Thyroid Function Screening in Children and Adolescents With Mood and Anxiety Disorders

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ABSTRACT

Objective: To determine the prevalence of abnormal thyroid-stimulating hormone (TSH) measures in youth with severe mood and anxiety disorders and to examine clinical and demographic predictors of abnormal TSH measures.

Methods: We retrospectively examined screening TSH concentrations in psychiatrically hospitalized children and adolescents (3–19 years) with mood/anxiety disorders (*DSM-IV* and *DSM-5* criteria) at a large, urban, pediatric hospital between September 2013 and April 2017. Symptoms were extracted from the medical record using adaptive natural language processing algorithms, and the utility of demographic, clinical, and treatment variables as predictors of abnormal TSH measures was evaluated using logistic regression.

Results: In this sample (N = 1,017, mean ± SD age = 14.7 ± 2.24 years), 62 patients had a TSH concentration > 3.74 µIU/mL (5.3% [n = 6] of patients < 12 years of age and 6.2% [n = 56] of patients ≥ 12 years of age), and 7 patients had a TSH concentration < 0.36 µIU/mL. Elevated TSH concentrations were associated with a recent weight gain (odds ratio [OR] = 3.60; 95% CI, 1.13–9.61; *P* = .017), a history of thyroid disease (OR = 6.88; 95% CI, 2.37–10.7; *P* ≤ .0001), abnormal menstrual bleeding/menometrorrhagia (OR = 2.03; CI, 1.04–3.63; *P* = .024), and benzodiazepine treatment (OR = 2.29; 95% CI, 1.07–4.52; *P* = .02). No association was observed for sex, age, or body mass index *z* score. Among patients with elevated TSH measures, 12.9% (n = 8, mean ± SD age = 16.5 ± 1.5 years, 87.5% female) had an abnormal free/total thyroxine (T_4) level or other biochemical findings consistent with thyroid disease. Patients with thyroid disease (compared to those patients with elevated TSH and normal active thyroid hormone concentrations) were older (16.5 ± 1.5 vs 14.6 ± 2.3 years, *P* = .020) but did not differ in sex distribution (87.5% vs 63.6% female, *P* = .444).

Conclusions: TSH concentrations are abnormal in approximately 6% of psychiatrically hospitalized youth, although thyroid disease was present in < 1% of the total sample. Targeted screening should focus on patients with recent weight gain, those treated with benzodiazepines, and girls with a history of abnormal uterine bleeding/menometrorrhagia.

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Evaluation of depressive and anxiety disorders requires clinicians to exclude nonpsychiatric etiologies and confounds. Thyroid dysfunction represents one of the most common and most frequently evaluated nonpsychiatric etiologies. Indeed, hypothyroidism may present as fatigue, weight gain, increased appetite, diminished concentration, and psychomotor slowing as well as constipation in children and adolescents, while hyperthyroidism in children and adolescents is frequently characterized by anxiety, tremulousness, autonomic symptoms, and weight loss as well as decreased appetite and poor concentration/distractibility. In pediatric patients, hyperthyroidism—which occurs in about 1 in 5,000 children and adolescents—mostly commonly results from Graves disease[1] wherein thyrotropin receptor autoantibodies stimulate thyroid growth and increase thyroid hormone synthesis. Given symptomatic overlap between hyper- and hypothyroidism and anxiety and depressive disorders, respectively, thyroid dysfunction is considered in the differential diagnosis of anxiety and depressive disorders.[2–4] In fact, clinical trials of pharmacotherapy in children and adolescents with anxiety,[5–8] depressive disorders,[9–11] and bipolar disorder[12–14] generally require that youth be biochemically and clinically euthyroid as an inclusion criterion.

Practice Parameters from the American Academy of Child and Adolescent Psychiatry (AACAP) for the assessment and treatment of depressive disorders recommend consideration of hypothyroidism in the differential diagnosis of patients with depressive disorders and in patients who have failed to respond to initial antidepressant pharmacotherapy.[2,4] Similarly, the AACAP Practice Parameters for the assessment and treatment of pediatric anxiety disorders recommend that the psychiatric assessment consider "physical conditions that may mimic anxiety symptoms" as a minimum standard, and these explicitly include thyroid disease.[2]

However, the utility of routine laboratory screening in children and adolescents with mood or anxiety disorders has received limited attention. In fact, the only examination of

