Elevated Thyrotropin in Bipolar Youths Prescribed Both Lithium and Divalproex Sodium

BARBARA L. GRACIOUS, M.D., ROBERT L. FINDLING, M.D., CHRISTOPHER SEMAN, D.O., ERIC A. YOUNGSTROM, PH.D., CHRISTINE A. DEMETER, B.A., AND JOSEPH R. CALABRESE, M.D.

ABSTRACT

Objective: To examine the effect of combined lithium and divalproex sodium on thyroid-stimulating hormone (TSH) levels in children and adolescents with bipolar disorders and to identify risk factors for lithium-induced hypothyroidism. **Method:** Bipolar youths aged 5 to 17 years participating in an open-label clinical trial received treatment with lithium and divalproex sodium for up to 20 weeks. TSH levels were measured at baseline and at the end of the study. Subjects were divided into two groups for analysis: group 1 had TSH levels of less than 10.0 mU/L at the end of the study and group 2 had TSH levels of 10.0 mU/L or more at end of the study. **Results:** Twenty of the 82 subjects (24.4%) showed TSH elevations of at least 10 mU/L within an average exposure of less than 3 months. The mean baseline TSH level for group 2 was significantly higher than for group 1 (2.97 [SD = 1.48] versus 2.05 [SD = 0.89], $p < .05$). Mean lithium levels at the end of the study were 1.00 mEq/L for group 2 compared to 0.76 mEq/L for group 1 ($t = -2.41$, $p = .019$). **Conclusions:** Lithium is associated with significant rates of thyrotropin elevation in bipolar youths. Factors associated with elevation in TSH in lithium-treated subjects include a higher baseline TSH level and a higher lithium level. Close monitoring of thyroid function in children and adolescents taking lithium is recommended. *J. Am. Acad. Child Adolesc. Psychiatry,* 2004;43(2):215–220. **Key Words:** lithium, pediatric, hypothyroidism, thyroid-stimulating hormone, divalproex sodium.

Lithium-induced hypothyroidism (LIH) has been well documented in the adult population. Prevalence studies, largely retrospective, have estimated that as many as 34% of Western adults with bipolar disorder develop LIH (Transbol et al., 1978). Risk factors for LIH in the adult population include duration of exposure to lithium (Transbol et al., 1978), rapid cycling (Bauer et al., 1990), preexisting autoimmune disease (Lazarus, 1986; Transbol et al., 1978), female gender (Johnston and Eagles, 1999); and age (Bocchetta et al., 1991; Transbol et al., 1978).

No systematic studies have examined the effects of lithium on the pediatric thyroid or data on risk factors for and sequelae of LIH in children and adolescents. The purpose of this study was to examine the effect of lithium on thyrotropin/thyroid-stimulating hormone (TSH) levels in children and adolescents with bipolar disorder and to identify potential risk factors for LIH in this group.

METHOD

Youths aged 5 to 17 years were enrolled into an open-label clinical trial that was comparing the safety and efficacy of lithium and divalproex sodium in the treatment of pediatric bipolar disorder. The study design is outlined in detail in Findling et al. (2000). Inclusion criteria included (1) having a hypomanic or manic episode as defined by *DSM-IV* criteria within 3 months of entering the study; and (2) meeting *DSM-IV* criteria for bipolar disorder type 1 or 2 as per the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) (Kaufman et al., 1997) and agreement via clinical assessment by a child and adolescent psychiatrist. Exclusion criteria included (1) history of intolerance to lithium levels of 0.6 mEq/L or intolerance to divalproex sodium levels of 50 μg/mL; (2) history of a manic episode with a lithium

Accepted September 4, 2003.

From Strong Memorial Hospital at the University of Rochester Medical Center (B.L.G.), Rochester, NY; Case Western Reserve University (R.L.F., E.A.Y., J.R.C.), Cleveland; and University Hospitals of Cleveland (R.L.F., J.R.C., C.S., E.A.Y., C.A.D.).

This research was primarily supported by a Bipolar Disorder Clinical Research Center Grant from the Stanley Medical Research Institute. Study medications were provided in part by Abbott Laboratories. The authors thank Lisa Branicky, Raisa Papish-David, Denise DelPorto Bedoya, Lisa Townsend, Cara West, and Resa Whipkey for their assistance with this project. The authors also thank all the families that participated. Nicholas Rollins assisted in preparing the manuscript.

