/l, $p = 0.25$) or serum TSH (1.5 ± 0.9 vs. 1.5 ± 1.2 pmol/l, $p = 0.57$) concentrations.

Discussion

This study shows that 'high-normal', i.e. ⩾ upper 25th percentile of the normal range of serum TSH concentration is associated with greater severity of major depression. According to multivariate analyses, depressive patients with 'high-normal' TSH concentrations were more likely to have recurrent depression, previous suicide attempts, associated somatic and psychiatric disease conditions, melancholia and were treated by two or more antidepressants than those with 'low-normal' (< upper 25th percentile of the normal range) serum TSH concentrations.

The relationship between reduced thyroid axis function and depression has long been suspected. However, overt hypothyroidism is very rare among depressive patients (Fava et al., 1995; Gold et al., 1981). No specific study compared the prevalence rate of subclinical hypothyroidism among depressive patients with that in the general population. However, prevalence rates seem to be similar: subclinical hypothyroidism has been observed in 3.5–13.6% of depressive patients (Gold et al., 1981; Joffe and Levitt, 1992; Sternbach et al., 1983) and it is estimated to be 5.6–11.1% for women and 2.7–3.7% for men between the age range of 35 and 65 yr in the normal population (Danese et al., 1996). Subclinical hypothyroidism increases with age and is approximately twice as frequent among women than among men (Bagchi et al., 1990; Parle et al., 1991) as is the prevalence of depression.

The definition of subclinical hypothyroidism is based on the normal reference range of serum TSH concentrations. This reference range has been established in healthy subject populations (generally blood donors) without clinical signs of endocrinological thyroid dysfunction. It is not known whether this 'endocrinological' reference range can be applied to patients with depression. Recent studies suggest that 'high-normal' serum TSH concentration is associated with exaggerated TSH response to TRH in depressed patients (Kraus et al., 1997). Circadian difference in serum-free T4 concentration distinguishes between depressed and control subjects; depressed subjects have a higher mean TSH response to TRH than those with single episodes (Sullivan et al., 1997). It seems, therefore, that subtle thyroid underfunction, with serum TSH concentrations in the upper third or quarter of the usual 'endocrinological' reference range may be a contributory factor in patients with depression. A similar phenomenon has been found for high serum cholesterol levels. In persons with high serum cholesterol concentration T4 administration significantly reduced total and LDL-cholesterol only in subjects with 'high-normal' serum TSH concentrations and it had no effect in those persons who had 'low-normal' serum TSH levels (Michalopoulou et al., 1998).

Subtle thyroid axis modifications may account for up to 36% of the variance in antidepressant treatment outcome (Sullivan et al. 1997). Tricyclic antidepressant non-responders have a higher TSH response to TRH and a greater reduction in morning to evening difference in serum T4 levels (Sullivan et al., 1997). Alterations in thyroid function may influence not only central β-adrenergic (Whybrow and Prange, 1981) but also sero-

tonergic activities (Cleare et al., 1995) and this may lead to reduced treatment response. In further studies assessing predictors of antidepressant response, serum TSH concentration should be included as a putative factor which may contribute to treatment response.

Screening for mild thyroid failure and subsequent treatment with levothyroxine sodium is cost-effective because it lowers both hypercholesterolaemia and the risk of cardiovascular disease, and progression toward overt hypothyroidism (Danese et al., 1996). Similarly, screening for mild thyroid failure including 'high-normal' serum TSH concentrations may be a cue to the clinician to consider whether such patients have a more severe form of depression. Our findings also suggest that it would be useful to study whether adjunctive treatment with levothyroxine sodium may be beneficial for such patients when they fail to respond to antidepressants.

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References

American Psychiatric Association (1987). *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., revised). Washington, DC: American Psychiatric Association.

Bagchi N, Brown TR, Parish RF (1990). Thyroid dysfunction in adults over age 55 years. A study in an urban US Community. *Archives of Internal Medicine 150*, 785–787.

Bauer M, Hellweg R, Gräf K-J, Baumgartner A (1998). Treatment of refractory depression with high-dose thyroxine. *Neuropsychopharmacology 18*, 444–455.

Cleare AJ, McGregor A, Keane V (1995). Neuroendocrine evidence for an association between hypothyroidism, reduced central 5-HT activity and depression. *Clinical Endocrinology 43*, 713–719.