Clinical Points

- The prevalence and clinical risk factors for abnormal thyroid function test results in pediatric patients with mood and anxiety disorders are unknown.
- Thyroid-stimulating hormone concentrations are abnormal in approximately 6% of psychiatrically hospitalized youth, although thyroid disease is present in < 1% of these patients.
- Targeted screening should focus on patients with recent weight gain, treatment with benzodiazepines, and, in girls, a history of abnormal uterine bleeding/menometrorrhagia.

thyroid functioning screening in children is a retrospective examination of 150 adolescent inpatients that was conducted more than 2 decades ago.[15] Investigators reported that 8 and 9 patients had thyroid-stimulating hormone (TSH) concentrations > 3.6 μU/mL and < 0.5 μU/mL, respectively. None of the patients with elevated TSH concentrations had a thyroxine (T_4) level that was in the abnormal range, while all of the patients with suppressed TSH measures had T_4 concentrations consistent with hyperthyroidism (based on laboratory diagnosis). The authors concluded that their data did not support routine testing in this population, although they noted that screening decisions should be informed by the presence or absence of signs and symptoms of thyroid disease.[15] Because of the small sample size in this study, the ability to examine specific demographic or clinical factors that predict abnormal TSH concentrations was limited.[15]

In adults, abnormal TSH measures are present in 9%–14% of patients.[16–24] However, with the exception of 1 report, studies of psychiatrically hospitalized adults have included < 500 patients and generally fewer than 200 patients. Two studies have examined larger samples (> 1,000 patients). In the most recent study of psychiatrically hospitalized adults (N = 1,167), abnormal TSH measures were determined and 14% of patients had abnormal TSH concentrations with 69 patients (3%) having biochemical hypothyroidism (defined in this study as a TSH concentration > 4.0 mIU/mL). The authors concluded that their data do not support routine TSH screening.[17] An additional retrospective study of adult South African psychiatric inpatients (N = 1,080) observed only 16% of abnormal TSH tests resulted in clinically significant findings; however, in this sample testing was not performed on a routine basis but rather when "indicated."[25] In this sample, abnormal TSH concentrations were more common in females but were independent of other demographic factors and clinical diagnoses.[25]

American Academy of Pediatrics guidelines (and others) recommend screening for and treating anxiety and depression in primary care settings.[26] However, the literature does not provide pediatricians with information to adequately estimate the prevalence or clinical factors associated with thyroid disorders among anxious and depressed youth, making it difficult to determine when such evaluations are necessary in anxious or depressed youth. Additionally, data regarding the prevalence or clinical factors associated with thyroid disorders among anxious and depressed youth are lacking. Given the dearth of data concerning the utility of TSH screening in children and adolescents with mood (eg, major depressive disorder, bipolar disorder, dysthymia/persistent depressive disorder, unspecified mood disorder) and anxiety disorders, we sought to examine the prevalence of abnormal TSH measures in psychiatrically hospitalized youth and to identify predictors of abnormal TSH concentrations.

METHODS

Patients

A query was developed to identify potentially eligible patients in the electronic medical record (EMR) who were admitted to the inpatient psychiatric units at Cincinnati Children's Hospital Medical Center (CCHMC) between September 2013 and April 2017 and had 1 follow-up appointment at an affiliated outpatient location. Inclusion criteria were as follows: age < 19 years; a diagnosed anxiety and/or mood disorder, and a recorded TSH level. Patients were excluded if no height and weight was recorded within 1 week of TSH testing or if there was a diagnosis of traumatic brain injury, substance use disorder, intellectual disability, or congenital brain abnormality. Data were abstracted from the patients' EMR by a reviewer who was blind to reason for admission and thyroid status. The study protocol was approved by the Institutional Review Board at CCHMC.

For those patients with an EMR note in the week prior to TSH testing, the presence of specific symptoms (weight gain, drowsiness/tiredness, insomnia/dysomnia, constipation) was gathered through an adaptive natural language process that resulted in an algorithm that examined the presence of key terms in > 84,000 EMR notes, as previously described.[27,28] We first performed a manual review of the EMR notes to identify common words and phrases that providers used to document the presence of these documented signs and reported symptoms (eg, weight gain, drowsiness/tiredness, fatigue, difficulty concentrating). The resulting algorithm was used to scan the psychiatry encounter note recorded closest to time of TSH testing (limitation of 1 week before). Charts were manually reviewed to refine the algorithm and to achieve a false-positive rate < 10% for each symptom.[27,28] For example, for drowsiness and fatigue, terms included "drowsy," "drowsiness," "low energy," "no energy," "decreased energy," "fatigue," "fatigued," "lethargic," "lethargy," "sleepy," "tired," "tiredness," and "daytime somnolence" but excluded phrases like "no fatigue," "lack of drowsiness," and "no complaints of lethargy." Similarly, weight gain would be coded as positive with the presence of "increased weight," "weight increase," and "gained weight," but phrases such as "no weight gain" and "denies weight gain" would be ignored.