Correspondence to Dr. Gracious, Department of Psychiatry, University of Rochester Medical Center, 300 Crittenden Boulevard, Box PSYCH, Rochester, NY 14642; e-mail: Barbara_Gracious@URMC.Rochester.edu.

DOI: 10.1097/01.chi.0000101699.15837.32

level of 1.0 mEq/L or more or a divalproex sodium level of more than 80 μg/mL; (3) any neurological or medical contraindication to the use of divalproex sodium or lithium; (4) pervasive developmental disorder or clinically evident mental retardation; (5) pregnancy, intended pregnancy, or inadequate birth control if sexually active; (6) inability to swallow pills; and (7) primary medical or neurological cause of the mood disorder. Participants received both lithium and valproic acid openly for up to 20 weeks, with target daily doses at the end of week 2 being 20 mg/kg and 30 mg/kg, respectively. Medication doses were titrated according to clinical effectiveness and tolerability, with patients' divalproex sodium levels targeted between 50 and 100 μg/mL and lithium levels between 0.6 and 1.2 mmol/L. The purpose of the primary study was to collect data on the effectiveness of combination pharmacotherapy in achieving remission of symptoms in this patient population. The study endpoint for each subject was defined as occurring 4 weeks after syndrome remission, or sooner for those whose symptoms did not or were unlikely to meet remission criteria by 16 weeks. Thus the study duration varied for individual participants and could be up to 20 weeks. Children who did not complete at least 8 weeks of the study were excluded from these data analyses.

TSH levels were obtained at baseline and at the end of the study using the Advia Centar TSH Immunoassay (Bayer Corp.). The range of normal values was 0.35 to 5.50 mU/L. Subjects were divided into two groups based on TSH levels at the end of the study. Group 1 comprised subjects with TSH levels of less than 10.0 mU/L at the end of the study; group 2 comprised subjects with TSH levels of 10.0 mU/L or more at the end of the study. This convention was chosen because a TSH of 10.0 mU/L or more is often when synthetic thyroid hormone will be added clinically (Kleiner et al., 1999). Additionally, a baseline physical examination, electrocardiogram, urine toxicology screen, chemistry profile, hematology and coagulation profiles, and urinalysis were obtained. Females who had reached menarche received a urine pregnancy test. Side effects were monitored throughout the study.

Severity of illness at baseline was assessed using three instruments. Symptoms of mania were evaluated using the Young Mania Rating Scale (YMRS) (Young et al., 1978); depressive symptoms were assessed with the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al., 1985); and overall illness severity was measured by the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1985).

Children whose TSH was more than 10 mU/L were managed within the study by decreasing their lithium dose. They were maintained in the study if they did not worsen clinically and met the criteria for minimum lithium level of at least 0.6 mmol/L. If their mood worsened significantly or their TSH remained above 10 mU/L, they were discontinued from the study.

Between-group comparisons were made using χ^2, independent sample *t* tests, Mann-Whitney, or logistic regression, as appropriate.

RESULTS

Twenty of the 82 subjects (24.4%) included in this study had a TSH level greater than or equal to 10.0 mU/L at the end of the study (group 2). Table 1 shows the demographics of both groups. There were no significant differences between groups for gender, duration of illness, presence of rapid cycling, psychosis, age, and age of onset of illness. Table 2 compares the two outcome groups for average scores at baseline and at the end-of-study visit on the Y-MRS, C-GAS, and CDRS-R ($p > .05$). There were no significant differences, indicating comparable severity of illness between the two groups at both time points.

TABLE 1
Demographic Information for 87 Youths

	Group 1 (TSH < 10.0, *n* = 62)	Group 2 (TSH ≥ 10.0, *n* = 20)	Overall (*n* = 82)
Gender, *n* (%)			
Male	43 (69.4)	15 (75.0)	58 (70.7)
Female	19 (30.6)	5 (25.0)	24 (29.3)
Race, *n* (%)			
White	55 (88.7)	17 (85.0)	72 (87.8)
African American	2 (3.2)	1 (5.0)	3 (3.7)
Biracial	5 (8.1)	0	5 (6.1)
Hispanic	0	2 (10.0)	2 (2.4)
Diagnosis, *n* (%)			
Bipolar disorder type 1	60 (96.8)	18 (90.0)	78 (95.1)
Bipolar disorder type 2	2 (3.2)	2 (10.0)	4 (4.9)
Age at baseline,[a] mean (SD)	10.4 (3.5)	9.6 (2.3)	10.2 (3.2)
Age of onset of illness,[a] mean (SD)	6.6 (3.7)	6.5 (3.2)	6.6 (3.6)
Rapid cycling,[b] *n* (%)	42 (67.7)	9 (45.0)	51 (62.2)
Mixed states,[c] *n* (%)	4 (6.5)	3 (15.0)	7 (8.5)
Psychosis,[c] *n* (%)	8 (12.9)	2 (10.0)	10 (12.2)
Length of enrollment (wk),[a] mean (SD)	12.3 (4.5)	12.0 (3.5)	12.2 (4.3)