Danese MD, Powe NR, Sawin CT, Ladenson PW (1996). Screening for mild thyroid failure at the periodic health examination. *Journal of the American Medical Association 276*, 285–292.

Fava M, Labbate LA, Abraham ME, Rosenbaum JF (1995). Hypothyroidism and hyperthyroidism in major depression revisited. *Journal of Clinical Psychiatry 56*, 186–192.

Gold MS, Pottash ALC, Extein I (1981). Hypothyroidism and depression. Evidence from complete thyroid function evaluation. *Journal of the American Medical Association 245*, 1919–1922.

Haggerty JJ, Stern RA, Mason GA, Beckwith J, Morey CE, Prange AJ (1993). Subclinical hypothyroidism: a modifiable risk factor for depression? *American Journal of Psychiatry 150*, 508–510.

Hickie I, Bennett B, Mitchell P, Wilhelm K, Orlay W (1996). Clinical and subclinical hypothyroidism in patients with chronic and treatment-resistant depression. *Australian and New Zealand Journal of Psychiatry 30*, 246–252.

Howland RH (1993). Thyroid dysfunction in refractory depression: implication for pathophysiology and treatment. *Journal of Clinical Psychiatry 54*, 47–54.

Jackson I (1996). Does thyroid hormone have a role as adjunctive therapy in depression? *Thyroid 6*, 63–67.

Joffe RT, Levitt AJ (1992). Major depression and subclinical (grade 2) hypothyroidism. *Psychoneuroendocrinology 17*, 215–221.

Kraus RP, Phoenix E, Edmonds MW, Nicholson IR, Chandara PC, Tokmakejian S (1997). Exaggerated TSH responses to TRH in depressed patients with 'normal' baseline TSH. *Journal of Clinical Psychiatry 58*, 266–270.

Lecrubier Y, Sheehan D, Weiller E, Amorim P, Bonora I, Sheehan K, Janas J, Dunbar GC (1997). The MINI International Neuropsychiatric Interview (MINI): a short structured diagnostic interview: reliability and validity according to the CIDI. *European Psychiatry 12*, 224–232.

Michalopoulou G, Alevizaki M, Piperingos G, Mitsibounas D, Mantzos E, Adamopoulos P, Koutras DA (1998). High serum cholesterol levels in persons with 'high-normal' TSH levels: should one extend the definition of subclinical hypothyroidism? *European Journal of Endocrinology 138*, 141–145.

Nemeroff CB (1989). Clinical significance of psychoneuroendocrinology in psychiatry: focus on the thyroid and adrenal. *Journal of Clinical Psychiatry 50* (Suppl.), 13–20.

Ordas DM, Labbate LA (1995). Routine screening of thyroid function in patients hospitalized for major depression or dysthymia? *Annals of Clinical Psychiatry 7*, 161–165.

Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC (1991). Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. *Clinical Endocrinology (Oxford) 34*, 77–83.

Prange AJ (1996). Novel uses of thyroid hormones in patients with affective disorders. *Thyroid 5*, 537–543.

Sawin CT, Castelli WP, Heshman JM, McNamara P, Bacharach P (1985). The aging thyroid. Thyroid deficiency in the Framingham study. *Archives of Internal Medicine 145*, 1386–1388.

Spencer CA, LoPresti JS, Patel A, Guttler RB, Eigen A, Shen D, Gray D, Nicoloff JT (1990). Applications of a new chemiluminometric thyrotropin assay to subnormal measurement. *Journal of Clinical Endocrinology and Metabolism 70*, 453–460.

Sternbach HA, Gold MS, Pottash AC, Extein I (1983). Thyroid failure and protirelin (thyrotropin-releasing hormone) test abnormalities in depressed outpatients. *Journal of the American Medical Association 249*, 1618–1620.

Sullivan PF, Wilson DA, Mulder RT, Joyce PR (1997). The hypothalamic–pituitary–thyroid axis in major depression. *Acta Psychiatrica Scandinavica 95*, 370–378.

Szabadi E (1991). Thyroid dysfunction and affective illness. *British Medical Journal 302*, 923–924.

Whybrow PC, Prange AJ (1981). A hypothesis of thyroid–catecholamine receptor interaction. *Archives of General Psychiatry 38*, 106–113.