Statistical Analysis

Based on the literature and current practice guidelines, a number of variables were selected that we hypothesized would have a relationship with TSH concentrations. We

Table 1. Demographic and Clinical Characteristics of Psychiatrically Hospitalized Children and Adolescents[a]

	All Patients (N = 1,017)	Low TSH (n = 7)	Normal TSH (n = 948)	Elevated TSH (n = 62)	Group Difference	Significance
Age, mean (SD), y	14.7 (2.24)	15.0 (1.43)	14.7 (2.24)	14.8 (2.27)	$F = 0.0$	.998
Children, %	20.6	0	94.7	5.3	$\chi^2 = 1.0$	.60
Adolescents, %	79.4	0.8	93.0	6.2		
Race, %					$\chi^2 = 5.7$	.68
White	77.0	0.5	93.0	6.5		
Black	12.5	1.6	93.7	4.7		
Asian	1.6	0	93.8	6.3		
Mixed	3.0	0	100	0		
Other	5.9	1.7	91.7	6.7		
Ethnicity, %						
Hispanic	2.1	0	100	0	$\chi^2 = 1.6$	.46
Gender, %					$\chi^2 = 1.4$	.50
Female	64.9	0.9	92.9	6.2		
Male	35.1	0.3	93.8	5.9		
Psychiatric diagnosis, %						
ADHD	42.8	57.1	41.9	40.3	$\chi^2 = 0.7$	.69
Anxiety	52.9	0.7	92.9	6.8	$\chi^2 = 0.2$	.93
Mood disorder	89.6	1.0	93.3	5.9	$\chi^2 = 1.2$	.54
Psychotic spectrum	10.5	0.9	90.7	8.4	$\chi^2 = 1.2$	.54
Nonpsychiatric disorder, %						
Thyroid disease	**4.8**	**6.1**	**69.4**	**24.5**	$\chi^2 = 53.8$	**< .001**
Medication, %						
SGA	45.8	1.1	92.5	6.4	$\chi^2 = 2.1$	.36
Lithium	**2.2**	**0**	**77.3**	**22.7**	$\chi^2 = 11.0$	**< .001**
Benzodiazepine	**8.8**	**0**	**86.5**	**13.5**	$\chi^2 = 9.9$	**.01**
Estrogen-based contraceptive	5.3	0	92.6	7.4	$\chi^2 = 0.6$	.76
BMI, %					$\chi^2 = 1.9$	.93
Underweight	14.5	0	93.9	6.1		
Normal weight	50.3	0.8	93.4	5.9		
Overweight	16.4	1.2	92.2	7.1		
Obese	18.8	0.5	93.2	6.3		

[a]Boldface indicates statistical significance.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BMI = body mass index, SGA = second-generation antipsychotic, TSH = thyroid-stimulating hormone.

used χ^2 analyses for categorical variables (eg, race, gender, treatment with antipsychotic medications) and 1-way analysis of variance for continuous variables (eg, age) to test for associations of hypothesized covariates to each TSH variable separately. These variables were descriptively evaluated with regard to low (< 0.36 μIU/mL), high (> 3.74 μIU/mL), and normal screening TSH concentrations. Then, binomial logistic regressions were used to test whether variables were associated with increased TSH concentrations (TSH within reference range = 0, increased TSH = 1). All analyses were conducted in *R* (version 3.3.2). *P* values < .05 were considered statistically significant.