Note: TSH = thyroid-stimulating hormone.
[a] Comparing group 1 to group 2 using an independent *t* test, $p > .05$.
[b] Comparing group 1 to group 2 using a χ^2 analysis, $p > .05$.
[c] Comparing group 1 to group 2 using a Fisher exact test, $p > .05$.

TABLE 2
Baseline and End-of-Study (EOS) Outcome Measure Scores for 82 Children and Adolescents, Presented as Mean (SD)

Measure	Group 1 (TSH < 10.0, *n* = 62)	Group 2 (TSH ≥10.0, *n* = 20)	Overall (*n* = 82)
CDRS-R			
Baseline	30.2 (11.7)	28.75 (11.5)	29.9 (11.6)
EOS	19.6 (5.4)	20.2 (5.6)	19.7 (5.4)
Y-MRS			
Baseline	21.3 (8.3)	22.1 (7.4)	21.5 (8.0)
EOS	5.9 (9.1)	6.8 (9.2)	6.1 (9.0)
CGAS			
Baseline	50.8 (7.0)	49.8 (7.2)	50.5 (7.0)
EOS	68.9 (12.7)	66.1 (12.4)	68.2 (12.6)

Note: CDRS-R = Children's Depression Rating Scale–Revised; Y-MRS = Young Mania Rating Scale; CGAS = Children's Global Assessment Scale; TSH = thyroid-stimulating hormone.

Table 3 presents mean lithium and divalproex sodium levels at the end of the study, as well as baseline and end-of-study TSH levels and mean heart rate at the end of the study. Mean lithium levels at the end of the study for group 1 (0.76 mEq/L, SD = 0.37, range = 0.05–1.60) and group 2 (1.00 mEq/L, SD = 0.35, range = 0.13–1.68) were significantly different (t_{75} = –2.41, p = .019). However, divalproex sodium levels at the end of the study for group 1 (70.7, SD = 30.0, range = 3–122) and group 2 (85.8, SD = 31.4, range = 16–152) did not differ significantly (t_{77} = –1.88, p = .06). The mean duration of enrollment in the study for group 1 (12.3 weeks, SD = 4.5, range = 1.7–23.9) and group 2 (12.0 weeks, SD = 3.5, range = 5.0–19.7) was not statistically significant (t_{80} = 0.32, p = .75), although five subjects ended the study due to an elevated TSH level. All five had residual symptoms of mania that precluded decreasing the lithium dosage further. Also, the mean heart rate at the end of the study between the group 1 and group 2 did not differ significantly (t_{79} = 0.63, p = .53).

A significant difference in mean TSH levels at baseline between group 1 (2.05, SD = 0.89, range = 0.32–4.37) and group 2 (2.97, SD = 1.48, range = 0.98–6.79) was found (t_{80} = –3.38, p = .001). A paired t test indicated an overall significant change from the screening TSH level to the end-of-study TSH level (t_{81} = –10.57, p < .001). In addition, TSH levels at the end of the study compared with baseline differed significantly for both group 1 (5.14, SD = 2.04, range =

TABLE 3
Thyroid-Stimulating Hormone (TSH), Divalproex Sodium, and Lithium Dosing and Serum Levels for 87 Youths

	Group 1 (TSH < 10.0, *n* = 62)	Group 2 (TSH ≥ 10.0, *n* = 20)	Overall (*n* = 82)
EOS lithium serum levels (mmol/L)			
Mean (SD)	0.76 (0.37)	1.0 (0.35)	0.82 (0.37)
Range	0.05–1.60	0.13–1.68	0.05–1.68
EOS divalproex sodium serum levels (μg/mL)			
Mean (SD)	70.7 (30.0)	85.8 (31.4)	74.4 (30.9)
Range	3–122	16–152	3–152
Baseline TSH levels (mU/L)			
Mean (SD)	2.05 (0.89)	2.97 (1.45)	2.27 (1.13)
Range	0.32–4.37	0.98–6.79	0.32–6.79
EOS TSH levels (mU/L)			
Mean (SD)	5.14 (2.04)	14.12 (3.69)	7.33 (4.62)
Range	0.86–9.47	10.61–25.01	0.86–25.01
EOS heart rate (bpm)			
Mean (SD)	91.93 (13.98)	89.8 (9.61)	91.4 (13.0)
Range	59–126	71–105	59–126

Note: Independent samples t test performed. EOS = end of study.

0.86–9.47; $t_{61} = -12.44$, $p < .001$) and group 2 (14.12, SD = 3.69, range = 10.61–25.01; $t_{19} = -12.40$, $p < .001$). The mean TSH levels for males ($n = 58$; 70.7%) and females ($n = 24$; 29.3%) were, respectively, 7.60 and 6.68. A χ^2 analysis indicated there was not a significant difference in gender distribution ($\chi^2_1 = 0.233$, $p = .63$).

Logistic regression analysis was performed to examine which variables made a unique contribution to the prediction of elevated TSH levels at he end of the study. Candidate predictors were initial TSH level at screening, lithium level at the end of the study, divalproex sodium level at the end of the study, gender, rapid cycling status, and the interaction of lithium and divalproex sodium levels (the product of two terms). All of these variables except divalproex sodium levels were indicated as potential predictors of TSH level based on prior research documented in the literature. A forward-entry procedure indicated that both initial TSH level and lithium level at the end of phase 1 made unique contributions to the prediction of elevated TSH status at the end of phase 1. The model including these two predictors was highly significant, with a $\chi^2_2 = 14.23$, Nagelkerke $R^2 = 0.26$, $p = .001$. Using these variables to predict elevated TSH yielded 75.0% classification efficiency (TSH screening $B = 0.81$, lithium end of phase 1 $B = 2.51$, constant = −5.27, $p < .01$ for all). Baseline TSH and current lithium level appeared to provide a relatively specific but poorly sensitive test. Using a 50% probability threshold, these regression weights yielded a 78.3% negative predictive value and 93.1% specificity, but only a 57.1% positive predictive value and 16.7% sensitivity. This diagnostic performance is based on a sample where roughly a quarter of participants showed elevated TSH levels. Performance will vary in new samples, particularly as the base rate of TSH elevation changes.

DISCUSSION

In this study population, 24% of children and adolescents taking a combination of lithium and divalproex sodium developed significant elevations of TSH between 8 and 20 weeks of therapy. This incidence is similar to that reported in the adult population (Bocchetta et al., 1991; Joffe et al., 1988). Bocchetta et al. (1991) found that 19% of patients enrolled in a lithium clinic developed subclinical hypothyroidism. Many of these patients had been on lithium for months to years. Joffe et al. (1988) reported that 19% of their patients developed subclinical or overt hypothyroidism after 3 months or more of lithium treatment for bipolar disorder. The duration of lithium exposure in their hypothyroid group averaged 82.2 months, much longer than the duration of lithium exposure in this study. The fact that 24% of our subjects showed elevations in TSH after an average of only 3 months of treatment is of concern. One explanation is that there may be an increased sensitivity of the developing pediatric thyroid to lithium. Although duration of exposure was found to be a risk factor in adults for developing LIH, the fact that we did not see any significant difference between group 1 and 2 in duration of exposure to lithium is likely due to the 20-week limitation of phase 1 of the study.

This paper may be one of the first to examine whether lithium and divalproex sodium might interact synergistically to affect TSH levels. Our data showed a trend for children in the elevated TSH group to have slightly higher divalproex sodium levels. However, subjects with higher divalproex sodium levels also tended to have higher lithium levels ($r = 0.51$, $p < .0005$). When both lithium and divalproex sodium were considered simultaneously as potential predictors of elevated TSH, only lithium predicted a TSH elevation. However, there are two reports in the literature that found divalproex sodium effects on thyroid function. Elias et al. (1981) studied the effect of divalproex sodium on the TSH response to thyrotropin-releasing hormone and found that subjects treated with divalproex sodium had lower serum T3 levels and lower serum TSH levels. It was postulated that divalproex sodium treatment leads to an increase in γ-aminobutyric acid (GABA), which then acts at the pituitary gland to inhibit TSH secretion. Additionally, Eiris-Punal et al. (1999) published a report finding significant elevations in TSH along with reduced T4 and free T4 levels as well as T3 and thyroxine-binding globulin levels in a group of children with epilepsy who had been treated with divalproex sodium over a long period of time. The authors concluded that TSH levels should be monitored in children who are prescribed divalproex sodium. Thus subtle effects may be important in patients with borderline thyroid functioning. Given that children with bipolar spectrum disorders may use multiple medications, it will be important to further examine what effects divalproex sodium or other agents may have on thyroid function in patients also treated with lithium and other medications.