RESULTS

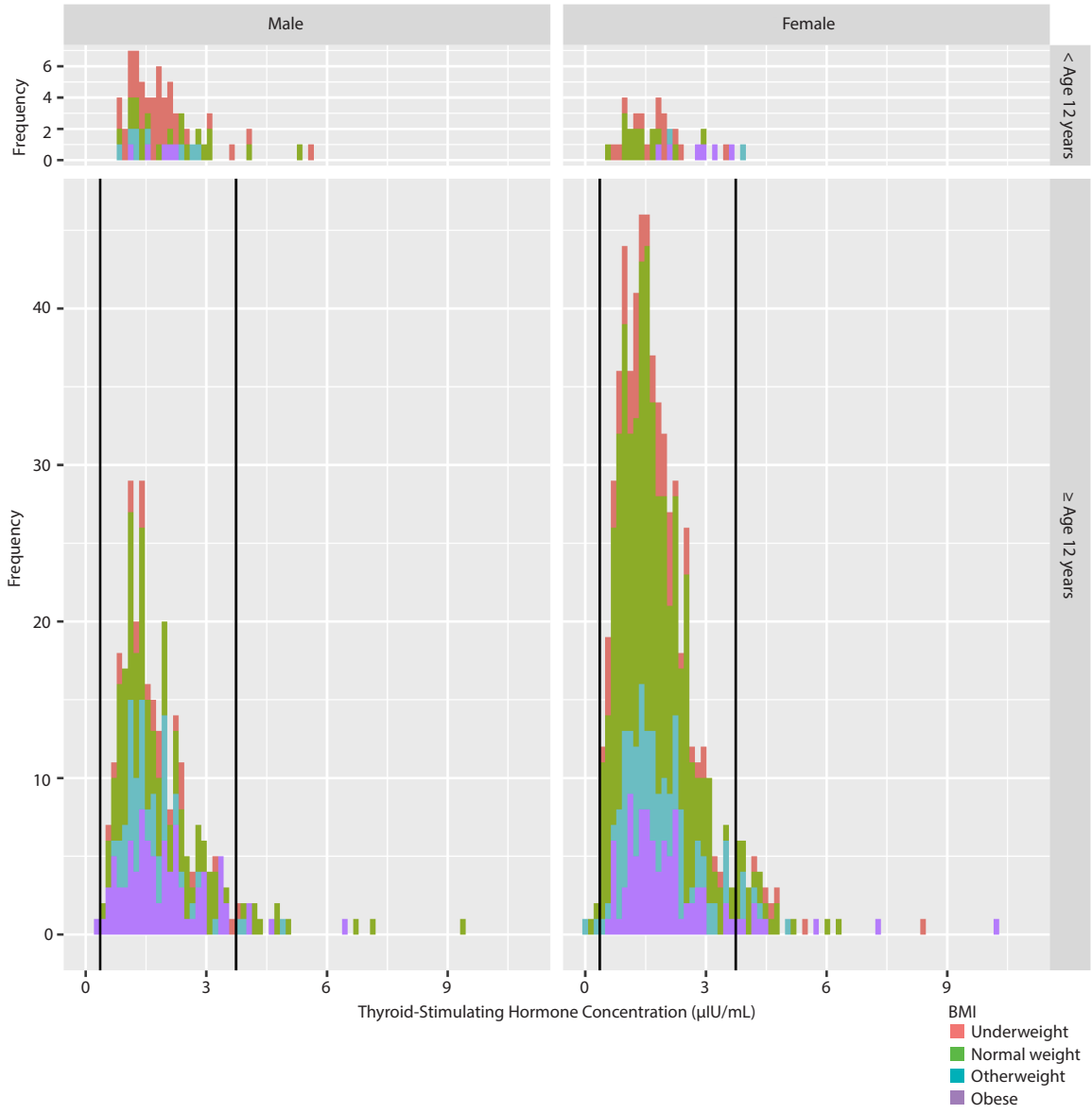
Patients

Of the original 1,319 patients identified by the EMR query, 1,244 patients had at least 1 TSH result and 1,017 met inclusion criteria. Patients were divided according to TSH measures into low (< 0.36 μIU/mL), normal (0.36–3.74 μIU/mL), and high (> 3.74 μIU/mL) screening TSH concentrations. When multiple TSH measures were present in the database, the earliest and most proximate to the admission date was used. Demographic variables for each group are reported in Table 1. Demographic and clinical characteristics, other than a history of thyroid disease and the use of either benzodiazepines or lithium, did not differ between the 3 groups. No significant differences were observed between suppressed, normal, and elevated TSH groups for age (*P* = .998), gender (*P* = .50), and body mass index (BMI) (*P* = .93) (Table 1).

Suppressed TSH

Seven patients had a suppressed TSH (mean TSH: 0.26 ± 0.12 μIU/mL); all were > 12 years of age and 85.7% (n = 6) were female; the mean age was 15.0 ± 1.43 years. More than half of patients with suppressed TSH measures (57.1%, n = 4) had a normal BMI *z* score, 28.6% (n = 2) were overweight, and 14.3% (n = 1) were obese (Figure 1). A history of thyroid disease was present in 42.9% (n = 3) of patients with a suppressed TSH at admission, and 2 patients were treated with levothyroxine at the time of testing. Second-generation antipsychotics were prescribed to 5 patients (71.4%), but none of the 7 patients were on lithium, benzodiazepines, anti-epileptic drugs, first-generation antipsychotics, corticosteroids, or estrogen-based contraceptives. All 7 patients had a history of mood disorder, and 57.1% (n = 4) had a history of anxiety disorders. Additional psychiatric diagnoses included a history of ADHD (71.4%, n = 5) and a history of psychotic spectrum disorders (14.3%, n = 1). None of the 7 patients had a history of gastrointestinal or neurologic diseases.

Figure 1. Distribution of Screening Thyroid Stimulating Hormone (TSH) Measures Between the Detection Limit and 10 µIU/mL at Admission in Psychiatrically Hospitalized Youth[a]



[a]Body mass index (BMI) is divided into the following categories: underweight (< 5th percentile, *z* score < −1.64), normal weight (5th–84th percentile, *z* score ≥ −1.64– < 1.04), overweight (85th–94th percentile, *z* score ≥ 1.04– < 1.64), and obesity (> 95th percentile, *z* score ≥ 1.64).

Elevated TSH

Sixty-two patients were identified as having an elevated TSH (mean TSH concentration: 8.60 ± 25.00 µIU/mL). Of these patients, 90.3% (n = 56) were > 12 years of age and 66.1% (n = 41) were female. BMI *z* score was in the normal range in 48.4% (n = 30) of patients, 14.5% (n = 9) were underweight, 17.7% (n = 11) were overweight, and 19.4% (n = 12) were obese (Figure 1). A history of thyroid disease was present in 19.4% (n = 12) of patients with elevated TSH at screening, and 5 of these patients were treated with levothyroxine. Nearly half of patients with an elevated TSH (48.4%, n = 30) were treated with a second-generation antipsychotic, 5.1% (n = 5) were treated with lithium, 19.4% (n = 12) were treated with a benzodiazepine, 6.5% (n = 4) were prescribed estrogen-based contraceptives, and 14.5% (n = 9) were treated with antiepileptic medications. No patients were being treated with either first-generation antipsychotics or corticosteroids. A history of mood disorder was present in 87.1% (n = 54) of patients, 40.3% (n = 25) had a history of ADHD, 54.8% (n = 34) had a history of anxiety, 22.6% (n = 14) had a history of PTSD, and 14.5% (n = 9) had a history of psychotic spectrum disorder. 11.3% (n = 7) of patients had a history of insomnia, 14.5% (n = 9) had a history of gastrointestinal complaints, 11.3% (n = 7) had a history of neurologic complaints, and 4.8% (n = 3) had a history of arrhythmias. A history of amenorrhea

Table 2. Binomial Logistic Regression Results of Demographic Variables, Psychiatric Diagnosis, Medication, Symptoms, and Nonpsychiatric Diagnosis Predicting Elevated TSH Values (n = 1,010)[a]