There are reports that thyroid abnormalities that occur early in the course of lithium treatment tend to stabilize or resolve. However, in this study group, TSH levels appeared to continue to rise unless lithium was decreased or stopped (unpublished data), making this explanation unlikely. Although others (Bocchetta et al., 1991; Joffe et al., 1988; Johnston and Eagles, 1999) have reported a tendency for females to be at higher risk, we did not detect any gender differences between the groups. Gender as a risk factor may be in part related to an increased rate of autoimmune thyroid disease in women in the general population and therefore would not be appreciated in our young population and relatively small sample size. Autoimmune thyroiditis has a 1% incidence among school-age children, although it is more common in girls, who are four to seven times more likely to develop it (Behrman et al., 2000). Antimicrosomal and antithyroglobulin antibodies, available for 6 of the 21 subjects in group 2, were all negative. This finding, along with the lack of gender differences in our group, suggests that lithium does not induce thyroid dysfunction through immune-mediated mechanisms, at least immediately.

Mechanisms by which lithium can affect thyroid function include (1) concentrating in and decreasing iodine absorption by the gland; (2) inhibiting the iodination of tyrosine; (3) interfering with the action of adenyl cyclase, thus limiting production of cyclic adenosine monophosphate (cAMP); and (4) inhibiting thyroid hormone release. These actions can lead to varying degrees of abnormal thyroid function, including both overt hypothyroidism and subclinical hypothyroidism, which is defined by an elevated TSH with a normal free T4 (thyroxine) level.

Kleiner et al. (1999) described the clinical sequelae of hypothyroidism and subclinical hypothyroidism as including lethargy, mental slowing, concentration and memory deficits, poorly controlled rapid cycling in patients with bipolar disorder, and numerous somatic symptoms. One of our 20 participants with a TSH level of at least 10 mU/L displayed clinical signs of hypothyroidism during the trial, which included rapid weight gain, peripheral edema, and development of a goiter. Consistent with no difference in heart rate between group 1 and group 2, bradycardia was not present, making this perhaps an insensitive marker of early elevation of TSH. In addition to physical and mental symptoms of low thyroid, detection of hypothyroidism in children prescribed lithium is important due to other special considerations in children. Chronic clinical hypothyroidism in children can lead to enlargement of the sella turcica, disturbances in sexual maturation and gonadal functioning, and abnormal musculoskeletal structure and function, which may include short stature and muscle hypertrophy (Rudolph et al., 1996).

In contrast to adult data, this study found no relationship between LIH and rapid cycling, age, gender, or duration of lithium exposure. In addition, no significant difference was detected between the two groups for the presence of psychosis, duration of illness, or severity of illness.

A significant difference was shown between the two groups in mean TSH at baseline. Group 2 had a level of 2.97 mU/L; the level in group 2 was 2.04 mU/L. This finding suggests that children and adolescents with higher baseline TSH levels may be at an increased risk for subclinical hypothyroidism or LIH. However, a single subject baseline TSH level was not predictive of developing subclinical hypothyroidism, since there was a large degree of overlap in individual TSH values between groups. It would be of interest to determine if this phenomenon also occurs in the adult population. Significantly higher lithium levels in group 2 at the end of the study suggests a dose effect where higher lithium levels yield a greater risk for developing LIH.

Limitations

Data about family history of thyroid disease, including autoimmune thyroid disease, were not systematically collected. Since this was an exploratory study, the effects of the study medications on other markers of thyroid function such as free T4, thyroglobulin, and thyrotropin-releasing hormone response were not examined. No standardized cognitive measures were given to assess for negative changes in cognitive functioning, since the subjects were acutely ill and received open treatment that resulted in improvement in mental status for many, confounding any negative changes related to thyroid that might occur. In addition, the brevity of the study prevented more long-term assessment. Differences in growth and sexual maturation were unlikely to be affected, as the period of elevated TSH was relatively brief.