Predictor	*B*	SE	*Z* Score	*P*	OR	95% CI
Demographics						
Intercept	−17.75	845.83	−0.02	.98	1.96×10^{-8}	NA
Age	0.10	0.34	0.31	.76	1.11	0.60–2.29
Race						
Black	−0.32	0.45	−0.73	.47	0.72	0.27–1.60
Asian	−0.07	1.05	−0.07	.95	0.93	0.051–4.79
Mixed	−14.83	701.39	−0.02	.98	3.6×10^{-7}	3.39×10^{-95}–6.65×10^{8}
Other	0.34	0.55	0.61	.54	1.40	0.41–3.67
Ethnicity	15.03	845.83	0.02	.99	3.38	NA
Gender	0.05	0.29	0.17	.87	1.05	0.60–1.89
Body mass index						
Normal weight	0.03	0.33	0.08	.94	1.03	0.54–1.99
Overweight	0.01	0.30	0.02	.99	1.01	0.55–1.80
Obesity	−0.13	0.27	−0.48	.63	0.88	0.53–1.52
Psychiatric diagnosis						
Intercept	−2.74	0.25	−11.04	< .001	0.06	0.04–0.10
Anxiety disorder	0.09	0.26	0.35	.72	1.10	0.66–1.85
Mood disorder	−0.16	0.28	−0.58	.56	0.85	0.51–1.55
Psychotic spectrum disorder	0.38	0.38	1.01	.31	1.46	0.66–2.93
Medication						
Intercept	−2.93	0.19	−15.06	< .001	0.05	0.04–0.08
Second-generation antipsychotic	−0.02	0.27	−0.06	.95	0.98	0.57–1.68
Lithium	1.14	0.61	1.86	.06	3.12	0.84–9.49
Benzodiazepines	**0.83**	**0.36**	**2.28**	**.02**	**2.29**	**1.07–4.52**
Levothyroxine	**1.73**	**0.62**	**2.80**	**.01**	**5.66**	**1.51–18.02**
Estrogen-based contraceptives	0.04	0.57	0.06	.95	1.04	0.28–2.82
Symptoms						
Intercept	−2.91	0.17	−17.54	< .001	0.05	0.04–0.07
Weight gain	**1.28**	**0.54**	**2.39**	**.02**	**3.60**	**1.13–9.61**
Drowsiness/tiredness	0.15	0.38	0.40	.69	1.16	0.52–2.34
Insomnia/dysomnia	0.40	0.35	1.17	.24	1.50	0.73–2.87
Problem list						
Intercept	−2.88	0.15	−18.95	< .001	0.06	0.04–0.07
Headaches	−0.83	0.63	−1.32	.19	0.44	0.10–1.28
Hypersomnia	−13.77	799.03	−0.02	.99	4.37×10^{-6}	NA
Constipation	0.36	0.49	0.74	.46	1.44	0.50–3.49
Arrhythmia	−0.15	0.67	−0.22	.83	0.86	0.19–2.79
History of thyroid abnormality	**1.93**	**0.37**	**5.15**	**.00**	**6.88**	**3.20–14.08**
Intercept (females only)	−2.31	0.22	−10.43	< .001	0.10	0.06–0.15
Abnormal uterine bleeding and menometrorrhagia (females only)	**0.71**	**0.31**	**2.26**	**.02**	**2.03**	**1.04–3.63**

[a]Boldface indicates statistical significance.
Abbreviations: OR = odds ratio, TSH = thyroid-stimulating hormone.

or dysmenorrhea was present in 19.5% (n = 8) of female patients.

Predictors of Elevated TSH

A history of thyroid disease (OR = 6.88; CI, 3.20–14.08; *P* < .001), treatment with levothyroxine (OR = 5.66; CI, 1.51–18.02; *P* = .01), and abnormal uterine bleeding/menometrorrhagia (OR = 2.03; CI, 1.04–3.63; *P* = .02) were associated with a higher likelihood of a high TSH value. Clinician-recorded weight gain (OR = 3.60; CI, 1.13–9.61; *P* = .017) but not drowsiness or insomnia was associated with an elevated TSH value. Additionally, treatment with benzodiazepines (OR = 2.29; CI, 1.07–4.52; *P* = .02) during the month prior to TSH screening was associated with elevated TSH (Table 2).

Incidence of Thyroid Pathology

Among patients with elevated TSH concentrations, thyroid disease was present in 12.9% (n = 8) of patients, as determined by free T_4 values, total T_4 values, or current treatment of hypothyroidism (Table 3). All 8 patients with laboratory-determined hypothyroidism were > 14 years of age and were older than those patients who had an elevated TSH but no history or biochemical findings consistent with hypothyroidism (16.5 ± 1.5 vs 14.6 ± 2.3 years, *t* = –2.735, *P* = .020).

All of the patients with hypothyroidism were white, and the majority of patients were female, although the sex distribution did not differ compared to those patients with an elevated TSH and no hypothyroidism (87.5%, n = 7 vs 63.6%, n = 35, $\chi^2 = 0.55$, *P* = .444). In patients with hypothyroidism, BMI *z* scores were in the normal range in 50% (n = 4) of patients, 25% (n = 2) were overweight, and 25% (n = 2) were obese. All patients with hypothyroidism were diagnosed with a mood disorder and 62.5% had anxiety (n = 5) and half of the patients were treated with levothyroxine at the time of testing, while 37.5% (n = 3) were prescribed second-generation antipsychotics, 12.5% (n = 1)

Table 3. Thyroid Indices of Adolescents Who Met Laboratory Criteria for Thyroid Disease

Patient	Age (y)	Sex	TSH, μIU/mL[a]	Free T_4, ng/dL[b]	Total T_4, μg/dL[c]	Imaging	Laboratory/Clinical Diagnosis
1	17.0	F	198	0.6			History of Graves disease, postoperative hypothyroidism
2	15.9	F	44.4	0.3			Acquired hypothyroidism, post Hashimoto's thyroiditis
3	16.0	F	10.2	1			
4	18.3	M	7.12		5.5	Diffusely enlarged thyroid gland with heterogenous signal (CT)	Acquired hypothyroidism, post autoimmune thyroiditis
5	14.5	F	6.33	2.3		Hypoechoic nodules (ultrasound)	Acquired hypothyroidism, post Hashimoto's thyroiditis
6	14.7	F	5.7				Hypothyroidism
7	17.3	F	4.42	2			Hypothyroidism
8	18.2	F	4.41	< 0.4			Acquired hypothyroidism, post Hashimoto's thyroiditis

[a]TSH normal range: 0.36–3.74 μIU/mL. [b] Free T_4 normal range: 0.78–1.33 ng/dL. [c]Total T_4 normal range: 4.9–11.7 μg/dL.
Abbreviations: CT = computed tomography, F = female, m = male, TSH = thyroid-stimulating hormone.

were prescribed benzodiazepines, and 12.5% (n = 1) were taking an estrogen-based contraceptive. In female patients with hypothyroidism, 42.9% (n = 3) reported abnormal menstrual bleeding/menometrorrhagia.

DISCUSSION

We report the largest examination of thyroid function testing utility in psychiatrically hospitalized youth with severe mood and anxiety disorders, and we observed abnormal TSH concentrations in approximately 7% (1% suppressed; 6% elevated). This study represents the first examination of predictors of elevated TSH concentrations in psychiatrically hospitalized youth with mood and anxiety disorder and identifies recent weight gain, treatment with benzodiazepines or lithium, a history of abnormal uterine bleeding/menometrorrhagia in females, and a history of thyroid disease as predictors of increased TSH. Despite being a routine screening test in pediatric patients at the time of psychiatric admission, the prevalence of thyroid disorders is poorly characterized in pediatric populations, and there is conflicting evidence on the utility of thyroid function screening in patients with severe mood and anxiety disorders. To date, only 1 study evaluated screening for thyroid dysfunction in psychiatrically hospitalized youth and revealed abnormal TSH concentrations in 13% (7% suppressed; 6% elevated) of their smaller cohort (N = 150),[15] whereas in the psychiatrically hospitalized adults, abnormal screening TSH concentrations are present in 9%–14% of patients.[16–24] Additionally, a study of children with ADHD (N = 277) suggests a similar rate of thyroid function testing abnormalities (5.4%) as that detected in our study, compared to < 1% in the "normal population."[29] However, it is noteworthy that the rates of ADHD diagnoses did not statistically differ between patients with and without abnormal TSH measures in our study.

Our study suggests that weight gain, a history of abnormal uterine bleeding/menometrorrhagia in females, and a history of thyroid disease may be predictors of increased TSH concentrations in pediatric patients with severe mood and anxiety disorders. At least 1 of the stated clinical indications for TSH testing was present in all 8 patients with thyroid disease. These patient-specific characteristics may inform targeted screening approaches and should be of high clinical interest to pediatricians, child and adolescent psychiatrists, and other pediatric mental health providers. Specifically, the cost-effectiveness of screening might be increased if testing is performed in those youth with severe mood and anxiety disorders who report weight gain, abnormal uterine bleeding/menometrorrhagia, or a history of thyroid disease as opposed to universal screening. In our sample, 20% of females with elevated TSH concentrations experienced abnormal menstrual bleeding/menometrorrhagia. Menorrhagia has been associated with hypothyroidism, ostensibly secondary to estrogen breakthrough bleeding that results from anovulation, a frequent finding in hypothyroidism. In adult women, menstrual abnormalities were present in 15.3% of patients with hypothyroidism, while 34.8% of patients with "severe hypothyroidism" (based on T_4 concentrations) experienced menstrual abnormalities (compared to 10.2% of those women with "mild" hypothyroidism).[30] The finding of recent weight gain—which is well described in adults with hypothyroidism—has been more difficult to examine in the pediatric population, and it is noteworthy that we did not find an association with BMI *z* score but rather with recent weight gain, which reflects the importance of assessing trajectory of weight gain rather than relying on categorical assessments of BMI or cross-sectional measures of weight. The finding of an association between a history of thyroid disease and abnormal TSH screening results underscores the importance of obtaining a thorough medical history in children with severe anxiety and mood disorders.