Clinical Implications

Children taking lithium alone or a combination of lithium and valproic acid are at relatively high risk for developing thyroid dysfunction that may occur early in treatment. Therefore, patients taking a combination of

lithium and valproic acid deserve close monitoring of thyroid function. A comprehensive examination of thyroid function is warranted at baseline and every 2 to 3 months after initiation of treatment. If TSH is elevated, a limited review of systems and physical examination should be performed to determine if signs and symptoms of clinical hypothyroidism are present. The need for this close monitoring is supported by the finding of a 24% incidence of thyroid dysfunction within 3 months of initiation of therapy.

Management options for patients who develop subclinical LIH include lowering the dose of lithium, using other mood stabilizers with equal effectiveness, or, if continuing lithium treatment is justified by the clinical response and the dose cannot be lowered, adding synthetic thyroid hormone. The decision-making process includes a review of the potential risks of thyroid hormone versus potential clinical benefits with the parent (and child, where appropriate) as well as a review of all potential management options so that informed consent may be documented. Consultation with a pediatric endocrinologist may be helpful, especially if the child psychiatrist is unfamiliar with the use of synthetic thyroid hormone in children.

We believe this is the first study reporting a significant effect of lithium on thyroid functioning in children and adolescents with bipolar disorder treated with concomitant lithium and divalproex sodium. Prospective studies examining complete thyroid functioning, antithyroid antibodies, and family history variables are needed to determine the effects of lithium on thyroxine (T4) in young patients, as well as other potential risk factors, including autoimmune thyroiditis. Studies with a longer duration of exposure will help to elucidate whether the incidence of LIH continues to rise with increasing length of lithium therapy in children, as our experience suggests. Replication of these findings of the effects of lithium and divalproex sodium (combined as well as individually) on the pediatric thyroid are needed. Further research should also focus on the appropriate clinical management of LIH.

REFERENCES

Bauer MS, Whybrow PC, Winokur A (1990), Rapid cycling bipolar affective disorder. *Arch Gen Psychiatry* 47:427–432

Behrman RE, Kliegman RM, Jenson HB (2000), *Nelson Textbook of Pediatrics,* 16th ed. Philadephia: Saunders

Bocchetta A, Bernardi F, Pedditzi M et al. (1991), Thyroid abnormalities during lithium treatment. *Acta Psychiatr Scand* 83:193–198

Eiris-Punal J, Del Rio-Garma M, Del Rio-Garma MC, Lojo-Rocamonde S, Novo-Rodriguez I, Castro-Gago M (1999), Long-term treatment of children with epilepsy with valproate or carbamazepine may cause subclinical hypothyroidism. *Epilepsia* 40:1761–1766

Elias AN, Valenta LJ, Szekeres AV, Grossman M (1981), Effect of di-N-propylacetic acid (valproic acid) on the TSH response to TRH—a presumptive role for gamma aminobutyric acid. *Metabolism* 30:1021–1023

Findling RL, Gracious BL, McNamara N, Calabrese J (2000), The rationale, design and progress of two novel maintenance treatment studies in pediatric bipolarity. *Acta Neuropsychiatr* 12:136–138

Joffe RT, Kutcher S, MacDonald C (1988), Thyroid function and bipolar affective disorder. *Psychiatry Res* 25:117–121

Johnston AM, Eagles JM (1999), Lithium-associated clinical hypothyroidism. *Br J Psychiatry* 175:336–339

Kaufman J, Birmaher B, Brent D et al. (1997), Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 36:980–988

Kleiner J, Altshuler L, Hendrick V, Hershman JM (1999), Lithium-induced subclinical hypothyroidism: review of the literature and guidelines for treatment. *J Clin Psychiatry* 60:249–255

Lazarus JH (1986), *Endocrine and Metabolic Effects of Lithium*. New York: Plenum

Poznanski EO, Freeman LN, Mokros HB (1985), Children's Depression Rating Scale-Revised. *Psychopharmacol Bull* 21:979–990

Rudolph AM, Hoffman J, Rudolph C (1996), *Rudolph's Pediatrics,* 20th ed. Stamford, CT: Appleton & Lange

Shaffer D, Gould MS, Brasic J et al. (1985), A children's global assessment scale (CGAS) (for children 4 to 16 years of age). *Psychopharmacol Bull* 12:747–748

Transbol I, Christiansen C, Baastrup PC (1978), Endocrine effects of lithium. *Acta Endocrinol* 87:759–767

Young RC, Biggs JT, Ziegler VE, Meyer DA (1978), A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 133:429–435