Several pharmacotherapies were associated with increased TSH measures and warrant additional discussion. Nineteen percent of patients with elevated TSH measures were prescribed a benzodiazepine in the month prior to thyroid function testing. Interactions between benzodiazepines and thyroid hormone function were first described by Turner and Sneddon (1967),[31] who evaluated patients treated with diazepam and chlordiazepoxide. Additionally, in a follow-up study of subacute (7 day) diazepam treatment, decreases in free T_4 levels and protein-bound iodine (a marker of bound T_3 and T_4) have been observed in adults.[32] In preclinical studies, benzodiazepine administration increases hepatic

thyroxine (T_4)-UDP-glucuronosyltransferase, accelerating T_4 clearance and decreasing circulating concentrations of active thyroid hormones with secondary increases in TSH biosynthesis and secretion.[33,34] Additionally, benzodiazepine administration decreases both the responsiveness and sensitivity to TRH stimulation, potentially through antagonism at TRH-binding sites.[35] Given our findings in youth, consistent with adult and preclinical studies, clinicians may consider a lower threshold for TSH screening in patients treated with benzodiazepines.

Our study found that 5% of patients with elevated TSH measures were prescribed lithium in the month prior to thyroid function testing. Retrospective studies of adults suggest that lithium treatment is associated with an odds ratio of 2.3 for developing hypothyroidism (confidence interval, 2.05–2.60; $P < .0001$) but did not suggest an association with hyperthyroidism,[36,37] and a recent meta-analysis of lithium-related adverse effects in adults confirmed significant increases in hypothyroidism risk (vs placebo) and treatment-emergent increases in TSH concentrations.[36] Recently, a randomized controlled trial of lithium in pediatric patients with bipolar disorder[12] observed that 17% of lithium-treated youth, over the course of 8 weeks of treatment, developed an elevated TSH level (12.5% of patients aged 7–11 years and 23.8% of adolescents aged 12–17 years).[12] While, in our sample, the association between lithium treatment and increased TSH trended toward significance ($P = .06$), the effect size for this association was large, and therefore clinicians should monitor TSH in lithium-treated patients consistent with current guidelines.[38]

While this is the largest study to examine the utility of thyroid function screening in psychiatrically hospitalized youth with severe mood and anxiety disorders, it relies on documented histories obtained by individual clinicians during encounters. Thus, underreporting of symptoms—either because they were not captured by clinicians or because they were not captured in our adaptive language processing algorithm—could increase type II error. Second, while limited to ≤ 10%, false-positives may still exist in the natural language processing algorithm that was used to capture symptoms in the EMR. Third, the natural language processing algorithm was limited in its ability to determine the temporal progression of symptoms and may lack the sensitivity to capture the clinical severity of the symptoms that were associated with a greater likelihood of abnormal TSH measures. For example, would a patient who had gained 0.5 kg over the past month be less likely to have an abnormal TSH measure than a patient who had gained 6 kg over the same time period? Fourth, standardized physical examinations were not included, and specific physical examination findings might increase the efficiency of screening by identifying specific signs of hypo- or hyperthyroidism. Fifth, compliance with regard to medications that were associated with abnormal screening TSH measures was not systematically assessed. Finally, the study was conducted at a single site, and, while the sample size was large, results may not be entirely generalizable.

In conclusion, TSH concentrations are abnormal in approximately 7% of psychiatrically hospitalized youth with significant mood and anxiety disorders, while elevated TSH concentrations were present in 6% of the sample. Importantly, in the total sample, <1% had a laboratory diagnosis of thyroid pathology. Finally, when considering thyroid assessment in youth with anxiety and mood disorders, targeted screening should focus on patients with recent weight gain, treatment with benzodiazepines or lithium, a history of abnormal uterine bleeding/menometrorrhagia (in girls), and a family history of thyroid disease.

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